



**ALO-01 (MORPHINE SULFATE EXTENDED-RELEASE WITH
SEQUESTERED NALTREXONE HYDROCHLORIDE) CAPSULES**

FOR THE

**MANAGEMENT OF MODERATE TO SEVERE PAIN WHEN A
CONTINUOUS, AROUND-THE-CLOCK OPIOID ANALGESIC IS
NEEDED FOR AN EXTENDED PERIOD OF TIME**

NDA 22-321

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November 14, 2008

Meeting of the Anesthetic and Life Support Drugs Advisory Committee

Open Session Briefing Package

Final: Advisory Committee Briefing Materials:

Available for Public Release

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1. ABBREVIATIONS

ADHD	Attention-Deficit Hyperactivity Disorder
AE	Adverse Events
AGENCY	US Food and Drug Administration
ALO-01	Research code name for: morphine sulfate extended-release with sequestered naltrexone hydrochloride capsules
ALPHARMA	Alpharma Pharmaceuticals LLC
ANOVA	Analysis of Variance
ARCI	Addiction Research Center Inventory
AUC	Area Under the Curve
BA	Bioavailability
BID	Twice Daily
BLQ	Below Limit of Quantitation
BPI	Brief Pain Inventory
CFB	Change from Baseline
CI	Confidence Interval
COWS	Clinical Opiate Withdrawal Scale
CRF	Case Report Form
CSR	Clinical Study Report
CV%	Geometric Mean
DAARP	Division of Anesthesia, Analgesia, and Rheumatology Products
DEQ	Drug Effect Questionnaire
DUI	Driving Under the Influence

ECG	Electrocardiogram
EtCO ₂	End-tidal Carbon Dioxide
FDA	US Food and Drug Administration
HCl	Hydrochloride
ITT	Intent to Treat
IV	Intravenous
KADIAN [®]	Morphine sulfate extended-release capsules
LOCF	Last Observation Carried Forward
Morphine	Morphine Sulfate
MOS	Medical Outcomes Study
MS	Morphine Sulfate
MSIR	Morphine Sulfate Immediate Release
Naltrexone	Naltrexone Hydrochloride
NT	Naltrexone Hydrochloride
NPRS	Numerical Rating Scale of Pain
OA	Osteoarthritis
OTC	Over-the-Counter
PD	Pharmacodynamic
PGIC	Patient Global Impression of Change
PK	Pharmacokinetic
QD	Once daily
REMS	Risk Evaluation and Mitigation Strategies
RMP	Risk Management Plan

RT	Room Temperature
SAE	Serious Adverse Event
SD	Standard Deviation
SDV	Subjective Drug Value
SEM	Scanning Electron Microscopy
SOWS	Subjective Opiate Withdrawal Scale
VAS	Visual Analog Scale
WOMAC	Western Ontario and McMaster Universities

2. DEFINITIONS OF TERMS

ABUSE	<p>Maladaptive pattern of opioid use leading to clinically significant impairment or distress, occurring in any of the following areas within a 12-month period: (American Psychiatric Association 2000)</p> <ul style="list-style-type: none">• Failure to fulfill major obligations at work, school, or home• Recurrent opioid use in hazardous situations, such as driving or operating heavy machinery while impaired• Opioid-related legal problems• Social and interpersonal problems caused, or exacerbated, by opioid use
ABUSE LIABILITY	<p>The potential of a drug to be abused, misused and diverted. It encompasses the risks associated with abuse, misuse or diversion of a drug demonstrated to lead to tolerance, dependence or addiction.</p>
ADDICTION	<p>Addiction is a psychological and behavioral disorder. Addiction is characterized by the presence of all three of the following traits: loss of control (i.e., compulsive use), continuation despite adverse consequences, and obsession or preoccupation with obtaining and using the substance.</p>
AUC_{0-t} :	<p>The area under the serum concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method.</p>
AUC_{inf} :	<p>The area under the serum concentration versus time curve from time 0 to infinity. AUC_{inf} was calculated as the sum of AUC_{0-t} plus the ratio of the last measurable serum concentration to the elimination rate constant.</p>
AUC/AUC_{inf} :	<p>The ratio of AUC_{0-t} to AUC_{inf}.</p>
C_{max} :	<p>Maximum measured serum concentration over the time span specified.</p>
DIVERSION	<p>Transfer of a controlled substance from a lawful to an unlawful channel of distribution or use. (Section 3303.(12) of the New York State Public Health Law)</p>

MISUSE	Use of legal medicines in a way not recommended by the doctor or the manufacturer; taking medicines in very large quantities that are dangerous to one's health. (www.nhsdirect.nhs.com (UK National Health Service))
OPIOID DEPENDENT	A state of adaptation to opioid that is manifested by drug class-specific signs and symptoms produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug and/or administration of an antagonist.
OPIOID EXPERIENCED	A subject who has received any opioid in the last 30 days.
OPIOID TOLERANT	A physiologic state resulting from regular use of an opioid in which an increased dosage is needed to produce a specific effect, or a reduced effect is observed with a constant dose over time
OPIOID NAÏVE	A subject who has not received any opioid in the last 30 days.
PHYSICAL DEPENDENCE	A state of adaptation that is manifested by a withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, or administration of an antagonist. (Schumaker et al. 2007)
PSEUDO-ADDICTION	Abuse-like behaviors that may develop in response to the undertreatment of pain. Examples include becoming focused on obtaining medications, "clock watching," and other "drug seeking" behaviors.
t_{max} :	Time of the maximum measured serum concentration. If the maximum value occurred at more than one time point, t_{max} was defined as the first time point with this value.
$t_{1/2}$:	Apparent first-order terminal elimination half-life calculated as $0.693/k_{el}$.
TOLERANCE	A physiologic state resulting from regular use of a drug in which an increased dosage is needed to produce a specific effect, or a reduced effect is observed with a constant dose over time. (Schumaker et al. 2007)
WITHDRAWAL	A syndrome that occurs due to the cessation or reduction of prolonged use of a drug. Acute opioid withdrawal is characterized by dysphoria, nausea or vomiting, muscle aches, lacrimation, rhinorrhea, pupillary dilation, diarrhea, yawning, fever, or insomnia.

2.1. Note to the Reader

- All trademarks used herein are the property of their respective owners.
- At the time of issuance of this document, the proposed established name of this investigational product (research name ALO-01), morphine sulfate extended-release with sequestered naltrexone hydrochloride capsules is under review by the Agency.
- Similarly, the proposed proprietary name of EMBEDA™, ALO-01 is under review by the Agency at the time of issuance of this document.
- In early clinical trials, ALO-01 was originally referred to as KADIAN® NT (morphine sulfate plus naltrexone hydrochloride extended-release) capsules. Therefore, KADIAN® NT and ALO-01 are synonymous and refer to the same product.
- Caution: at the time of the issuance of this document, ALO-01 NDA (22-321) is under active review by the Agency. Consequently, some information contained in this document will be subjected to revision. Specifically:
 - The Risk Evaluation and Mitigation Strategies plan described in Section 7.3 is a proposal that requires finalization with FDA upon their review.
 - The Full Prescribing Information and Labeling is under review.

3. EXECUTIVE SUMMARY

ALO-01 is a capsule comprised of individual pellets containing morphine sulfate with a sequestered naltrexone hydrochloride inner core. When ALO-01 is taken as prescribed, morphine is released in an extended-release profile to provide relief of moderate-to-severe chronic pain for up to 24 hours, when around-the-clock pain relief is needed. While the morphine is being released, naltrexone, an opioid antagonist, remains adequately sequestered in the core of each pellet. However, upon crushing, or complete chewing of the pellets, both the morphine and naltrexone would be available and if taken orally, absorbed as an immediate-release dosage form. Uniquely, the released and absorbed naltrexone would:

- mitigate the liking and euphoric effects of the morphine; and
- minimize the potential for abuse of morphine.

The clinical development plan for ALO-01 Capsules determined the appropriate pharmacological ratio of naltrexone that upon crushing or chewing the pellets would mitigate the euphoric effects of morphine. Studies were conducted to demonstrate the safety and efficacy of the formulation in a population that uses opioid analgesics for long-term therapy.

The clinical data demonstrate that:

- Under normal conditions of use, the disposition of plasma morphine following dosing with ALO-01 Capsules is bioequivalent to KADIAN[®] Capsules.
- The effective naltrexone-to-morphine ratio that provides clinically meaningful abatement of the abuse-related positive subjective effects of morphine (e.g., drug liking, feeling high, and euphoria) is 1:25.
 - Under normal conditions of ALO-01 Capsules use there is adequate sequestration of naltrexone
 - Under normal conditions of acute or chronic use, negligible clinically insignificant plasma naltrexone levels are detected.
- Efficacy and safety of ALO-01 Capsules are similar to KADIAN[®] Capsules in the treatment of chronic pain.
- Efficacy of ALO-01 Capsules is superior to placebo in the treatment of chronic pain.
- The presence of sequestered naltrexone in the core does not compromise the safety and efficacy of the extended-release morphine.

To further evaluate the potential for oral or IV drug abuse, crushed ALO-01 pellets were subjected to laboratory (in vitro) extraction studies using common solvents such as: water, aqueous acid/base solutions, and ethanol. The extractions were performed using typical abuser extraction techniques such as: soaking, stirring, and percolation. After crushing both, morphine and naltrexone were solubilized almost proportionally.

The intrinsic features of the formulation provide efficacy accompanied by specific safety advantages to a vulnerable subset of the target population (patients with chronic pain). ALO-01

Capsules are expected to provide a substantial improvement in the safety profile of the drug under conditions of attempted abuse, when compared to existing modified-release formulations of morphine, due to the presence of a sequestered antagonist. The commercialization of ALO-01 Capsules is expected to curtail the potential for prescription opioid abuse, a serious health condition that is accompanied by life-threatening co-morbidities. ALO-01 capsules may also provide a secondary benefit to the overall public health dilemma as formulations containing opioid antagonists are expected to be less attractive to the abusers' community, outside the chronic pain population.

4. INTRODUCTION

This briefing document summarizes the clinical trials conducted to support the regulatory filing of ALO-01 (morphine sulfate extended release with sequestered naltrexone hydrochloride) Capsules. The trials summarized herein describe the clinical pharmacokinetics, safety, and efficacy of both the morphine and naltrexone components of ALO-01.

Alpharma Pharmaceuticals LLC recognizes that while the potential abuse-deterrent formulation, ALO-01, could provide a partial remedy to the inherent risks of opioids, any remedy has the potential to introduce its own set of unintentional and intrinsic risks. Thus, the risks associated with the commercialization of ALO-01 Capsules, are identified and strategies and measures Alpharma Pharmaceuticals LLC intends to implement to mitigate these potential risks are summarized in this briefing document.

4.1. Background for Development

The non-medical use of prescription drugs is escalating and is a major public health issue. Although abuse and addiction are largely thought of in connection with other illicit drugs (such as marijuana and cocaine), prescription drug abuse is recognized as a serious societal problem and must be addressed by industry, health care professionals and legislators.

A number of formulations have been developed to deter the non-medical use of prescription opioid medications. The advantage of an extended-release (ER) formulation over an IR formulation is that the ER formulation provides a slow release of the analgesic for prolonged pain relief. KADIAN[®] (morphine sulfate extended-release) Capsules contain polymer-coated extended-release pellets of morphine sulfate targeted to deliver at least 12 hours of continuous pain relief. This slow-release technology serves to minimize plasma peaks and troughs, thereby providing a relatively flat pharmacokinetic profile upon multiple dosing. Thus an ER delivery mechanism is ideally suited for chronic dosing therapy.

The ability to crush extended-release (ER) formulations to cause a faster rate of release of opioid is one of the most important factors contributing to the subjective experience of euphoria and drug liking, thus increasing the risk of abuse. Persons deliberately and habitually abusing opioids are likely to tamper with controlled-release formulations in hopes of obtaining the entire 12 to 24-hour dose at one time (dose dumping) and use the concentrated dose to induce immediate euphoria. Previous research indicates that co-administration of an opiate agonist and antagonist resulted in a reduction of abuse compared to the administration of opiate agonist alone. (Fudala and Johnson 2006, Mendelson and Jones 2003, Strain et al. 2000, and Weinhold et al. 1992)

The pharmaceutical technology and delivery system design of ALO-01 represent an effort by Alpharma Pharmaceuticals LLC to offer an effective opioid analgesic for medical use in the treatment of moderate-to-severe chronic pain, with intrinsic formulation features that minimize the potential for abuse.

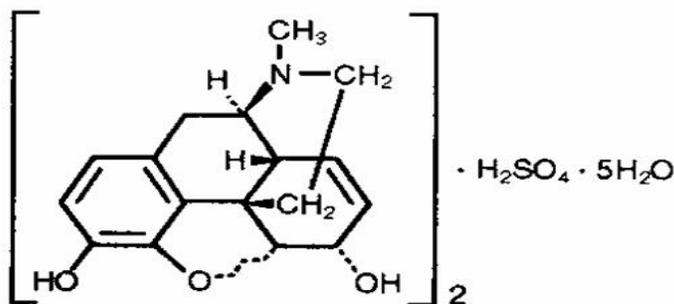
4.2. Description of ALO-01 Capsules Product Design

4.2.1. Active Ingredient: Morphine Sulfate

The chemical name of morphine sulfate is 7,8-didehydro-4,5 α -epoxy-17-methyl-morphinan-3,6 α -diol sulfate (2:1) (salt) pentahydrate. The empirical formula is $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$, and its molecular weight is 758.85. Its structural formula is shown in Figure 1.

Morphine is a pure opioid receptor agonist with good absorption and a plasma half-life of morphine of about 2-3 hours. In clinical settings, morphine exerts its principal pharmacological effect on the central nervous system and gastrointestinal tract. Morphine binds to a broad range of opioid receptors contributing to analgesia (μ , δ , and κ). μ receptors are also important for the adverse effects of sedation, euphoria, physical dependence and respiratory depression. κ receptor activation also contributes to analgesia but additionally has been associated with psychotomimetic effects of opioids.

Figure 1: Structural Formula of Morphine Sulfate



4.2.2. Sequestered Active Ingredient: Naltrexone Hydrochloride

The chemical name of naltrexone hydrochloride is (5 α)-17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride. The empirical formula is $C_{20}H_{23}NO_4 \cdot HCl$, and its molecular weight is 377.46. Its structural formula is shown in Figure 2.

Naltrexone is a pure opioid receptor antagonist with highest affinity for μ opioid receptor it is indicated for the management of alcohol dependence and opioid dependence. It is available in 50 mg tablets and is marketed generically as naltrexone hydrochloride and under the trade names ReVia[®] (50 mg tablets) and Depade[®] (50 and 100mg tablets). An extended release formulation for intramuscular injection is marketed under the name Vivitrol[®] (380 mg/ vial of microspheres).

Naltrexone has rapid and nearly complete (96%) absorption from the gastrointestinal tract with peak plasma levels within 1 hour of dosing. It is subject to first pass hepatic metabolism resulting in 5-40% oral bioavailability. It is 21% protein bound and undergoes renal elimination.

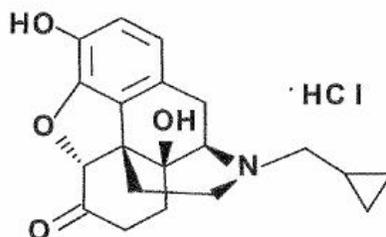
Naltrexone is metabolized mainly to 6 β -naltrexol by the liver enzyme dihydrodiol dehydrogenase. 6 β -naltrexol is active, retaining approximately 1/25 the receptor blocking activity of naltrexone (range 1/100 – 1/12). (Vereby 1980) Other minor metabolites include 2-hydroxy-3-methoxy-6 β -naltrexol and 2-hydroxy-3-methoxy-naltrexone. Further metabolism is through conjugation with glucuronide. Both naltrexone and 6 β -naltrexol are competitive antagonists at mu, and kappa opioid receptors and to a lesser extent at delta opioid receptors. The plasma half-life of naltrexone is about 4 hours and 13 hours for 6 β -naltrexol. Higher doses of opioid agonists can overcome naltrexone blockade due to the competitive opioid receptor binding.

Clinical studies indicate that 50 mg of orally administered naltrexone hydrochloride will block the pharmacologic effects of intravenously administered heroin for as long as 24 hours. Higher doses prolong the effective blockade. Naltrexone is not aversive therapy and does not cause a disulfiram-like reaction either from opiate or alcohol ingestion.

In both the treatment of alcoholism and opioid dependence the recommended dose is 50 mg per day for up to 12 weeks. This dose can be administered orally in various regimens from daily to 100 mg three times a week. Although the clinical studies have reported that naltrexone is generally safe even in the alcoholic population. However single doses, well above 50 mg, have been associated with increasing hepatocellular toxicity. Evidence of hepatotoxicity is derived primarily from one placebo-controlled study in obese subjects at a dose of 300 mg (approximately 6 times the recommended dose). After three to eight weeks of treatment, 5 of 26 subjects developed elevations of serum transaminases with peak ALT values ranging from 121 to 532 or 3 to 19 times the baseline values. These patients were asymptomatic and for those subjects with follow-up, values returned to the normal range weeks after drug discontinuation.

- Peak plasma concentration of naltrexone following a single 50 mg dose is 8.6 ng/mL. (Revia Package Insert (Dupont-Canada) Rev. 2/97)
- After five days of maintenance therapy, 25 mg of oral naltrexone produced a plasma level of approximately 3 ng/mL and 100 mg produced a level of approximately 15 ng/mL, 5.5 hours post dose. (Schuh et al. 1999)

Figure 2: Structural Formula of Naltrexone Hydrochloride

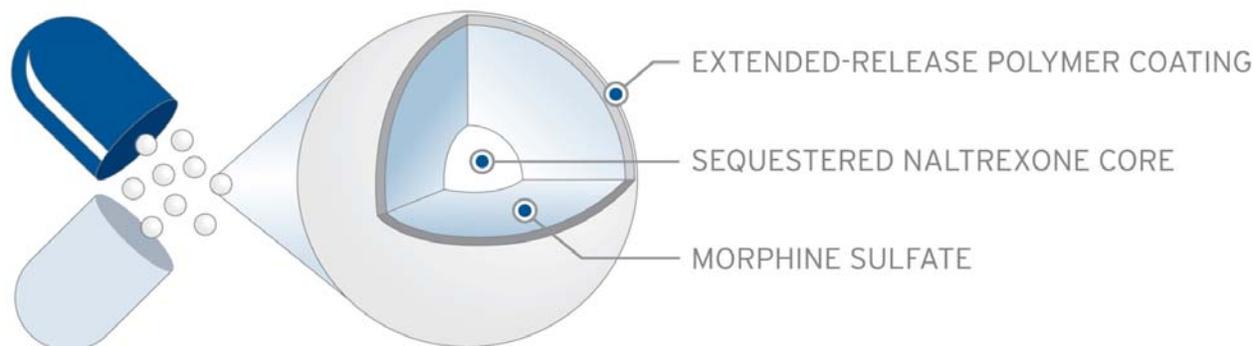


4.2.3. Formulation

ALO-01 capsules and pellets are formulated using inactive ingredients commonly found in solid oral dosage formulations. All ingredients are listed in the Inactive Ingredients Guide and in the United States Pharmacopeia.

Figure 3: ALO-01 Delivery System Design

PHARMACOLOGIC CORE TECHNOLOGY



4.2.4. In-vitro Extractability Studies

In vitro studies have been performed by an independent laboratory to demonstrate that, when ALO-01 pellets are crushed and then dissolved in solvents [water, acid, base and alcohol], the sequestered naltrexone is completely released as intended by the formulation technology. Crushed pellets were dissolved in each solvent. Samples were taken after 10 minutes from both stirred and soaked conditions and analyzed for both morphine and naltrexone.

Table 1 presents the data from the in vitro studies and Figure 4 summarizes the data from the

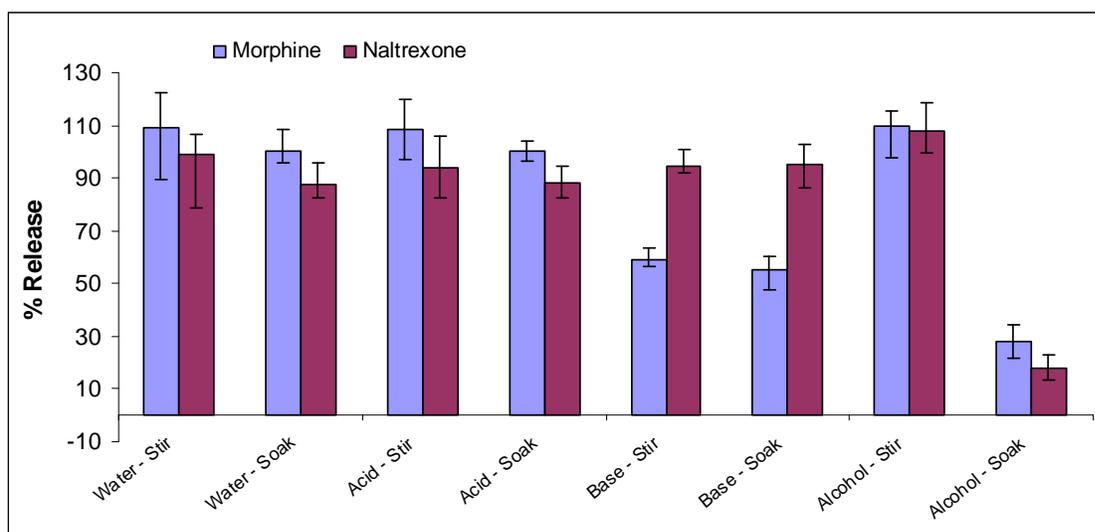
in vitro studies with a side-by-side comparison. The error bars in Figure 4 represent the range of data from triplicate preparations.

Table 1: In-vitro Extractability Studies on Crushed ALO-01 Pellets.

Condition	1	2	3	Average	% RSD
	% Release				
Water - Stir - MS	122.1	104.0	101.0	109.1	10.5
Water - Stir - NT	118.1	78.8	99.4	98.8	19.9
Water - Soak - MS	100.8	108.5	92.0	100.4	8.2
Water - Soak - NT	91.9	88.1	82.5	87.5	5.4
Acid - Stir - MS	96.0	109.0	119.9	108.3	11.1
Acid - Stir - NT	82.5	93.8	105.0	93.8	12.0
Acid - Soak - MS	102.2	104.3	94.1	100.2	5.4
Acid - Soak - NT	90.0	91.9	82.5	88.1	5.6
Base - Stir - MS	53.0	63.6	61.4	59.3	9.4
Base - Stir - NT	97.5	91.9	93.8	94.4	3.0
Base - Soak - MS	60.5	47.7	58.4	55.5	12.3
Base - Soak - NT	95.6	103.1	86.3	95.0	8.9
Alcohol - Stir - MS	99.0	114.0	115.7	109.6	8.4
Alcohol - Stir - NT	105.0	99.4	120.0	108.1	9.9
Alcohol - Soak - MS	23.0	26.0	34.3	27.8	21.0
Alcohol - Soak - MS	16.9	13.1	24.4	18.1	31.6

MS: Morphine Sulfate, NT: Naltrexone

Figure 4: In-vitro Extractability Studies on Crushed ALO-01 Pellets.



Although the morphine and naltrexone data exceeded 100% in some instances due to the analytical technique, the morphine and naltrexone were proportionally released from ALO-01 pellets in all instances with the exception of the base solution. The base solution utilized a carbonate/bicarbonate, and even though the naltrexone was fully released, only 55% - 60% of the morphine was available in the base solution.

Based on these studies, if an individual crushes or chews ALO-01 pellets, both morphine and naltrexone will be liberated and the naltrexone will minimize the euphoric effect of the morphine, defeating the intended outcome of abuse (euphoria).

4.3. Proposed Indications and Dosing Recommendations

As proposed in the Full Prescribing Information submitted in NDA 22-321, to be finalized upon the Agency's review, ALO-01 Capsules are indicated for:

- the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time

The sequestered naltrexone is intended to have no clinical effect when ALO-01 Capsules are taken as directed, but when the formulation is tampered with by crushing or chewing, the naltrexone is rapidly released and absorbed, mitigating the effects of the morphine.

ALO-01 Capsules are not indicated for acute/postoperative pain or if the pain is mild or not expected to persist for an extended period of time. ALO-01 Capsules are only indicated for postoperative use if the patient is already receiving chronic opioid therapy prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate.

4.3.1. Proposed Dosage and Administration

ALO-01 Capsules may be administered once or twice daily.

Alternatively, the contents of ALO-01 Capsules may be sprinkled on apple sauce. The pellets in the capsules are not to be crushed, dissolved, or chewed before swallowing.

Table 2: Proposed Dosage and Strengths

CAPSULES	ALO-01 20	ALO-01 30	ALO-01 50	ALO-01 60	ALO-01 80	ALO-01 100
Morphine sulfate	20 mg	30 mg	50 mg	60 mg	80 mg	100 mg
Sequestered naltrexone hydrochloride	0.8 mg	1.2 mg	2.0 mg	2.4 mg	3.2 mg	4.0 mg

Low initial doses of ALO-01 Capsules should be used in patients who are opioid-naïve and those receiving concurrent treatment with muscle relaxants, sedatives, or other CNS-active medications.

4.3.2. Proposed: Initiating Therapy with ALO-01 Capsules

Physicians should individualize treatment using a progressive plan of pain management. Health care professionals should follow appropriate pain management principles of 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. In the selection of the initial dose of ALO-01 Capsules, attention should be given to:

1. the total daily dose, potency and kind of opioid the patient has been taking previously;
2. the reliability of the relative potency estimate used to calculate the equivalent dose of morphine needed (Note: potency estimates may vary with the route of administration);
3. the patient's degree of opioid experience and opioid tolerance;
4. the general condition and medical status of the patient;
5. concurrent medication;
6. and the type and severity of the patient's pain.

The following dosing recommendations can be considered approaches to what is actually a series of clinical decisions over time in the management of an individual patient's pain.

Use of ALO-01 Capsules as the First Opioid Analgesic

The lowest dose of ALO-01 Capsules may be used as the initial opioid analgesic in patients with chronic pain. During the clinical development program, 657 opioid-naïve patients received a starting dose of 20 mg capsules at bedtime for three days without serious adverse events. Patients were subsequently titrated to a once-a-day or twice-a-day dosage which adequately managed their pain.

Individualization of Dosage

Most patients will rapidly develop some degree of tolerance, requiring dosage adjustment until they have achieved their individual balance between effective analgesia and opioid side effects such as confusion, sedation and constipation.

- ALO-01 Capsules should be titrated no more frequently than every-other-day to allow patients to stabilize before escalating the dose.
- If breakthrough pain occurs, the dose may be supplemented with a small dose (less than 20% of the total daily dose) of a short-acting analgesic.
- Patients who exhibit signs of excessive opioid side effects such as sedation should have their dose reduced.
- Patients who experience inadequate analgesia on once-daily dosing should be switched to twice-a-day with an appropriate dosage adjustment.
- ALO-01 Capsules should not be dosed more frequently than every 12 hours.

No guidance can be given as to the recommended maximal dose, especially in patients with chronic pain of malignancy. In such cases the total dose of ALO-01 Capsules should be

advanced until the desired therapeutic endpoint is reached or clinically significant opioid side effects occur. Appropriate titration would include trying to minimize the side effects to patients.

Alternative Methods of Administration

Patients who have difficulty swallowing whole capsules or tablets may benefit from an alternative method of administration. In a study conducted with healthy volunteers, ALO-01 pellets sprinkled over apple sauce were bioequivalent to ALO-01 Capsules swallowed whole with water under fasting conditions. Other foods have not been tested.

- Sprinkle the pellets onto a small amount of apple sauce.
- The patient must be cautioned not to chew the pellets.
- Use immediately.
- Rinse mouth to ensure all pellets have been swallowed.
- Patients should consume entire portion and should not divide apple sauce into separate doses.

4.3.3. Proposed: Cessation of Therapy

In general, ALO-01 Capsules should not be abruptly discontinued. However, ALO-01 Capsules, like other opioids, can be safely discontinued without the development of withdrawal symptoms by slowly tapering the daily dose.

4.4. Regulatory Information

4.4.1. Regulatory Background

The FDA has recognized the special need to develop fixed-combination prescription drug products in which a component is added “to minimize the potential for abuse of the principal active component” (21CFR§ 300.50).

The Agency has previously approved two such products which combine an opioid with a pure antagonist, naloxone: Talwin NX and Suboxone. Approval for both drugs was based on the potential that these formulations would decrease prescription opioid abuse. However, limited data were available to support the notion that the addition of formulation barriers would reduce potential for abuse of these prescription opioid products.

Talwin NX, a combination of pentazocine and naloxone, was introduced with the aim of decreasing abuse of Talwin, the parent product (Arfken and Cicero 2003). Post-marketing data suggested that abuse of pentazocine decreased significantly with the introduction of Talwin-NX, although the reasons for this reduction are still debated. Some researchers believe that this decrease is correlated with simultaneous availability of inexpensive heroin on the street rather than the addition of naloxone to the formulation.

Buprenorphine has been approved in two forms: Subutex, which is comprised of buprenorphine alone and Suboxone, which contains buprenorphine plus naloxone, and is aimed at preventing or reducing parenteral abuse of the parent compound (Comer and Collins 2002, Fudala and Johnson

2006). Follow-up research indicates that abusers are not as interested in products that have such tamper-deterrent features. (Butler et al. 2006)

4.4.2. Regulatory Agreements During the Development of ALO-01 Capsules

4.4.2.1. Clinical Development Program

Following a Pre-IND Meeting with FDA on March 16, 2005, Alpharma followed with the Division of Anesthesia, Analgesia, and Rheumatology Products' (DAARP) recommendations on the clinical program:

- One adequate and well-controlled trial could be sufficient to establish the efficacy of this ALO-01 assuming there is no effect from the naltrexone component of the product.
- A minimum exposure population of 800 unique subject exposures with 100 subjects exposed daily for at least 6 months and 50 subjects exposed daily for at least 1 year is sufficient unless unexpected safety signals arise.

On December 14, 2006, a final agreement was reached with DAARP on the protocol of the pivotal efficacy study ALO-KNT-301, under Special Protocol Assessment.

The double-blind, parallel-group design used in this study is generally acknowledged as standard for unbiased estimates of treatment group differences. Placebo was chosen as the control in order to assess the analgesic efficacy of ALO-01. A washout period of 1 to 7 days for all prohibited medications and pain medications was included to minimize the effect of any of these agents on the study endpoints and to establish a minimum pain score of ≥ 5 on the BPI (Brief Pain Inventory). The enriched enrollment randomized withdrawal design and the mixed imputation strategy were agreed to, under the Special Protocol Assessment.

4.4.2.2. Label Claim

Additionally, during drug development, DAARP confirmed to Alpharma Pharmaceuticals LLC that a claim for reduced abuse potential in a product label is difficult to establish. The Division suggested that the development of a post-marketing program could be worthwhile to support such label claim. Alpharma Pharmaceuticals is committed to perform post-marketing studies in partnership with the Agency. We are considering several alternatives to design epidemiologic studies that could collect, trend and analyze post-marketing data to demonstrate that ALO-01 represents a meaningful incremental reduction in abuse potential.

4.4.2.3. Pediatric Indication

ALO-01 was not studied in a pediatric population of the proposed indication. The development of a new formulation is required to address the need of children less than or equal to 12 years of age. Alpharma Pharmaceuticals has submitted an outline of the pediatric clinical development plan for children between 12 and 18 years of age, for the proposed indication.

4.4.2.4. Risk Evaluation and Mitigation Strategies (REMS)

Alpharma Pharmaceuticals LLC submitted a comprehensive Risk Management Plan in the NDA. In accordance with the FDA Amendment Act 2007, DAARP requested upon the Agency review of the filing, that Alpharma submits a REMS plan to ensure that the benefits will outweigh the risks.

4.5. Clinical Development Program

The clinical development program includes twelve clinical studies:

- Three studies contributed information concerning the analgesia efficacy and safety of ALO-01 Capsules (see Figure 5, yellow boxes).
 - Study ALO-KNT-202 was designed to assess the pharmacokinetics of morphine and naltrexone following multiple doses of ALO-01. A secondary objective was to assess the efficacy of ALO-01 compared to KADIAN[®].
 - Study ALO-KNT-301 was an adequate and well-controlled study conducted to confirm the efficacy of ALO-01 observed in Study ALO-KNT-202.
 - Study ALO-KNT-302 was an open-label, uncontrolled, 12-month study to obtain 100 subjects exposed daily for at least 6 months and 50 subjects exposed daily for at least 1 year.
- Three pharmacodynamic studies were conducted to establish and confirm the proper naltrexone-to-morphine ratio needed to provide clinically meaningful mitigation of positive subjective effects of morphine (e.g., drug liking, feeling high, and euphoria) associated with opioid abuse. These three studies contributed information concerning the reduction of abuse potential (see Figure 5, blue and green lined boxes).
 - Study ALO-KNT-201 (Study 201) established the ratio of naltrexone to morphine that was sufficient to provide mitigation of positive subjective effects of morphine.
 - Study ALO-01-07-205 (Study 205) confirmed that the ratio from Study ALO-KNT-201 was effective when the planned commercial product was crushed and orally consumed.
 - In Study ALO-01-07-106 (Study 106), equivalent doses of morphine and naltrexone in a 30 mg ALO-01 capsule (30 mg morphine, 1.2 mg naltrexone) were administered intravenously. This study was conducted to provide clinical evidence as to whether the planned ratio of naltrexone to morphine would be effective in abating the positive subjective effects of morphine if the product was injected.
- Four Phase 1 studies 20-903-AU, ALO-01-07-101 (Study 101), ALO-01-07-102 (Study 102), and ALO-01-07-104 (Study 104) were pharmacokinetic and safety studies conducted in healthy adult volunteers.

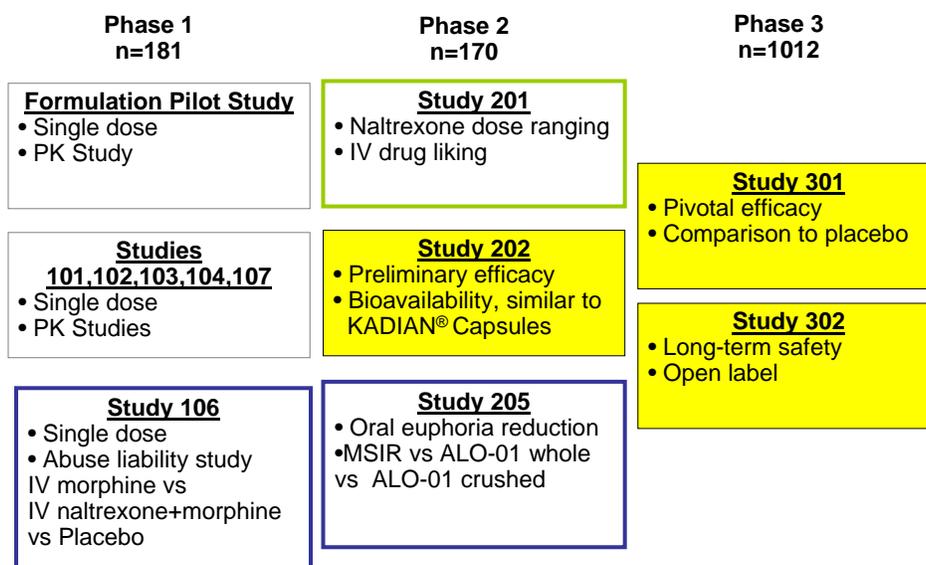
- Study 101 established the bioequivalence of single oral doses of ALO-01 Capsules to KADIAN® Capsules.
- For the purpose of the present document, results and design of Study 20-903-AU, Study 102, Study 104 will not be presented. However, they were submitted in the NDA 22-321.
- One Phase 1 bioavailability study ALO-01-07-103 (Study 103) was conducted in subjects with a history of moderate alcohol consumption. For the purpose of the present document, results and design of Study 103 will not be presented. However, they were submitted in the NDA 22-321.
- One Phase 1 study ALO-01-07-107 (Study 107) evaluated withdrawal symptoms in subjects currently using opiates for chronic moderate-to-severe nonmalignant pain. For the purpose of the present document, results and design of Study 107 will not be presented. However, they were submitted in the NDA 22-321.

Figure 5 summarizes the components of the clinical program. It indicates the number of subjects who were treated, receiving at least one dose of ALO-01, for each phase of development. As mentioned in section 4.4.2.1, the following commitments were fulfilled:

- One adequate and well-controlled trial to demonstrate efficacy of ALO-01 Capsules
- A minimum exposure population of 800 unique patient exposures with 100 patients exposed daily for at least 6 months and 50 patients exposed daily for at least 1 year.

The details of each study design, objectives and outcomes are provided under section 6.

Figure 5: Components of ALO-01 Capsules Clinical Program



5. PUBLIC HEALTH AND MEDICAL NEEDS

Referring to pain treatment, Manchikanti et al. states: “In the United States, physicians are faced with two opposing dilemmas in the treatment of pain – the potential for drug abuse and diversion, and the possible under-treatment of pain”. (Manchikanti et al. 2005)

ALO-01 Capsules were developed in an effort to address two public health issues: adequate management of pain and the need to minimize the potential for morphine abuse.

5.1. Burden of Disease –Chronic Pain

According to the American Chronic Pain Association, chronic pain is pain that continues a month or more beyond the usual recovery period for an injury or illness, or that goes on for months or years due to a chronic condition. The initial cause may have been an accident or serious infection. There may be an identifiable, ongoing cause of pain such as arthritis or cancer but the patient may also suffer from chronic pain in the absence of any past injury or evidence of physical injury.

The main goal of pain treatment is to provide sufficient relief of pain to allow the patient to return to a normal or near-normal quality of life.

There are many options to treat chronic pain, ranging from medications, physical therapy, complementary therapies, psychological therapies, injections and surgery. Opioids are an effective option for treating pain for many individuals. When used appropriately, opioid medications can significantly improve function and quality of life for people living with chronic pain.

Recently, the U.S. House of Representatives took a critical step in helping to improve pain care by passing the “National Pain Care Policy Act of 2008” (HR 2994). This legislation recognizes that the under-treatment of pain is a public health issue.

“The present legislation authorizes an Institute of Medicine (IOM) conference on pain care, creates an interagency coordinating committee charged with identifying critical gaps in pain research, expands collaborative pain research across federal agencies and the private sector, and provides for a grant program to improve health professionals' understanding and ability to assess and treat pain. It also requires the Secretary of Health and Human Services (HHS) to develop and implement a national outreach and awareness campaign to educate patients and caregivers on the significance of pain as a public health problem.”

Incidence of this public health issue:

- More than one-quarter of Americans (26%) age 20 years and over - or, an estimated 76.5 million Americans - report that they have had a problem with pain of any sort that persisted for more than 24 hours in duration.
- Adults age 45-64 years were the most likely to report pain lasting more than 24 hours (30%). Twenty-five percent (25%) of young adults age 20-44 reported pain, and adults age 65 and over were the least likely to report pain (21%).

More than half of all hospitalized patients experience pain in the last days of their lives and although therapies are present to alleviate most pain for those dying of cancer, research shows that 50-75% of patients die in moderate to severe pain.

An estimated 20% of American adults (42 million people) report that pain or physical discomfort disrupts their sleep a few nights a week or more. (<http://www.theacpa.org/>)

Unfortunately, most healthcare professionals have little or no training in pain management and often are unable to effectively relieve their patients' pain. Additionally, many people living with pain and even some healthcare providers falsely believe opioids are universally addictive.

5.2. Burden of Disease-Prescription Opioid Abuse

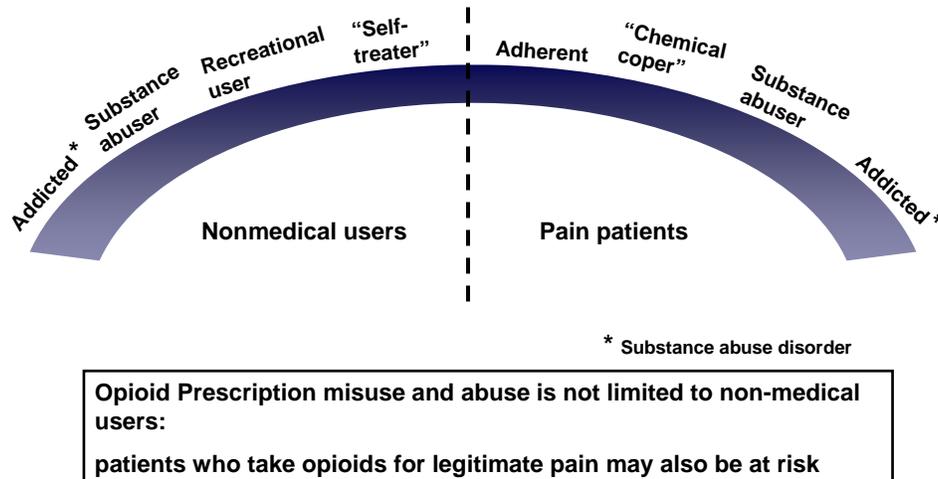
The terms "abuse" and "addiction" have been widely used over the years; however, there is no universally accepted definition for either term. In the case of substance abuse, a frequently cited definition is from the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) issued by the American Psychiatric Association. According to the DSM-IV, substance abuse is "a maladaptive pattern of substance use leading to clinically significant impairment or distress," as manifested by one or more of the following occurring within a 12-month period: (1) recurrent substance use related problems at work, home, and school; (2) problems with family or friends; (3) physical danger; and/or (4) trouble with the law.

Drug addiction is generally described as "a compulsive need for, and use of, a habit-forming substance (i.e., heroin, nicotine, or alcohol). Prolonged drug use alters brain function and behavior, which can partly explain the drug-seeking behavior observed in addicts.

Another term used in connection with addiction, but describing a condition less known to the general public, is "pseudo-addiction." The term was first used in 1989 to describe the iatrogenic syndrome that develops as a direct consequence of inadequate pain management and appears to mimic behaviors that are commonly associated with addiction (Weissman et al, 1991). The appropriate treatment for pseudo-addiction is adjustment of the analgesic regimen/dosage so that analgesia is provided at an appropriate dose and dosing interval with improved function.

The reasons for using diverted drugs were not addressed in the medical literature until recently. Motives were studied by McCabe et al. in 2007. The three most common motives associated with the non-medical use of prescription opioids were to relieve pain, obtain a "high", and experiment. (Arria et al. 2008)

Figure 6: Opioid Users are a Heterogeneous Population



(Data on file at Alpharma.)

Prescription drug abuse causes substantial harm not only directly to the user but indirectly to society as well. Law enforcement data show that the impact of prescription drug abuse on criminal activity is increasing and in fact, involvement of pharmaceuticals may account for at least 70% of the enforcement cases. Prescription pharmaceuticals contributed to violence and property crime in more than 4% of state and local law enforcement agencies in the Northeast (National Drug Threat Assessment 2005).

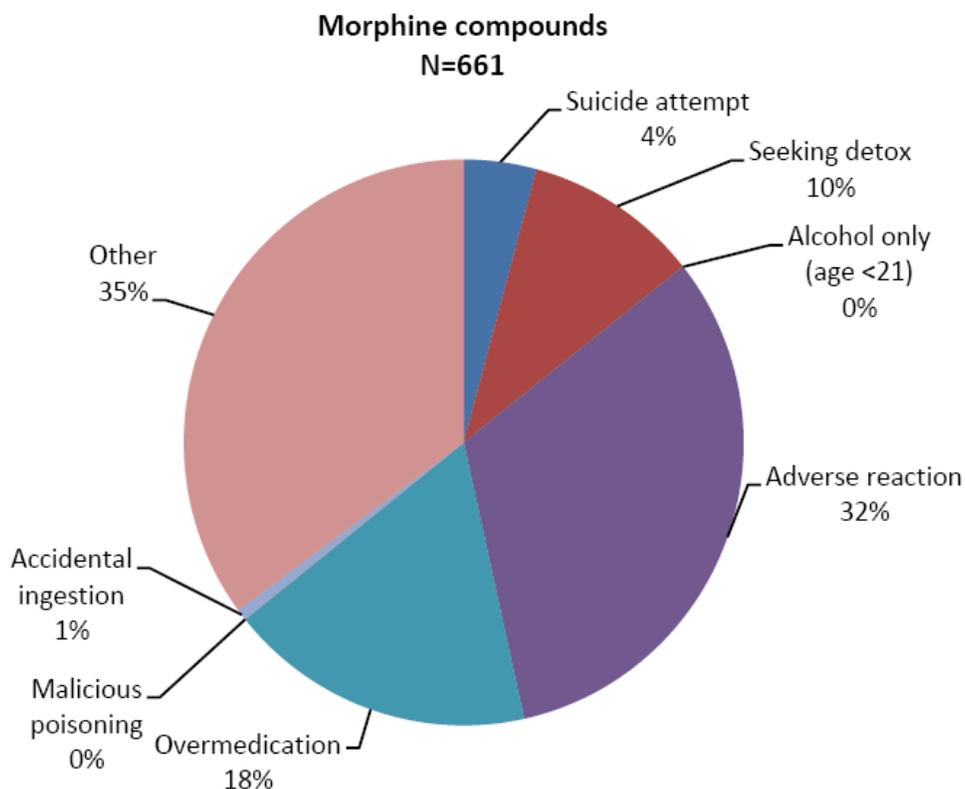
Some experts assert that prescription drug abuse has reached epidemic proportions, adversely affecting millions of Americans.

The increasing number of adolescents and teenagers misusing prescription medications has become a growing concern for society. In fact, roughly a quarter of 12th graders report having abused a prescription drug (Prescription for Danger 2008). Research also indicates that adolescents who abuse prescription drugs are twice as likely to engage in delinquent behavior and three times as likely to experience an episode of major depression compared to teens who did not abuse prescription drugs over the past year. Other studies have also linked the abuse of prescription drugs by adolescents and young adults in the US with cigarette smoking, heavy drinking, and use of marijuana and other illicit drug use (Volkow 2008).

Further illustrating the alarming increase in prescription drug abuse over the past decade and the associated escalating medical costs, the number of adolescents entering treatment for prescription analgesia addiction has increased by more than 300% in the last ten years (ONDCP, 2008).

In their 2nd Quarter 2008 report, NAVIPPRO™ presented more recent statistics on drug-related visits to hospital emergency departments (ED). DAWN cases reported in 2008 represented 81,283 reports of drug-related events. The majority of reports were adverse reactions (38%) and "other reasons" (37%). For morphine compounds in particular, there were 661 reports filed in the DAWN database with 38% of ED visits attributed to "other reasons" 32% for adverse reactions, and 18% for overmedication as shown in Figure 7. (NAVIPPRO™ August 2008 Safety Report for KADIAN®)

Figure 7: Non-Medical Use of Morphine Related Cases Reported in 2008



Of the 661 morphine-related ED visits reported, 50% were related to non-medical drug use (cases categorized as over-medication, malicious poisoning, and other). The majority of these cases involved individuals between the ages of 45 to 54 years, using morphine compounds.

The abuse of prescription drugs poses a variety of risks ranging from the risk for addiction and overdose to innumerable health risks.

Prescription opioid misuse or abuse presents significant risks to patients such as:

- Mental and physical impact of the drug itself;

- Worsened medical conditions (ie, diabetes, hypertension);
- Worsened brain disorders (ie, depression, sleep, anxiety);
- Unintentional injury or violence;
- Dependence (which may require multiple treatment services);
- Pregnancy complications (ie, low birth weight, developmental disorders, premature delivery);
- Child abuse and neglect;
- Legal issues (ie, DUI, domestic violence, incarceration);
- Economic hardship (ie, unemployment, bankruptcy);
- Public health issues (ie, infectious diseases: HIV, Hepatitis C);
- Suicidality; and
- Homelessness.

(SAMHSA 2008)

5.3. Potential Solutions or Alternatives

In 2007, the FDA was petitioned by citizens to require pharmaceutical companies manufacturing controlled substances:

- To demonstrate and certify in their application materials for FDA approval of new drugs that they have made every effort to formulate the drug in such a way that avoids or at least minimizes the drug's potential for both intentional and unintentional abuse without compromising its therapeutic effectiveness; and,
- To include proactive risk management plans in all new applications for controlled drugs, demonstrating strong evidence of a prescription drug's safety, as well as concrete steps that will be taken to prevent the abuse of the drug while maintaining its maximum therapeutic effectiveness.

A general solution was proposed by Griffiths et al. in 2003. They describe initial abuse liability testing of a new compound; in volunteers with histories of drug abuse using a classic acute dose-effect comparison. This trial design is most appropriate for predicting the likelihood of use by abusers, and for predicting the extent of drug diversion and illicit street sales of the novel compound.

An additional solution is the use of combinations.

In 2006, Robinson reported on a sublingual formulation combining buprenorphine with naloxone (Suboxone) that is effective in both maintenance therapy and detoxification of individuals addicted to opioids. The introduction of a sublingual formulation combining naloxone with buprenorphine further reduces the risk of diversion to illicit intravenous use (Robinson 2006).

A similar advance in formulation design is the extended-release treatment for ADHD (Vyvance), that tends to reduce euphoric qualities of immediate-release ADHD drugs. (Griffiths et al. 2003, Faraone and Upadhyaya 2007)

A variety of techniques and approaches may be employed to deter the nonmedical user from tampering with or abusing prescription pain relievers. These include regulatory approaches (i.e., radio-label prescription packaging tracking, prescription monitoring through medical licensure) as well as approaches that begin with the product design such as:

- Physical barriers (i.e., hard to crush capsule, inextricable active ingredient) and
- Pharmacological barriers, such as
 - Pro-drug (i.e., main ingredient inactive until ingestion/metabolism) and
 - Antagonist (pharmacological competitor for receptor-binding or sub-therapeutic levels of a deterrent).

In summary, decreasing abuse potential with innovative opioid formulations such as ALO-01 Capsules may be a suitable alternative to help curb opioid prescription illicit use.

6. SUMMARY OF CLINICAL DATA

Note to the Reader:

In early clinical trials, ALO-01 was originally referred to as KADIAN[®] NT (morphine sulfate plus naltrexone hydrochloride extended release) capsules. Therefore, KADIAN[®] NT and ALO-01 are synonymous and refer to the same product. Although all possible efforts have been made to ensure that the term ALO-01 is used consistently, in some instances the electronic format of graphs and tables extracted from the original clinical study reports, was not conducive of replacing the term KADIAN[®] NT or EMBEDA[™] by ALO-01.

6.1. SUMMARY OF CLINICAL PHARMACOKINETIC DATA

Seven clinical pharmacology studies were performed to characterize the pharmacokinetics, pharmacodynamics, and pharmacokinetic/pharmacodynamic relationships of ALO-01.

- Three single-dose, double-blind, placebo-controlled, pharmacodynamic and pharmacokinetic studies were performed in nondependent, recreational opioid drug users (Studies ALO-KNT-201, ALO-01-07-205, and ALO-01-07-106; hereinafter referred to as Studies 201, 205, and 106).
- Study ALO-KNT-101 (hereinafter referred to as Study 101) established the bioequivalence of single oral doses of ALO-01 and KADIAN[®] Capsules.
- Three other studies conducted in healthy volunteers, Study ALO-01-07-102, ALO-01-07-103 and ALO-01-104, will not be presented for the purpose of this document.

It should be noted that the pharmacokinetic/pharmacodynamic (PK/PD) results of Study 205 and Study 106 presented in this section also constituted the component of the clinical development

plan to demonstrate the abuse reduction potential efficacy of ALO-01. Thus, the results of Study 205 and Study 106 could also appropriately have been included in Section 6.3. These results may be mentioned but the data will not be repeated in Section 6.3. Rather the reader will be referred back to this section.

All of Phase 1 and Phase 2 PK and PK/PD studies utilized a randomized, single-dose, crossover study design to evaluate different dosing conditions within the same subject/patient. The Phase 3 safety study was long-term and open-label.

Table 3 presents a brief description of PK studies in healthy subjects, opioid-experienced patients, and patient populations and Table 4 highlights the PK assessments for each of these studies.

Table 3: Studies with Pharmacokinetic Data

Study	Population	N#	Treatment/Dose
ALO-01-07-101	Healthy subjects under fasted conditions	34	Oral <ul style="list-style-type: none"> • KADIAN[®] Capsule 100mg, single dose • ALO-01 Capsule 100mg, single dose
ALO-KNT-201	Opioid-experienced non-dependent subjects	27	Oral <ul style="list-style-type: none"> • MSIR 120 mg • MSIR 120 mg + naltrexone HCl* • placebo
ALO-01-07-106	Opioid-experienced non-dependent subjects	28	Intravenous (iv) <ul style="list-style-type: none"> • morphine sulfate 30 mg • morphine sulfate 30 mg + naltrexone HCl 1.2 mg • placebo
ALO-01-07-205	Opioid-experienced non-dependent subjects	32	Oral <ul style="list-style-type: none"> • ALO-01 Capsule whole (2x 60 mg) • ALO-01 Capsule crushed (2x 60 mg) • MSIR 120-mg • placebo
ALO-KNT-202	Patients with moderate to severe chronic pain due to knee or hip osteoarthritis	67	Oral <ul style="list-style-type: none"> • ALO-01 Capsule • KADIAN[®] Capsule
ALO-KNT-302	Patients with moderate to severe nonmalignant chronic pain	94	Oral <ul style="list-style-type: none"> • ALO-01 Capsule

MSIR=morphine sulfate immediate-release

* Varying doses of naltrexone HCl treatments were utilized.

PK Population

Table 4: PK Assessments

Study	PK Assessment		
	Morphine Bioavailability	Naltrexone Bioavailability	Calculated PK parameters*
ALO-01-07-101	X		X
ALO-KNT-201 [†]	X	X	X
ALO-01-07-106 [†]	X	X	X
ALO-01-07-205 [†]	X	X	X
ALO-KNT-202 [§]	X	X	
ALO-KNT-302 [#]	X	X	

* Including, but not limited to, peak concentration (C_{max}), area under the concentration-time curve (AUC), rate of exposure (t_{max})

[†] Studies in opioid-experienced subjects

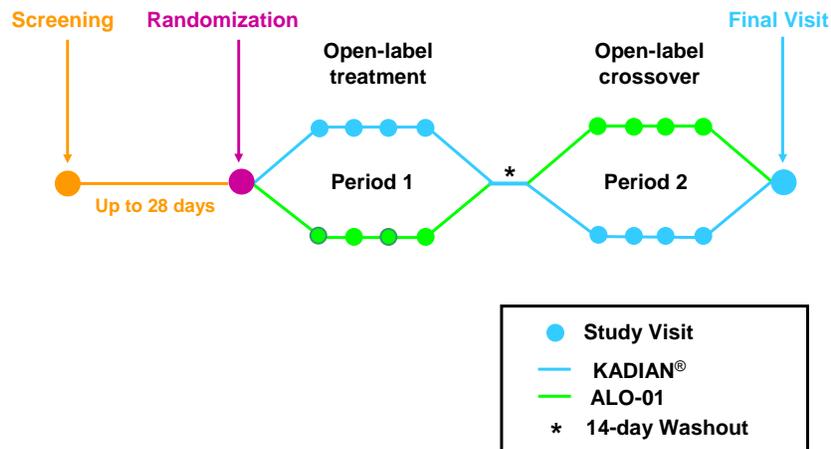
[§] Phase 2 randomized, crossover study in patients with moderate to severe pain due to knee or hip osteoarthritis

[#] Phase 3 long-term, open-label study with sparse blood sampling in a PK subset of patients with moderate to severe nonmalignant pain

6.1.1. Study ALO-01-07-101 (Study 101)

ALO-01-07-101 was an open-label, randomized, single-dose, 2 way crossover comparative bioavailability study between single 100 mg oral doses of ALO-01 (morphine sulfate extended-release with sequestered naltrexone hydrochloride) capsules and KADIAN[®] (morphine sulfate extended-release) capsules administered to healthy subjects under fasted conditions. The study provides evidence of morphine bioequivalence of ALO-01 to KADIAN[®].

Figure 8: Diagram of Study ALO-01-07-101 Design



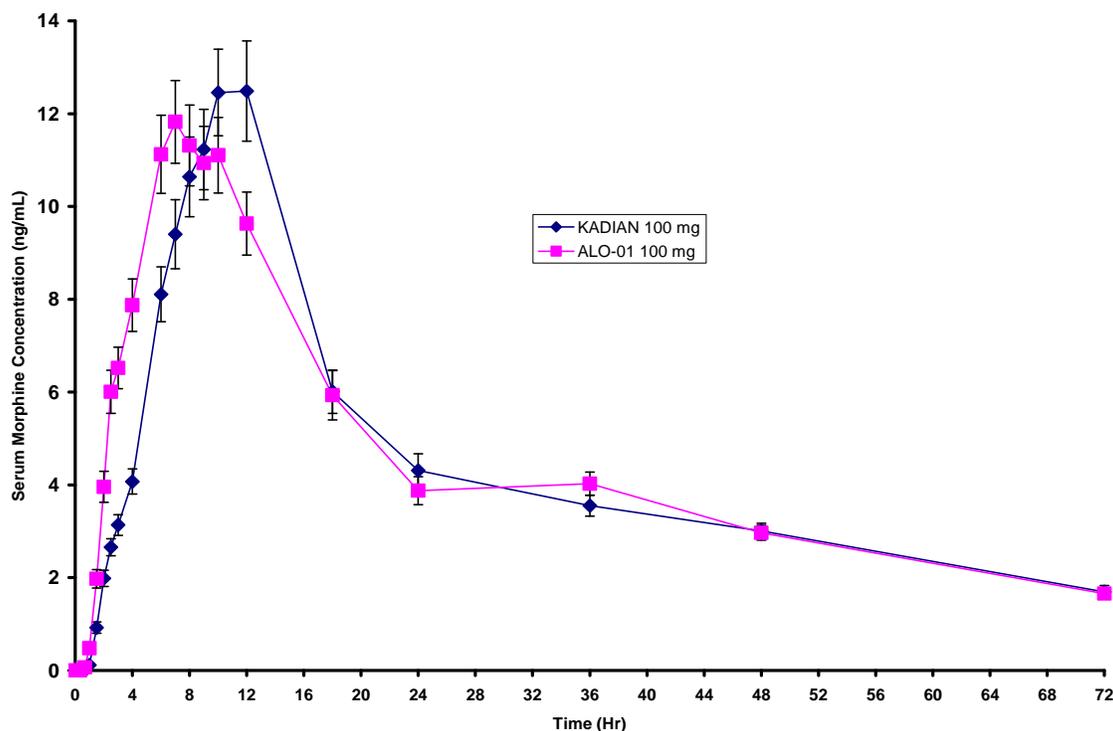
The primary endpoints were the 90% confidence interval of the ratios of least-squares means for the morphine pharmacokinetic parameters AUC_{0-t} , AUC_{inf} and C_{max} of single 100 mg doses of ALO-01 and KADIAN®.

Morphine doses were selected to achieve serum levels of morphine and its metabolites sufficient to characterize the pharmacokinetic profiles, and on the basis of projected doses in a clinical setting.

Results

A mean concentration-time plot (linear scale) is presented in Figure 9.

Figure 9: Mean Serum Morphine Concentrations (Linear Plot)



Descriptive statistics for all PK parameters for morphine in serum are presented in the following table.

Table 5: Summary of Pharmacokinetic Results for Morphine (N=34)

Parameter*	ALO-01 (A)	KADIAN® (B)
AUC _{0-t} (ng·h/mL)	310.90 (25.3%)	304.52 (25.8%)
AUC _{inf} (ng·h/mL)	384.01 (24.1%)	390.98 (29.9%)
C _{max} (ng/mL)	12.31 (36.8%)	13.19 (45.7%)
t _{max} (h)	7.50 (2.50-18.00)	10.00 (6.00-24.00)

*Geometric mean (CV%) is presented for AUC and C_{max}, median (range) for t_{max}.

ANOVA results for morphine in serum derived from the analyses of the ln-transformed AUC_{0-t}, AUC_{inf} and C_{max} PK parameters are summarized in Table 6.

Table 6: ANOVA Results for Morphine in Serum (ALO-01 vs KADIAN[®])

	Ratio of Least Square Means (%)	CI: Lower Limit (%)	CI: Upper Limit (%)	CV (%)
Including all completed subjects				
AUC _{0-t} (ng·h/mL), N=34	102.2	98.6	105.9	8.6
AUC _{inf} (ng·h/mL), N=30	97.4	91.2	104.1	13.9
C _{max} (ng/mL), N=34	93.8	82.4	106.7	32.2

Conclusion

The confidence intervals for the ratios of least-squares means derived from the analyses of the ln-transformed pharmacokinetic parameters AUC_{0-t}, AUC_{inf} and C_{max} for morphine in serum following oral administration of ALO-01 as compared to KADIAN[®] under fasting conditions were within the 80-125% range.

Based on results including all subjects, ALO-01 100 mg (morphine sulfate extended-release with sequestered naltrexone hydrochloride) capsules and KADIAN[®] 100 mg (morphine sulfate extended-release) capsules are bioequivalent under fasting conditions.

6.1.2. Study ALO-KNT-201 (Study 201)

ALO-KNT-201 was a restricted-randomized, double-blind, crossover, placebo-controlled single center study to evaluate the most effective and appropriate amount of naltrexone required to abate the euphoric effect of morphine in nondependent, recreational opioid drug users. The study consisted of three periods: a Pre-Randomization Period, a double-blind Treatment Period (two dosing stages) and a post-treatment Follow-up Period.

Figure 10 summarized the design of the study. For the purpose of protecting Alpharma's proprietary information, the varying doses of naltrexone are not indicated with the exception of the dose found to be effective.

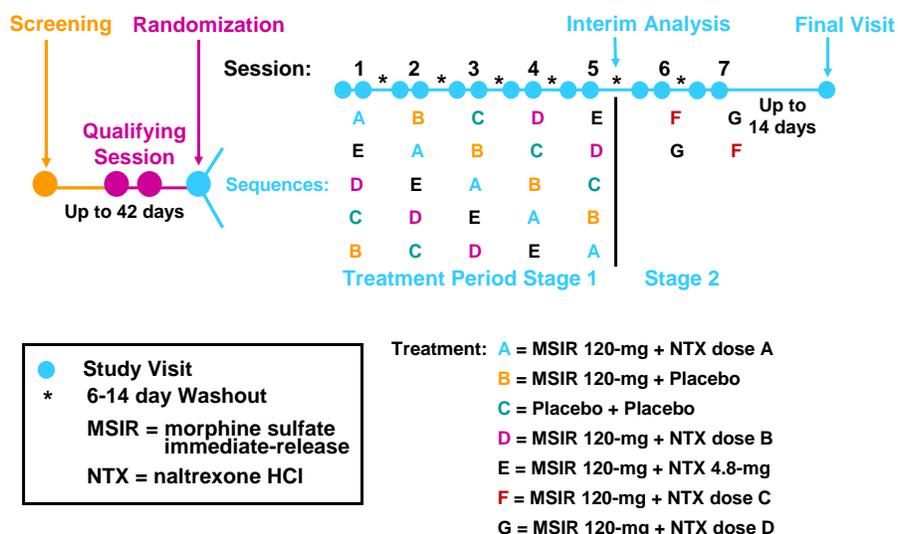
The objectives of the study included:

- Assess the appropriate naltrexone to morphine ratio required to abate the euphoric effects of morphine in nondependent, recreational opioid drug users.
- Assess morphine and naltrexone pharmacokinetics when the drugs are administered together.

ALO-01 capsules were not administered on this study. Only commercially available morphine sulfate immediate-release or naltrexone products were used.

Note: Clinical pharmacodynamic results of Study ALO-KNT-201 are reported in Section 6.2.1.

Figure 10: Diagram of Study ALO-KNT-201 Design



Plasma morphine concentrations were measured and PK parameters were calculated after each single-dose treatment with MSIR or MSIR with co-administered naltrexone. Morphine PK parameters included AUC_{0-8h} , C_{max} , and t_{max} .

Table 7: PK Parameters for Morphine Administered Orally

Study Treatment [†]	AUC_{0-8h}	C_{max}	t_{max}
	(ng*h/mL)	(ng/mL)	(h)
MSIR alone	243.1 (59.9)	75.0 ± 23.8 (31.7)	1.1 (0.6-2.2)
MSIR + NTX dose A	263.2 (72.3)	80.9 ± 25.8 (31.9)	0.8 (0.6-4.2)
MSIR + NTX 4.8-mg	256.8 (78.1)	74.0 ± 26.3 (35.6)	0.7 (0.6-4.1)
MSIR + NTX dose B	274.6 (87.0)	85.0 ± 40.1 (47.1)	0.6 (0.6-6.1)
MSIR + NTX dose C	285.6 (76.2)	90.1 ± 34.0 (37.7)	0.7 (0.6-4.2)
MSIR + NTX dose D	306.3 (88.4)	101.3 ± 34.7 (34.3)	0.7 (0.6-2.2)

AUC_{0-8h} =area under the concentration-time curve from time zero to 8 hours, C_{max} =maximum (peak) concentration, MSIR=morphine sulfate immediate-release, NTX=naltrexone HCl, t_{max} =time to reach C_{max}

* For AUC, C_{max} values geometric means \pm error (standard deviation and (% coefficient of variation); for t_{max} , values are median with range (minimum-maximum)

† Oral morphine sulfate immediate-release (MSIR) 120-mg alone or with naltrexone HCl oral solution (NTX)

Study ALO-KNT-201 showed that:

- Co-administration of increasing doses of naltrexone with MSIR 120-mg resulted in small, but not clinically relevant increases in peak morphine concentrations (C_{max}).
- The rate of exposure (t_{max}) was similar between MSIR alone in comparison to MSIR with naltrexone.
- Co-administration of MSIR with naltrexone resulted in small, but not clinically relevant increases in the morphine 8-hr exposure compared to MSIR alone.

6.1.3. Study ALO-01-07-106 (Study 106)

Study ALO-01-07-106 was a single-center, randomized, double-blind cross-over trial in non-dependent, recreational opioid drug users to characterize the effect of naltrexone on the euphorogenic effects of morphine as reflected in the subjective responses to the DEQ and Cole/ARCI. Equivalent doses of morphine and naltrexone in a 30 mg ALO-01 capsule were administered intravenously.

ALO-01 capsules were not administered on this study. Only commercially available morphine sulfate immediate-release or naltrexone products were used.

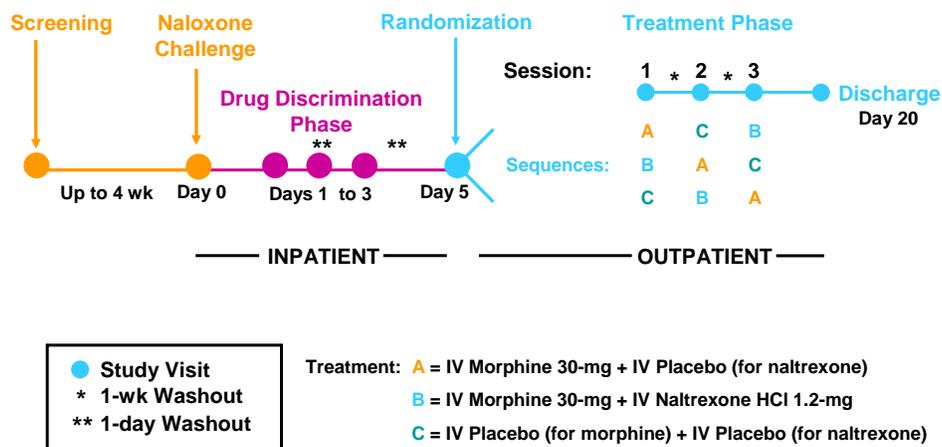
This study was conducted to provide clinical evidence as to whether the planned ratio of naltrexone to morphine would be effective in abating the positive subjective effects of morphine if the crushed product was injected.

The objectives included:

- Determine the relative drug-liking and euphoric effects of IV morphine alone to IV morphine combined with IV naltrexone.
- Determine the relative drug-liking and euphoric effects of IV morphine alone and IV morphine combined with IV naltrexone to placebo.

Note: Clinical pharmacodynamic results of Study ALO-01-07-106 are reported in section 6.2.2.

Figure 11: Diagram of Study ALO-01-07-106 Design



Plasma morphine concentrations were measured and PK parameters were calculated after each single-dose treatment with morphine sulfate or morphine sulfate and naltrexone HCl. Morphine PK parameters included AUC_{0-8h} and initial plasma concentration (C_0).

Table 8: PK Parameters for Morphine Administered Intravenously

	AUC_{0-8h} (ng*h/mL)	C_0 (ng/mL)
ALO-01-07-106[§]		
IV morphine alone	260 (23)	826 (94.4)
IV morphine + IV NTX	276 (25)	923 (92.5)

AUC_{0-8h} =area under the concentration-time curve from time zero to 8 hours,
 IV=intravenous, MSIR-morphine sulfate immediate-release, NTX=naltrexone HCl,
 For AUC equal means \pm error (standard deviation or % coefficient of variation)
[§] Intravenous morphine sulfate 30 mg alone or with intravenous naltrexone HCl 1.2 mg

Study ALO-01-07-106 demonstrated that:

- Mean PK parameters for treatment with morphine plus naltrexone were similar to treatment with morphine alone and
- Co-administration of naltrexone with morphine had no apparent effect on morphine PK.

6.1.4. Study ALO-01-07-205 (Study 205)

This single center randomized, double-blind, triple-dummy, 4-way crossover study confirmed that the ratio established in Study ALO-KNT-201 was effective when the ALO-01 pellets were crushed and orally consumed.

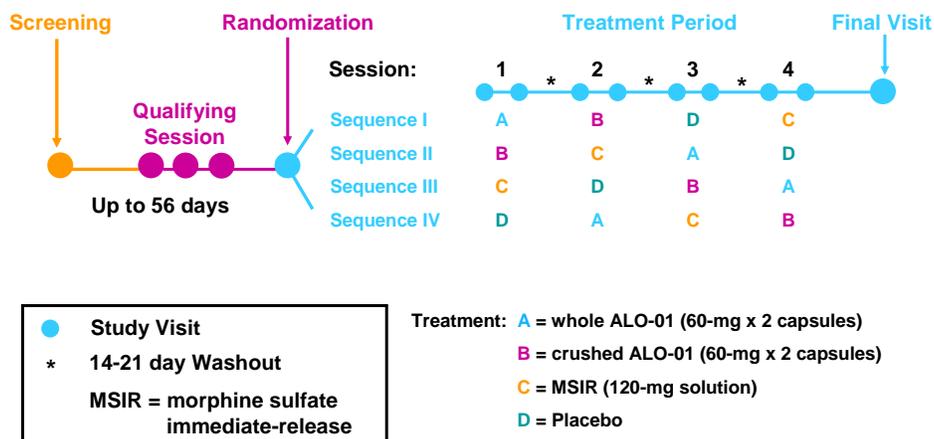
The objectives of the study were to:

- Determine the relative pharmacodynamic effects and safety of crushed ALO-01 pellets and intact ALO-01 capsules compared to MSIR (morphine sulfate immediate release) and to Placebo, and of crushed ALO-01 to intact ALO-01.
- Determine the relative bioavailability of plasma morphine from crushed ALO-01 pellets and intact ALO-01 capsules compared to MSIR, and from crushed ALO-01 to intact ALO-01.
- Determine the relative bioavailability of plasma naltrexone and 6-β-naltrexol from crushed ALO-01 pellets to intact ALO-01 capsules.

The study consisted of three periods: a screening/qualifying period, a double-blind treatment period, and a post-treatment follow-up period.

Note: Clinical pharmacodynamic results of Study ALO-01-07-205 are reported in section 6.2.3.

Figure 12: Diagram of Study ALO-01-07-205 Design



Plasma morphine and naltrexone concentrations were measured and PK parameters were calculated after each single-dose treatment with ALO-01 intact capsules or crushed pellets, after

oral administration to 32 opioid-experienced, non-dependent subjects. Plasma morphine and naltrexone PK parameters included AUC_{0-8h}, AUC_{0-inf}, C_{max}, and t_{max}.

Table 9: PK Parameters for Plasma Morphine in ALO-01 Capsule Taken Intact (Whole) or Crushed and for MSIR

Study Treatment [†]	Morphine PK Parameter*			
	AUC _{0-inf} (pg*h/mL)	AUC ₀₋₈ (pg*hr/mL)	C _{max} (pg/mL)	t _{max} (h)
ALO-01-07-205				
ALO-01 whole	427230 (327436)	80658 (42240)	19256 (7683)	8.1 (6 – 10)
ALO-01 crushed	480741 (330135)	259742 (90766)	80588 (38805)	1.1 (0.58-2.2)
MSIR	362597 (119507)	262621 (92799)	92516 (38051)	1.15 (0.62 – 2.07)

* For AUC, C_{max}, values are means (coefficient of variation); for T_{max}, values are median with range (minimum-maximum)

† Doses for treatments were: ALO-01 Capsules 2x 60 mg whole or crushed

Table 10: PK Parameters for Naltrexone in ALO-01 Capsule Taken as Directed (Intact) or Crushed

Study Treatment [†]	Naltrexone PK Parameters*		
	AUC _{0-inf} (pg*h/mL)	C _{max} (pg/mL)	t _{max} (h)
ALO-01-07-205			
ALO-01 whole	BLQ	BLQ	BLQ
ALO-01 crushed	4075 (1996.4)	1265 (706.3)	1.1 (0.6-1.1)

AUC_{0-inf}=area under the concentration-time curve from time zero to infinity, BLQ=below the limit of quantitation for plasma naltrexone concentration, C_{max}=maximum (peak) concentration, CI=confidence interval, MSIR=morphine sulfate immediate-release, t_{max}=time to reach C_{max}

* For AUC, C_{max} values are means ± error (standard deviation or % coefficient of variation); for t_{max}, values are median with range (minimum-maximum or lower-upper quartile)

† Doses for treatments were: ALO-01 Capsules 2x 60 mg whole (intact) or crushed

Study ALO-01-07-205 demonstrated the following findings:

- Naltrexone remained sequestered in the ALO-01 capsule when taken whole (intact) (Table 9). Negligible amounts of naltrexone were detected in 5/32 subjects after ALO-01 whole treatment (with only 1 value above the limit of quantitation reported for each of the 5 subjects).
- Plasma naltrexone was detectable in all subjects after treatment with ALO-01 crushed pellets with naltrexone PK parameters for crushed ALO-01 pellets within expected ranges.

6.1.5. Study ALO-KNT-202 (Study 202)

ALO-KNT-202 was a Phase 2, multi-center, randomized double-blind study in patients with chronic pain due to OA of the hip or knee. This study was designed to:

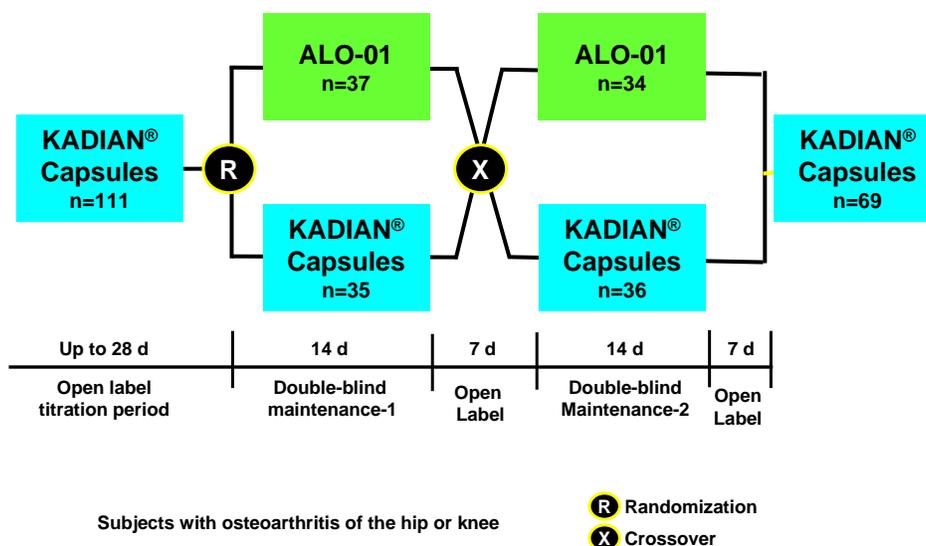
- Characterize and assess the plasma morphine and plasma naltrexone pharmacokinetics of ALO-01 following multiple doses in patients with chronic pain due to OA of the hip or knee.
- Assess the safety and efficacy of ALO-01 following multiple doses in patients with chronic pain due to OA of the hip or knee.
- Assess the pharmacokinetics of morphine and naltrexone following multiple doses of ALO-01.
- Assess the efficacy of ALO-01 capsules compared to KADIAN[®] Capsules.

This study had a crossover design with five distinct treatment periods:

1. Titration with KADIAN[®]
2. Randomization to double blind crossover treatment with KADIAN[®] or ALO-01
3. Receive open label KADIAN[®] only
4. Crossover to alternate medication of Period 2
5. Receive open label KADIAN[®] only

Note: Clinical efficacy and safety results of Study ALO-KNT-202 are reported in section 6.3.5 and 6.4 respectively.

Figure 13: Diagram of Study ALO-KNT-202 Design



Morphine, naltrexone, and 6- β naltrexol PK were assessed. Serum morphine concentrations were measured and PK parameters were calculated for each treatment period with KADIAN® or ALO-01 (on Days 1, 7, and 14). Morphine PK parameters included the AUC_{0-inf} , C_{max} , t_{max} . Trough blood sampling for plasma morphine, naltrexone and 6- β -naltrexol determinations were performed on Days 1 and 7.

Study ALO-KNT-202 demonstrated the following finding:

- ALO-01 and KADIAN® showed similar relative bioavailability for total morphine exposure (AUC_{0-inf}) and peak morphine concentration (C_{max}) (Figure 14 and Table 11).

Figure 14: Relative Bioavailability of Morphine in ALO-01 Capsule and KADIAN[®] Capsule Administered to Patients with Moderate to Severe Chronic Pain Due to Osteoarthritis: Study ALO-KNT-202 (N=67)

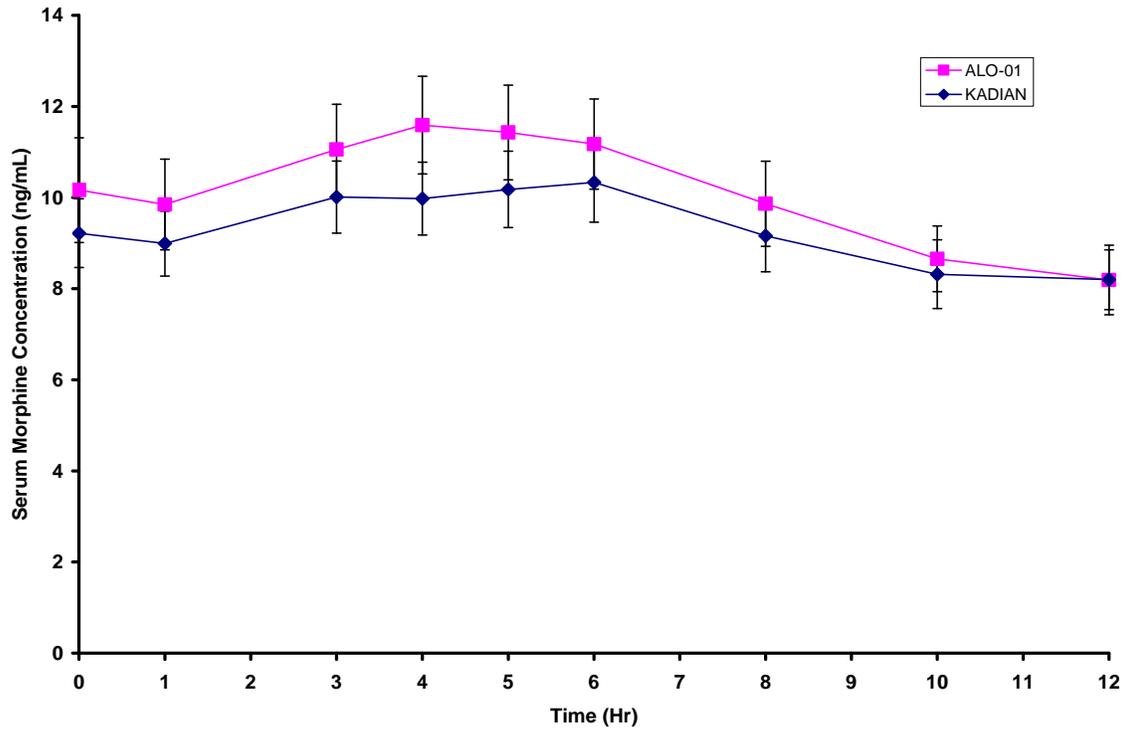


Table 11: Summary of Morphine Calculated Parameters, Bioequivalent Population

Parameter Statistic	KADIAN [®] N = 67	ALO-01 N = 67
AUC ₀₋₁₂ [pg*h/mL]		
N	67	67
Mean (± SD)	111,965.7 (± 72,913.2)	122,545.1 (± 87,961.6)
%CV	65.1	71.8
Median (Minimum; Maximum)	89,045 (21,105; 348,235)	89,300 (21,816; 420,550)
Ratio AUC(ALO-01)/AUC(KADIAN [®]) ^a	1.07	
95% CI for Ratio AUC(ALO-01)/AUC(KADIAN [®]) ^a	[0.94, 1.21] ^b	
C _{max} [pg/mL]		
N	67	67
Mean (± SD)	12,434.3 (± 7737.8)	14,130.1 (± 10,976.0)
%CV	62.2	77.7
Median (Minimum; Maximum)	9830 (2630; 35,600)	10,300 (2420; 57,600)
Ratio C _{max} (ALO-01)/ C _{max} (KADIAN [®]) ^a	1.07	
95% CI for Ratio C _{max} (ALO-01)/C _{max} (KADIAN [®]) ^a	[0.93, 1.22] ^b	
t _{max} [h]		
N	67	67
Mean (± SD)	4.93 (± 3.37)	4.30 (± 3.07)
%CV	68.5	71.4

Abbreviations: AUC₀₋₁₂ = area under the concentration-time curve from Hour 0 to Hour 12; CI = confidence interval; C_{max} = observed peak plasma drug concentration; %CV = percent coefficient of variation; PK-BE = pharmacokinetic-bioequivalence; t_{max} = observed time to peak plasma drug concentration.

- a Ratio and 95% CI are calculated by exponentiating the between-group difference and confidence bounds for the log transformed data, using the linear mixed effects model for a two-period crossover, including fixed effect terms for Sequence, Period, and Treatment, and a random effect term for Patient nested within Sequence.
- b The tests for Sequence and Period effects are not statistically significant (p=0.6 and 0.7, respectively).

Conclusions:

- The 95% CI for log AUC₀₋₁₂ of ALO-01/AUC₀₋₁₂ of KADIAN[®] was 0.94 to 1.21, and thus demonstrated bioequivalence limited to the extent of exposure at steady state for morphine in the ALO-01 and KADIAN[®] formulations.
- The mean steady state C_{max} of morphine was approximately 7% greater for ALO-01 treatment compared with KADIAN[®] treatment.
- The mean t_{max} of morphine was 4.3 hours for ALO-01 treatment compared with 4.9 hours KADIAN[®] treatment demonstrating that the rate of exposure to plasma morphine in ALO-01 was slightly greater than that in KADIAN[®].

6.1.6. Study ALO-KNT-302 (Study 302)

This long-term, open-label study evaluated the safety of ALO-01 administered once daily (QD) or twice daily (BID) over a 12-month period. ALO-01 was available in dosage strengths of 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 80 mg, and 100 mg. There was no maximum allowable daily dose set for this study. Patients titrated upward in a manner consistent with the current KADIAN[®] Capsules labeling and in accordance with the investigator's best medical judgment for the most effective pain management in an open-label, uncontrolled, 12-month study. The total safety population was 465 subjects exposed to at least one dose of ALO-01 capsules.

The secondary objectives of the study were to:

- Evaluate the long-term efficacy of ALO-01 during a 12-month period by assessing pain intensity in the last 24 hours using the BPI Short Form and the Global Assessment of Study Drug.
- Evaluate opioid withdrawal symptoms in all patients who received ALO-01 upon completion of 12 month exposure or who terminated early from the study using the COWS.
- Evaluate the population pharmacokinetics of plasma morphine, naltrexone, and 6- β -naltrexol at trough (just before dose) in selected male and female patients. (N=94)

Note: Clinical efficacy and safety results of Study ALO-KNT-302 are reported in section 6.3.6 and 6.4 respectively.

All 94 patients had at least one evaluable result during the study. An evaluable result was defined as a quantifiable concentration or a value below the limit of quantification (BLQ) of plasma morphine, naltrexone, or 6- β -naltrexol. Blood sampling for plasma morphine, naltrexone, and 6- β -naltrexol were taken at trough every 4 weeks for the 52-week duration of the study. Therefore, each patient could have up to 13 values for each analyte.

Morphine:

- Mean plasma morphine concentrations for each visit ranged from 18.6 to 26.9 ng/mL during the study; lower concentrations tended to occur early in the study when patients were undergoing titration, then leveled off.
- A total of 446 (96.7%) trough samples for plasma morphine determination were above the lower limit of quantification ranging from 0.214 to 204 ng/mL.

Naltrexone:

- Of all samples (444) assayed for plasma naltrexone determination only 11.0% (49 of 444) were above the lower limit of quantification ranging from 4.03 to 145 pg/mL.

6- β -naltrexol:

- A total of 338 of 457 (74.0%) samples assayed for plasma 6- β -naltrexol determination were above the lower limit of quantification ranging from 0.471 to 3720 pg/mL.

6.1.6.1. Plasma Naltrexone and 6-β-Naltrexol Results

The assessment of plasma naltrexone and 6-β-naltrexol data is based upon evaluation of individual concentrations and median values. Due to the effect of outliers on mean values, it was determined that the median was a more accurate representation of population plasma naltrexone and 6-β-naltrexol data.

- Of the 49 detectable plasma naltrexone concentrations, the median value over all study weeks was 10.1 pg/mL. After setting all plasma naltrexone concentrations below the limit of quantification to zero, the median value across all study weeks was zero. The overall mean plasma naltrexone concentration was 2.31 pg/mL.
- Of the 338 detectable 6-β-naltrexol concentrations, the median value over all study weeks was 18.5 pg/mL and, including all BLQ values set to zero, the median value was 10.3 pg/mL. The overall mean 6-β-naltrexol concentration was 73.7 pg/mL.

Due to a high first-pass effect, naltrexone is rapidly converted to 6-β-naltrexol which results in several-fold greater 6-β-naltrexol concentrations than naltrexone. Additionally, the lower limit of detection of the plasma 6-β-naltrexol assay is more sensitive than that of plasma naltrexone. As a result, there are greater and more numerous plasma 6-β-naltrexol concentrations than naltrexone. However, 6-β-naltrexol has a much smaller antagonistic effect. (See Section 4.2.2)

One can gain perspective on these detectable naltrexone concentrations by comparing them to published pharmacology of naltrexone. As indicated earlier in section 4.2.2, a 50 mg oral dose of naltrexone will result in plasma levels of approximately 9 ng/mL or 9,000 pg/mL. (Wong et al. 2006) performed a positron emission tomography (PET) study with naltrexone in 9 healthy obese subjects (BMI>25kg/m²) who were randomized to receive total oral daily doses of 16, 32, and 48 mg. The results of the study showed the plasma naltrexone curve yielded a maximal occupancy (E_{max}) of 90.2% and an EC₅₀ (concentration at half E_{max}) of 1600 pg/mL.

The highest naltrexone concentration detected in study ALO-KNT-302 was 145 pg/mL, approximately 10-fold less than the EC₅₀ from the PET study.

In another study in intravenous heroin addicts, (Verebey et al. 1980) determined the lowest effective naltrexone plasma level was 2.0 ng/mL or 2000 pg/mL to achieve 86.5% blockade of the effects of 25 mg heroin.

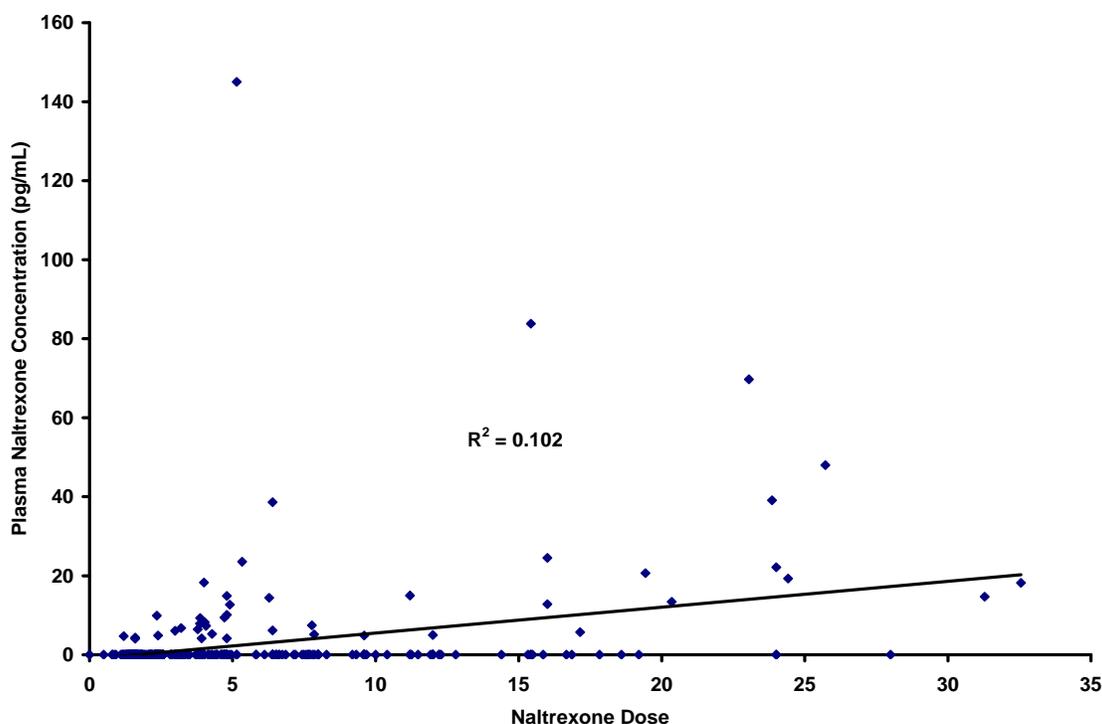
According to (Misra 1980), the primary metabolite of naltrexone, 6-β-naltrexol, although more bioavailable, is a weaker opioid antagonist than naltrexone, having only 1/50th to 1/25th of antagonist potency. As such, 6-β-naltrexol concentrations 25- to 50-times greater than the EC₅₀ naltrexone concentration of 1600 pg/mL would be necessary to achieve similar opioid antagonism (Wong et al. 2006). Using the most conservative fraction of antagonistic potency of 1/25th and EC₅₀, 1600 pg/mL, an approximate minimum 6-β-naltrexol concentration of 40,000 pg/mL may be necessary to achieve opioid antagonism. However, since the EC₅₀ represents only 50% of the plasma naltrexone concentration necessary to achieve 90% occupancy of the mu-opioid receptors, it is quite possible that levels much higher than 40,000 pg/mL of 6-β-naltrexol would be required to achieve similar occupancy. The highest plasma 6-β-naltrexol concentration recorded in study ALO-KNT-302 was 3720 pg/mL, 10.7-fold less than 40,000 pg/mL.

It is also noteworthy that there were several plasma naltrexone and 6- β -naltrexol outliers (values > 1 standard deviation from the mean) during the study. These outliers are described in section 6.1.6.4.

6.1.6.2. Assessment of potential for dose-related increases

Individual plasma naltrexone concentrations vs. naltrexone dose are presented in Figure 15. If the dose for a given visit was not provided, the matching plasma naltrexone concentration was excluded from the analysis ($N_{\text{excluded}}=90$).

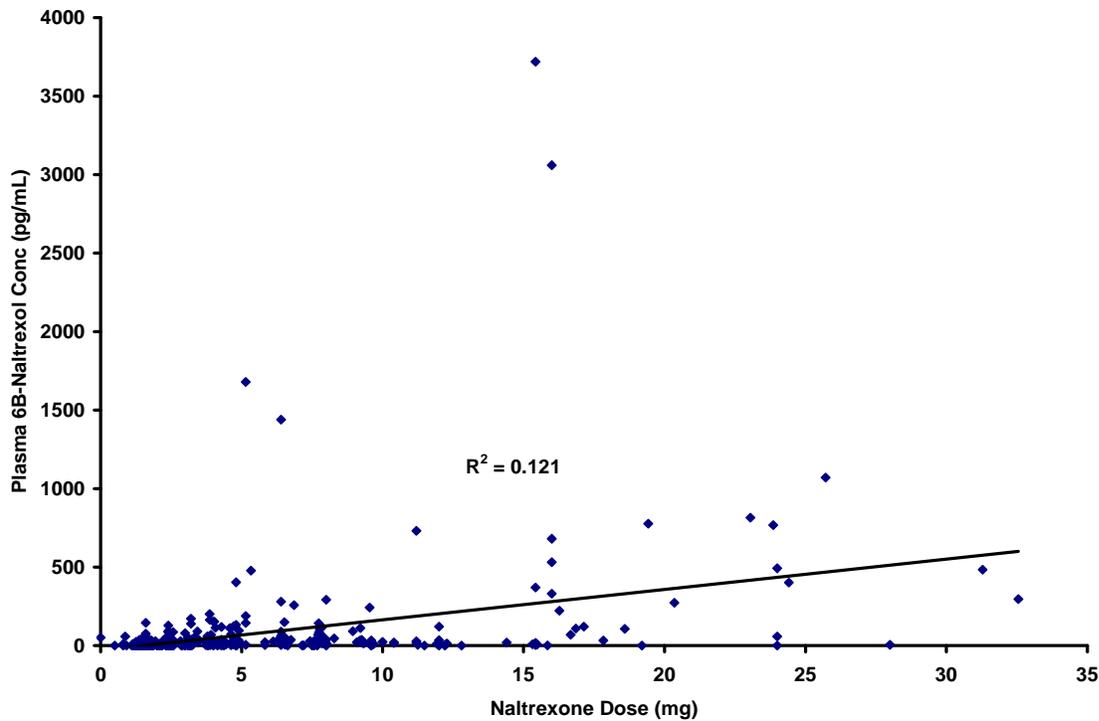
Figure 15: Individual Plasma Naltrexone Concentrations by Naltrexone Dose (ALO-01 daily dose in naltrexone content, mg), (N=354)



There was no clear correlation between ALO-01 dose and plasma naltrexone concentrations (the R^2 of 0.1 indicates that merely 10% of the data variability can be explained by the regression line). At the highest doses, naltrexone concentrations were either very low or below the limit of quantification and had no observable clinical effect.

Individual plasma 6- β -naltrexol concentrations vs. naltrexone dose are presented in Figure 16. If the dose for a given visit was not provided, the matching plasma 6- β -naltrexol concentration was excluded from the analysis ($N_{\text{excluded}}=83$).

Figure 16: Individual Plasma 6-β-naltrexol Concentrations by Naltrexone Dose, (ALO-01 daily dose in naltrexone content, mg), (N=374)



As shown in Figure 16, in a fashion similar to plasma naltrexone, there was no clear correlation between ALO-01 dose and plasma 6-β-naltrexone concentrations (the R^2 of 0.12 indicates that merely 12% of the data variability can be explained by the regression line). Again, at the highest doses, 6-β-naltrexol concentrations were either very low or below the limit of quantification and had no observable clinical effect.

Figure 17: Overall Negligible Exposure to Naltrexone + 6-β-naltrexol Observed With ALO-01

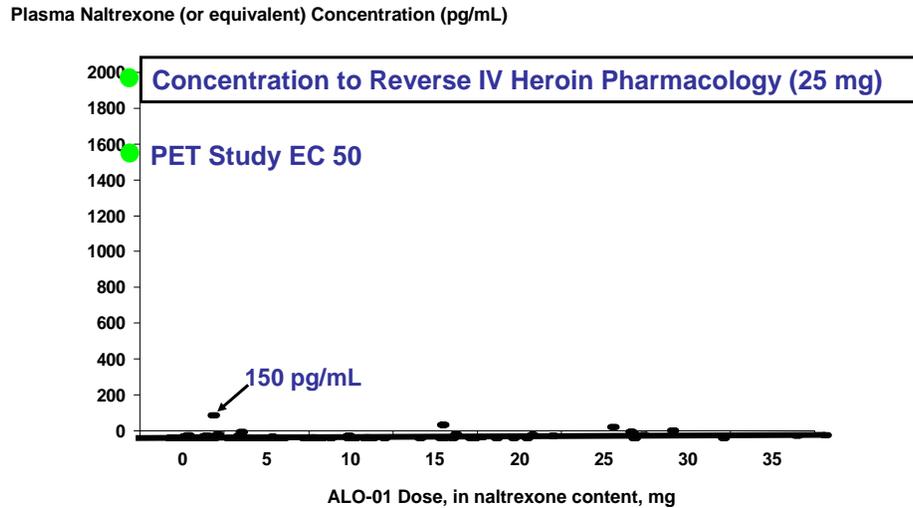


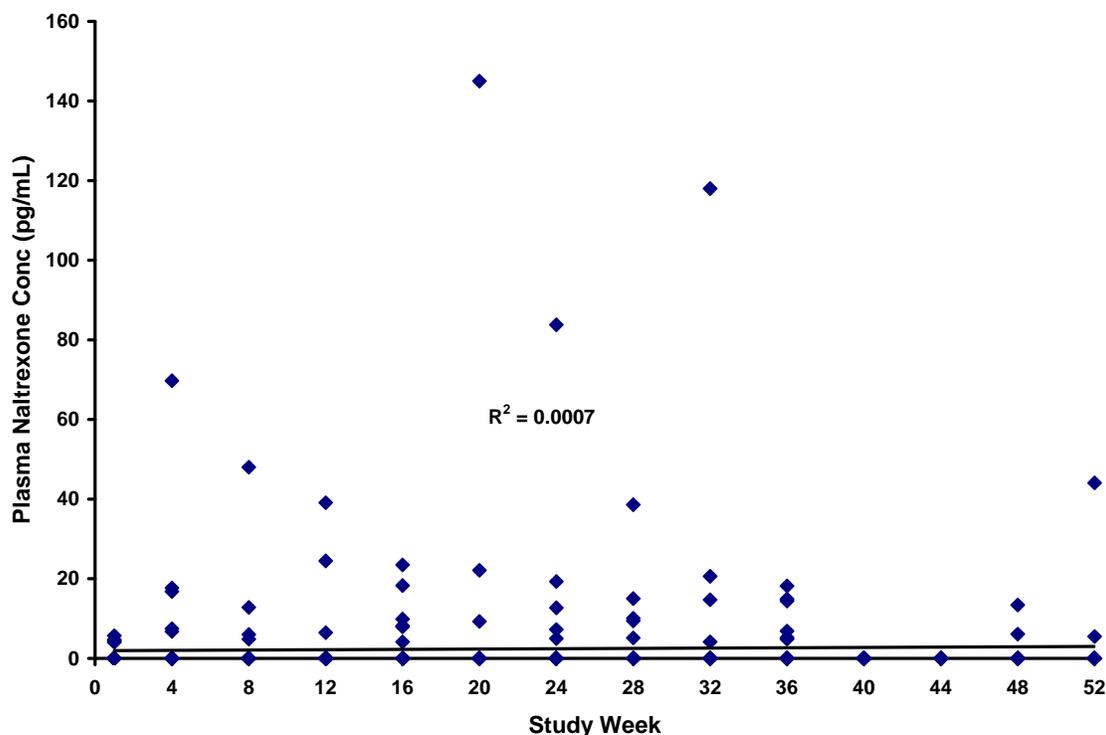
Figure 17 represents total opioid antagonist activity in naltrexone equivalents, which is the sum of naltrexone and potency-adjusted 6-β-naltrexol concentrations. 150 pg/mL was the highest naltrexone equivalent (naltrexone + 6-β-naltrexol) concentration in the study, approximately 10-fold less than the EC₅₀ determined from the PET study (see section 6.1.6.1). This outlier is due to the subject that had 145 pg/mL of naltrexone.

Overall, there was negligible exposure to naltrexone or its metabolite during this study.

6.1.6.3. Assessment of Potential for Accumulation of Naltrexone

A scatter plot of all (with BLQ's set to 0) plasma naltrexone concentrations by study week is presented in Figure 18. All evaluable subjects are included (N=94).

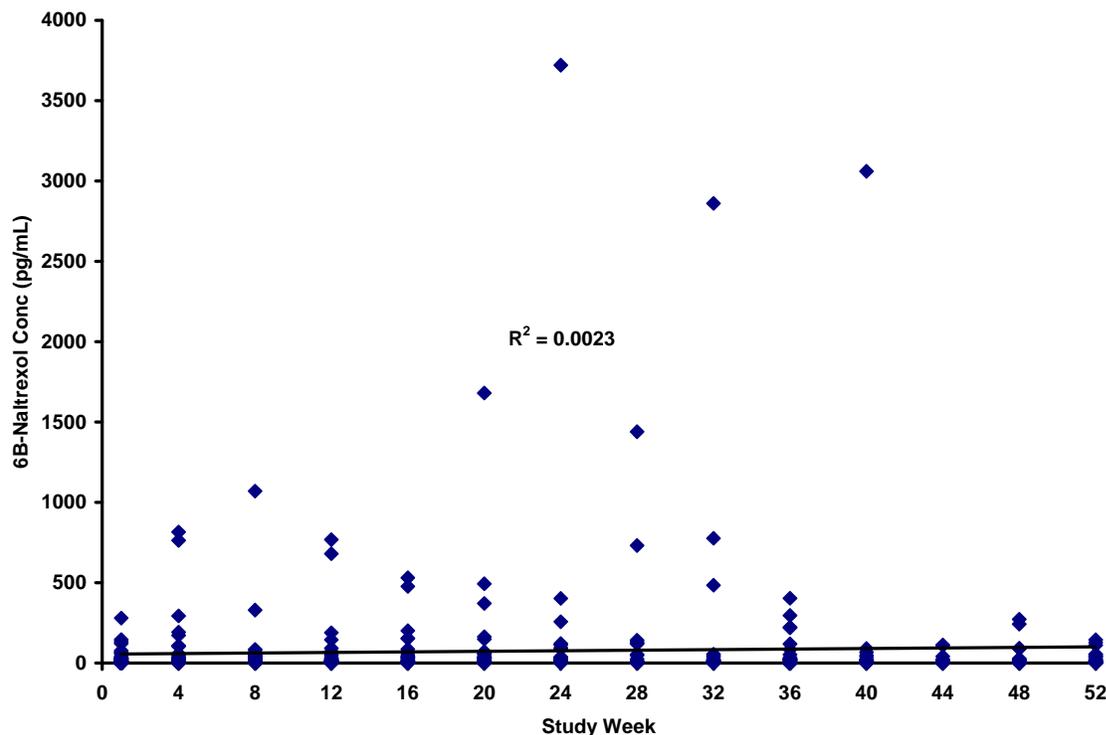
Figure 18: Individual Plasma Naltrexone Concentrations by Study Week (Number of values=437)



As shown in Figure 18, there was no clinically relevant trend ($R^2 = 0.0007$) toward increasing plasma naltrexone concentrations during the course of the study. The outlying value in Figure 18, (145 pg/mL on Day 139) is from Patient 222-2002 discussed at section 6.1.6.4. There were overlapping zero values due to many BLQ's on the x-axis. The data from Figure 18 suggest that when detectable plasma naltrexone concentrations do occur, they tend to occur randomly and do not accumulate. Additionally, no individual patient had a trend toward increasing plasma naltrexone concentrations during the study.

A scatter plot of all (BLQ's set to zero) individual plasma 6- β -naltrexol concentrations by study week is presented in Figure 19. If the dose for a given visit was not provided, the matching plasma 6- β -naltrexol concentration was excluded from the analysis (N=77).

Figure 19: Individual Plasma 6-β-naltrexol Concentrations by Study Week (N=380)



As shown in Figure 19, there was no clinically relevant trend ($R^2 = 0.0023$) toward increasing plasma 6-β-naltrexol concentrations during the course of the study. The outlying value of 3720 pg/mL is from Patient 222-2002 previously discussed. The data from Figure 19 suggest that when detectable plasma 6-β-naltrexol concentrations do occur, as with detectable plasma naltrexone, they tend to occur randomly and do not accumulate. Additionally, no individual patient had a trend toward increasing plasma 6-β-naltrexol concentrations during the study.

6.1.6.4. Discussion of Outlying Plasma Naltrexone Values

Three patients had at least one outlying plasma naltrexone concentration during the study. An outlier is a plasma naltrexone concentration outside of one standard deviation of the arithmetic mean (> 49.4 pg/mL).

Patient 222-2002 (initial dose, 40 mg/day), a 30-year old male, had 2 outlying plasma naltrexone concentrations, which were the highest values recorded during the study, 118 and 145 pg/mL at Weeks 32 and 20, respectively.

- The only adverse event recorded at Week 32 was an upper respiratory tract infection, not likely to be related to the naltrexone concentration of 145 pg/mL.
- Although his average daily morphine dose was recorded as 184.6 mg, plasma morphine concentrations during the study were only 2.81, 0.693, 0.000, 2.90, 27.7, 22.1, 0.684, 10.1, and 40.9 ng/mL at Weeks 1, 4, 8, 12, 16, 20, 24, 28, and 32, respectively.

- During routine urine drug screening and reflex testing, he had no detectable levels of morphine and therefore, his data was considered suspect. Because he had no detectable morphine in his urine, he was suspected of non-compliance and was subsequently discontinued from the study, however his data are included in the PK evaluation.
- His baseline pain score was 7 which decreased to 3 at Week 8 and to 2 by Weeks 24 and 28. His Clinical Opiate Withdrawal Scale (COWS) scores were either 0 or 1 during the 4 weeks when detectable naltrexone concentrations were recorded. In particular his COWS scores were 0 and 1 at Weeks 20 and 32 when he had the highest naltrexone concentrations.
- Therefore, it is concluded that there was no observable clinical effect from these detectable naltrexone concentrations.

Patient 212-2005 (starting dose, 120 mg/day; average daily dose, 508.7 mg/day), a 56 year old male, had one outlying plasma naltrexone concentration of 83.8 pg/mL at Week 24. He also had detectable naltrexone levels at Weeks 4, 8, 12, 28, 32, and 48. His plasma morphine concentration at Week 24 was 125 ng/mL.

- He had no adverse events reported at the time of the plasma naltrexone concentration of 83.8 pg/mL. He was receiving ALO-01 for neck pain. His relevant medical history was discogenic disorder, neuropathy, rheumatoid arthritis, psoriatic arthritis, spinal stenosis, and post traumatic arthritis. He was tapered over 5 days to a total daily dose of 400 mg at which he remained for 360 days. His baseline pain score was 10, then decreased to 8 at Week 4, 7 at Week 8, and 6 at Week 12. From Week 16, his pain scores increased from 6 to 7-9 until study completion.
- His highest COWS score was 4 during an unscheduled visit, and was 1, 2 or 3 for other study visits. Therefore, it can be concluded that Subject 212-2005 had intractable pain that was moderately controlled with ALO-01 400 mg/day. As a COWS score of 13 is indicative of withdrawal, his COWS score of 2 at Week 24, when he had his highest plasma naltrexone concentration of 83.4 pg/mL, suggests that this and his other detectable naltrexone concentrations were not related to clinical presentations.

Patient 234-2005 (starting dose, 400 mg/day; average daily dose, 800 mg/day), a 41-year old female, had 1 outlying plasma naltrexone concentration of 69.7 pg/mL at Week 4.

- The only adverse events recorded at the time of the outlying plasma naltrexone concentration were a sinus infection and sore throat, not likely to be related to the naltrexone concentration. Her plasma morphine concentration at Week 4 was 118 ng/mL. Detectable plasma naltrexone concentrations (range, 48.0 to 14.7 pg/mL) were recorded in all subsequent blood samples at Weeks 8, 12, 20, 24, 32, and 36 in a generally decreasing trend.
- She was receiving ALO-01 400 mg/day for neck and shoulder pain. She was also receiving Cymbalta and Clonazepam for depression and anxiety. Her baseline pain score was 7 which did not appreciably decrease during the study.

- Her COWS scores ranged from 0 at Week 4, when her highest plasma naltrexone concentration of 69.7 pg/mL was recorded, to 4 at Week 20 when a lower naltrexone concentration of 22.1 pg/mL was recorded. Her final COWS score at study completion was 0. Therefore, it can be concluded that none of these naltrexone concentrations were associated with any symptoms of withdrawal.

6.1.6.5. Summary of Pharmacokinetic Findings

- At the highest doses of ALO-01, plasma naltrexone concentrations were either below the limit of quantification or very low- at least an order magnitude below relevant pharmacologically active concentrations.
- Plasma naltrexone and 6- β -naltrexol concentrations had no observable trend to dose
- Mean plasma morphine concentrations were driven by dose titration and increased in a dose-related manner. Plasma morphine concentrations for subjects \geq 65 yrs were similar to patients <65 yrs. Plasma morphine concentrations appeared to be similar for female and male subjects.
- Due to the high first pass effect and more sensitive assay method, the frequency of detectable 6- β -naltrexol concentrations was consistently higher than naltrexone at approximately 60% to 80% throughout the study. However, since the 6- β -naltrexol metabolite has markedly lower antagonist activity, the detectable concentrations are consistent with no observable clinical effect.
- The frequency (%) of detectable naltrexone concentrations was low (11%) and did not increase during the study.
- Plasma naltrexone and 6- β -naltrexol concentrations when detectable were low, without predictability and did not accumulate during the study.
- Plasma naltrexone and 6- β -naltrexol concentrations had no observable trend to dose, and at the highest doses, naltrexone concentrations were both below the limit of quantification or were both negligible and had no observable clinical effect.
- Plasma naltrexone and 6- β -naltrexol concentrations were not correlated to age.
- There were no observable differences between male and female patients for plasma naltrexone and 6- β -naltrexol concentrations.

6.2. SUMMARY OF CLINICAL PHARMACODYNAMIC DATA

Three PD studies have been conducted in opioid-experienced, non-dependent subjects to evaluate the ability of naltrexone to significantly abate drug-liking and euphoria induced by morphine.

The PD assessments utilized in each study are summarized in Table 12. A description of each PD assessment and scoring method is provided in Table 13.

Table 12: PD Assessments in Studies of Opioid-experienced Subjects

PD Assessment	ALO-KNT-201	ALO-01-07-106	ALO-01-07-205
VAS DEQ Drug Liking	X		X
VAS DEQ Other	X	X	X
ARCI and Cole/ARCI	X	X	X
Subjective Drug Value	X		X
Pupillometry	X	X	X
End-tidal CO ₂ capnography		X	

VAS DEQ=visual analog scale, Drug Effects Questionnaire, ARCI=Addiction Research Center Inventory, Cole/ARCI=Cole modification of the ARCI

Table 13: Description of PD Assessments

PD Scale	Subscales	Measure	Assessment
VAS-Drug Liking	---	Horizontal line: integer 0–100 0=strong disliking 100=strong liking Computer-aided scale*	Drug liking at the moment the question is asked Overall Drug Liking=global experience of drug
VAS Drug Effects Questionnaire (DEQ)-Other	<u>Positive Effects:</u> High Good Effects <u>Negative Effects</u> Bad Effects Sick Nausea Sleepy Dizzy <u>Other Effects</u> Any Drug Effects	Horizontal line: integer 0–100 0=strong disliking 100=strong liking Computer-aided scale*	Positive, negative, and other subjective effects to evaluate pharmacologic response to opioid study medication
Addiction Research Center Inventory (ARCI) short form	MBG Amphetamine scale BG LSD PCAG	77 questions on 5 subscales	Morphine-Benzedrine Group=Euphoria Amphetamine scale=Stimulant Benzedrine Group=Stimulant LSD=Dysphoria Pentobarbital-Chlorpromazine-Alcohol Group=Sedation
Cole/ARCI (ARCI with modification by Cole, et al)	Sedation-Motor Sedation-Mental Unpleasantness-Physical Unpleasantness-Mental Stimulation-Motor Stimulation-Euphoria Abuse Potential	77 questions on 7 subscales for combined ARCI and Cole/ARCI scales	Sedation, unpleasantness, stimulation, abuse potential

Table 13: Description of PD Assessments (Continued)

PD Scale	Subscales	Scoring	Measure
Subjective Drug Value	---	6 questions	Estimate of crossover point at which subject is indifferent between choice of drug and a specific amount of money
Pupillometry	---	Pupil diameter	Physiologic measure of opiate-mediated pupil constriction (miosis)
End-tidal CO ₂ capnography	---	Amount of CO ₂ exhaled from lungs	Assessed because morphine is associated with depressed respiration and increased end-tidal CO ₂

VAS DEQ=Visual Analog Scale, ARCI=Addiction Research Center Inventory, CO₂=carbon dioxide
 *As shown in Figure 20.

Figure 20: Visual Analog Scale (VAS) for Drug Liking



6.2.1. Naltrexone Dose-finding Data, Study ALO-KNT-201

The objective of this study was to assess the appropriate naltrexone to morphine ratio required to abate the euphoric effects of morphine in opioid-experienced, non-dependent subjects. (See section 6.1.2 for details on the design of the study).

For the purpose of protecting Alpharma’s proprietary information, the varying doses of naltrexone are not indicated with the exception of the dose found to be effective.

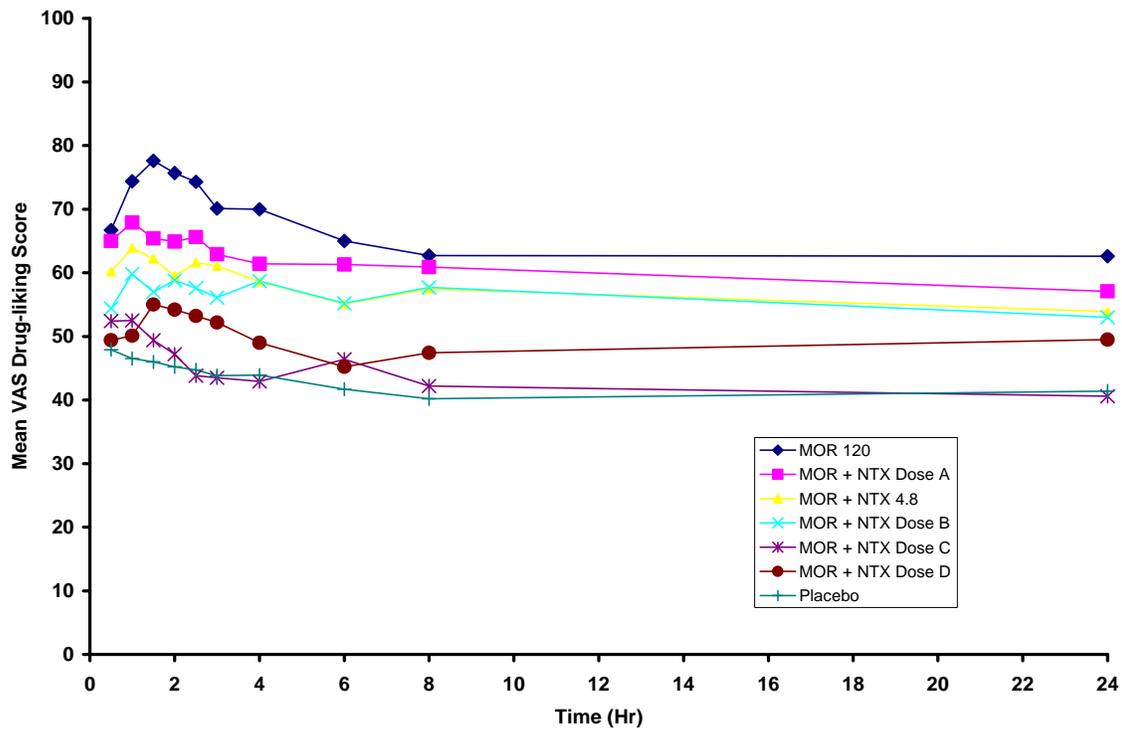
Summary of results:

MSIR dosing induced significantly higher peak subjective positive effects and greater pupil reduction compared to placebo, confirming the validity of the study. Co-administration of oral naltrexone HCl with MSIR 120 mg significantly reduced morphine-induced subjective positive effects in a naltrexone dose-dependent manner, as shown in Figure 21. For E_{max} (maximum drug effect), there were some significant differences between naltrexone treatments for some of the measures of positive effects, generally when the Dose A or 4.8 mg doses were compared to Dose C and D.

Conclusions:

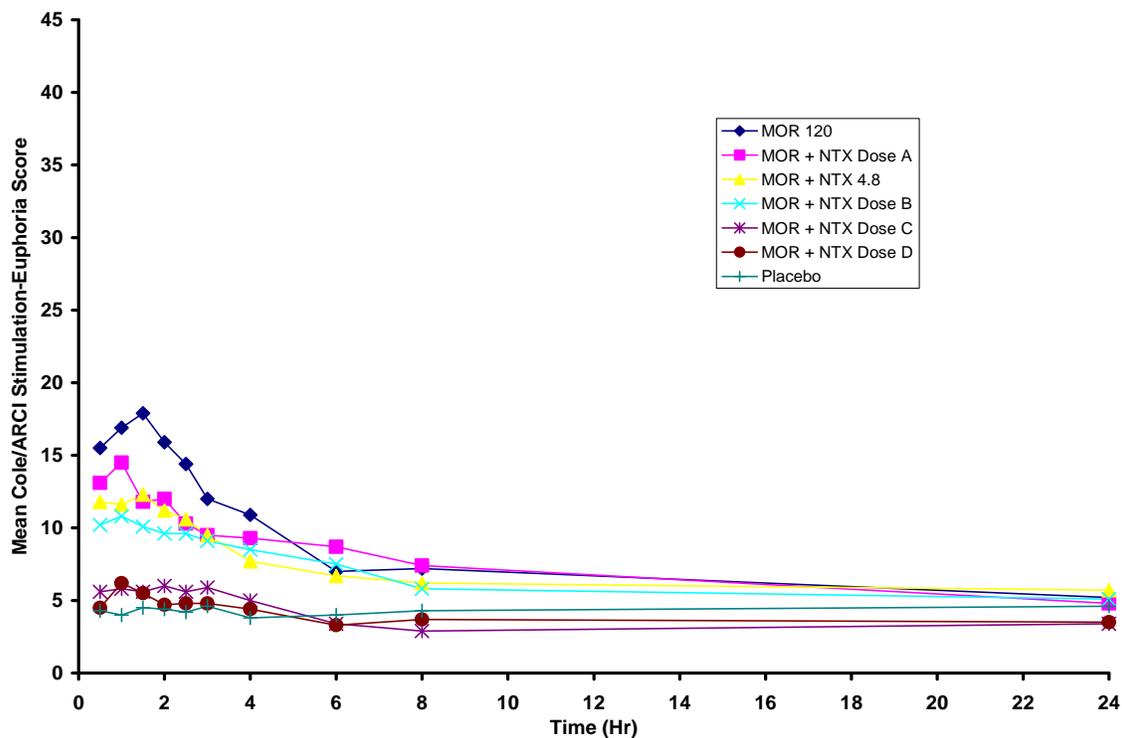
Naltrexone HCl 4.8 mg showed a dose dependent reduction in morphine-induced subjective positive effects of MSIR 120 mg. Naltrexone HCl 4.8 mg co-administration resulted in $\geq 30\%$ reduction in morphine-induced euphoria for $>50\%$ of subjects who completed the study, assessed by VAS-Drug Liking. This degree of reduction in morphine drug liking mitigated by naltrexone HCl would be expected to reduce morphine abuse potential.

Figure 21: VAS DEQ Drug Liking Results: Study ALO-KNT-201



MOR=morphine sulfate immediate-release, NTX=naltrexone HCl

Figure 22: Cole/ARCI Stimulation-Euphoria Results: Study ALO-KNT-201



MOR=morphine sulfate immediate-release, NTX=naltrexone HCl

6.2.2. Single Dose Abuse Liability Study, Study ALO-01-07-106

Study ALO-01-106 provides evidence to determine the relative drug liking and euphoric effects of IV morphine alone or with IV naltrexone HCl.

The primary PD variable was the result of the VAS DEQ Question #5, “How high are you now?”. The secondary PD variable was the result of the Cole/ARCI Stimulation-Euphoria assessment. (See section 6.1.3 for details on the design of the study).

The Treatment Phase was comprised of 3 inpatient visits, each separated by a 1-week washout. Twenty-eight subjects were randomized to receive 1 of 3 treatments per visit for a total of 3 treatments, including morphine 30 mg, morphine 30 mg with co-administered naltrexone 1.2 mg (identical ratio of naltrexone to morphine 1:25, as in ALO-01 Capsule) , and placebo.

Intravenous administration was used to simulate and characterize the effect of naltrexone on the PD profile of morphine if oral ALO-01 pellets were crushed and injected. The effect of study medication on euphoria and positive effects was measured up to 24 hours postdose.

Summary of results:

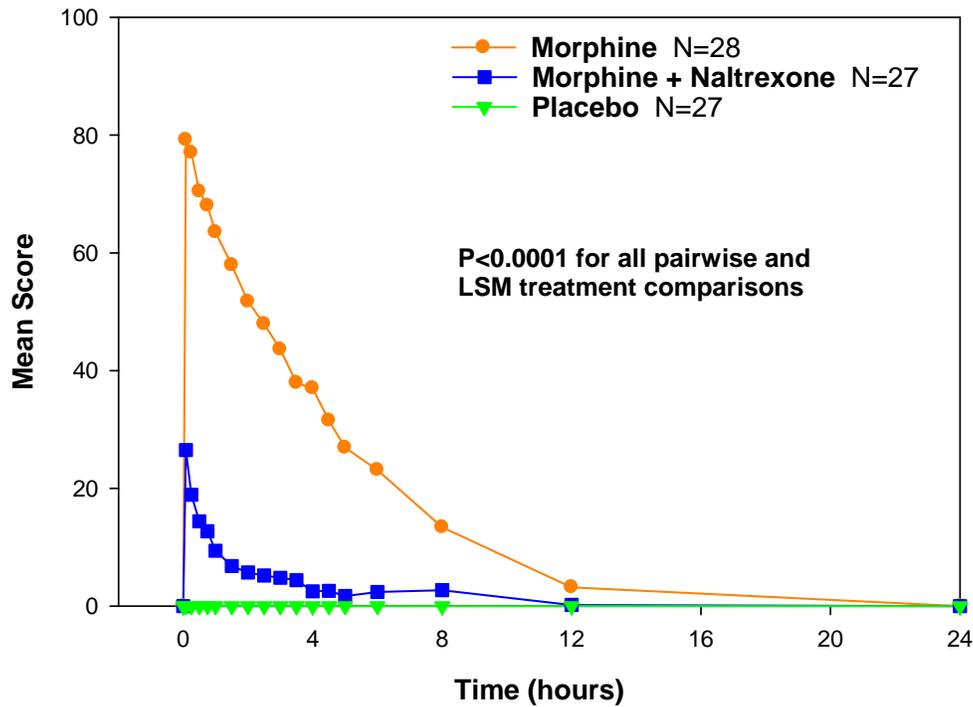
Morphine-induced response to the question “How high are you now?” was about 11-fold greater for morphine alone than morphine plus naltrexone (E_{max} geometric LSM: 84.2 vs 7.6 mm). Euphoric response, as determined by Cole/ARCI, was about 2-fold greater for morphine alone

than for morphine plus naltrexone (E_{max} LSM: 27.8 vs 13.7). The mean results for DEQ Question #5 and Cole/ARCI Stimulation–Euphoria are presented in Figure 20 and Figure 21 respectively.

Conclusions:

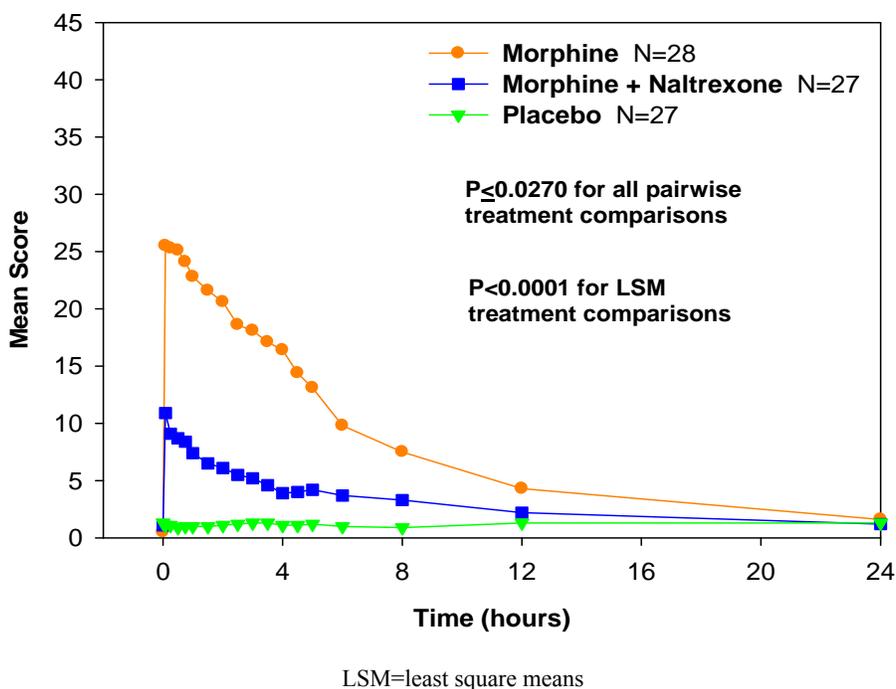
Intravenous morphine plus IV naltrexone, given in the same proportion as the ALO-01 Capsule formulation, reduced drug liking and euphoria compared to IV morphine alone. The study suggests that the selected naltrexone to morphine ratio (1:25) provides an adequate reduction of abuse potential.

Figure 23: VAS DEQ Question #5 “How High Are You Now?” Results: Study ALO-01-07-106



LSM=least square means

Figure 24: Cole/ARCI Stimulation-Euphoria Results: Study ALO-01-07-106



6.2.3. Euphoria Reduction MSIR vs Crushed ALO-01 Pellets, Study ALO-01-07-205

Study ALO-01-07-205 evaluates the relative PD effects of whole or crushed ALO-01 pellets compared with MSIR and placebo and of crushed ALO-01 pellets to whole ALO-01 Capsules

The primary PD variables included Drug Liking measured on a VAS, Subjective Drug Value, ARCI-MBG, Cole/ARCI-Abuse Potential, Cole/ARCI-Stimulation-Euphoria, and pupillometry.

The Treatment Period was comprised of 4 inpatient treatment sessions, each separated by a 14 to 21 day washout. Thirty-two opioid-experienced subjects were randomized to receive 1 of 4 treatments per visit for a total of 4 treatments, including whole ALO-01 (60 mg x 2 capsules), crushed ALO-01 (60 mg x 2 capsules), MSIR (120-mg solution), and placebo. The effect of study medication on subjective drug measures was assessed up to 24 hours postdose. (See section 6.1.4 for study design details).

Summary of results:

Administration of MSIR elicited a characteristic and expected increase in scores for subjective positive effects compared to placebo. Compared with MSIR, treatment with ALO-01 whole and crushed resulted in a reduced response on measures of positive effects, as shown in Figure 25 and Figure 26. Peak effects of ALO-01 were at 6-10 hr postdose, compared to the 1-1.5-hr peak for MSIR, suggesting ALO-01 may not provide immediate positive subjective effects.

Evaluation of the positive, negative, and other drug effects revealed that response patterns for ALO-01 whole and crushed were similar.

Conclusions:

Subjective positive effects after dosing with crushed or whole ALO-01 120 mg were significantly less than MSIR 120 mg, suggesting a lower abuse potential for ALO-01. Generally, there were no significant differences between ALO-01 whole and crushed on any subjective measure, suggesting a similar abuse potential whether ALO-01 is taken as directed (whole) or after tampering (crushed).

Figure 25: VAS Drug Liking Results: Study ALO-01-07-205

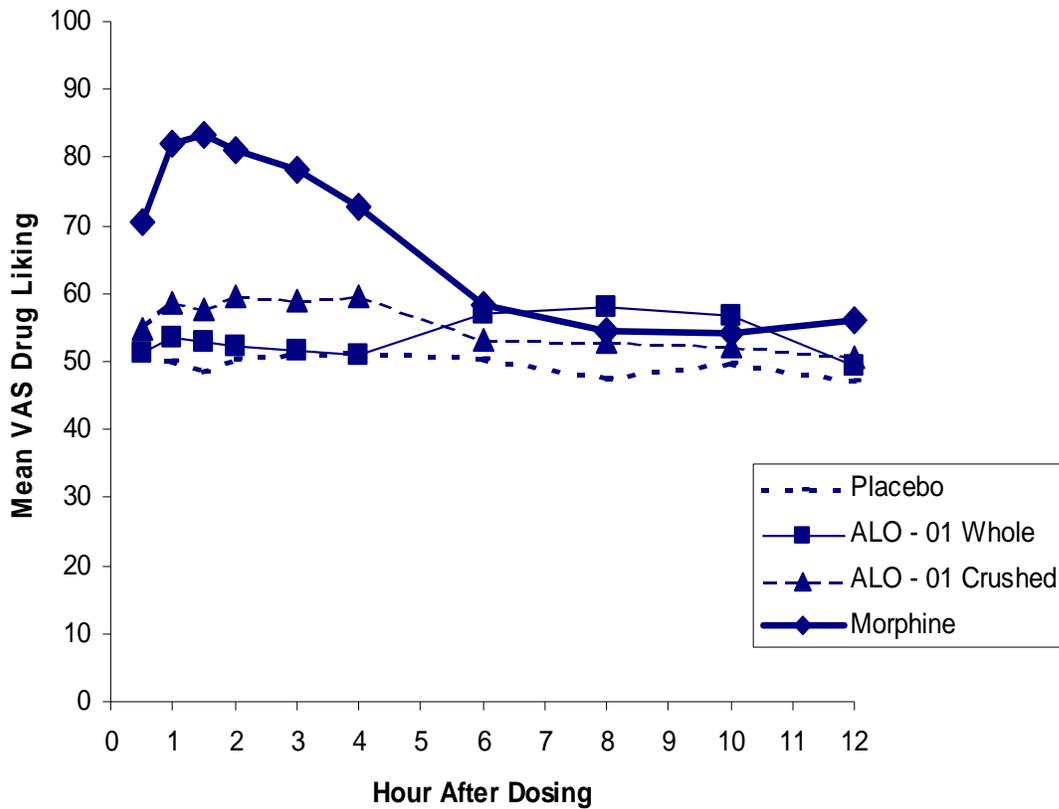
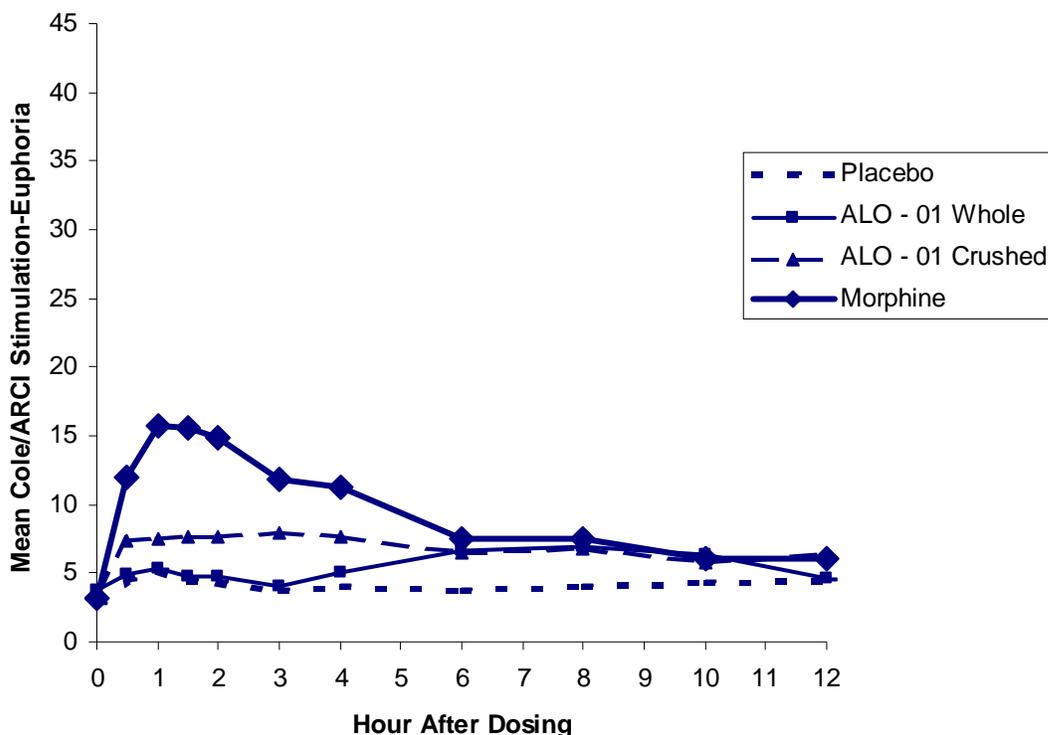


Figure 26: Cole/ARCI Stimulation-Euphoria Results: Study ALO-01-07-205



6.3. SUMMARY OF EFFICACY DATA

The efficacy of ALO-01 Capsules has been evaluated in three clinical trials (ALO-KNT-202, ALO-KNT-301, and ALO-KNT-302) in patients with chronic moderate to severe pain. These studies showed that ALO-01 is effective for the treatment of chronic pain as expected based on its morphine pharmacokinetics similar to KADIAN[®]. The studies also showed that the sequestered naltrexone in ALO-01 performed as designed and did not alter the safety or efficacy of ALO-01.

The 3 studies established the analgesic efficacy of ALO-01.

- In the pivotal double-blind Phase 3 Study ALO-KNT-301, ALO-01 treatment was statistically superior to placebo on the primary efficacy measure of mean change from randomization baseline to endpoint in in-clinic BPI average pain intensity score.
- In the double-blind Phase 3 Study ALO-KNT-301, ALO-01 treatment demonstrated statistically significantly greater efficacy than placebo on the secondary efficacy measures of worst, least, average and current BPI pain intensity scores.
- In the double-blind Phase 2 Study ALO-KNT-202, ALO-01 treatment demonstrated similar efficacy to KADIAN[®], an effective pain control agent, on the BPI pain intensity scores with no significant treatment differences.

- In the double-blind Phase 3 Study, ALO-KNT-301, ALO-01 treatment demonstrated statistically significantly greater efficacy than placebo on the secondary efficacy measures of WOMAC Osteoarthritis composite scores and pain subscale scores.
- In the open-label Phase 3 Study, ALO-KNT-302, ALO-01 treatment persistently reduced 24-hour pain scores over 1 year among patients who remained on the study.
- In the open-label Phase 3 Study, ALO-KNT-302, 94% of patients gave overall positive ratings of ALO-01 after 1 year of open-label treatment.

6.3.1. Overview of Studies of Moderate to Severe Chronic Pain

A total of 416 patients with moderate to severe chronic pain due to osteoarthritis of the hip or knee were randomized and treated with ALO-01, placebo, or KADIAN[®] in the double-blind period of two controlled studies. Of these 416 patients, 243 were treated with ALO-01 and assessed for efficacy. An additional 465 subjects were treated with ALO-01 in a long-term, Phase 3 open-label study of patients with nonmalignant chronic pain (conditions may have included, but were not limited to: osteoarthritis of any joint, chronic low back pain with or without radiculopathy, diabetic peripheral neuropathy, and post-herpetic neuralgia). Table 14 provides an overview of the design of all trials that collected efficacy data.

Table 14: Overall Study Design for Studies of Moderate to Severe Chronic Pain

Study Number Phase	Design	Treatment Duration*	Open-label Titration		Double-blind Treatment	
			Study Drug	N Treated	Treatment Group	N Treated
ALO-KNT-202 Phase 2	Randomized, double-blind, crossover following open-label titration with KADIAN [®] to evaluate efficacy	14 days	KADIAN [®]	111	KADIAN [®]	71
					ALO-01 40- 160 mg/day	71
ALO-KNT-301 Phase 3	Randomized, double-blind, parallel group following open-label titration with ALO-01 to evaluate efficacy	12 weeks	ALO-01 20- 160 mg/day	547	Placebo	173
					ALO-01 20-160 mg/ day	171
ALO-KNT-302 Phase 3	Open-label, uncontrolled, flexible-dose	12 months	ALO-01 No maximum dose	465	NA	NA

NA=not applicable

* Double-blind treatment periods for studies ALO-KNT-301 and ALO-KNT-202 are exclusive of pre-randomization open-label titration phases

6.3.1.1. Moderate to Severe Chronic Pain Due to Osteoarthritis of the Knee or the Hip

Studies ALO-KNT-202 and ALO-KNT-301 were two short-term, double-blind studies that assessed efficacy in patients with moderate to severe chronic pain due to osteoarthritis of the hip or knee. Both studies utilized enriched enrollment designs in which patients were titrated to an effective dose of open-label study drug (KADIAN[®] in Study ALO-KNT-202 and ALO-01 in Study ALO-KNT-301) prior to randomization. Study ALO-KNT-202 was a Phase 2 cross-over study primarily designed to assess the PK of multiple doses of ALO-01 that also assessed efficacy versus an effective pain control agent. ALO-KNT-301 was a Phase 3, placebo-controlled study designed to evaluate the efficacy of ALO-01 compared with placebo.

In both of these studies, the lowest mean pain scores for both treatment groups were expected at the end of the open-label titration (randomization baseline); minimal change from that baseline would indicate continuing control of pain while increases from baseline would indicate increased severity of pain.

6.3.1.2. Moderate to Severe Chronic Nonmalignant Pain

Long-term efficacy in patients with moderate to severe chronic nonmalignant pain was assessed in Study ALO-KNT-302, a Phase 3, open-label, flexible-dose study primarily designed to assess safety and as a secondary objective, efficacy. In this study, baseline scores were indicative of unmanaged pain, and decreases in score would indicate improvement in pain control

6.3.2. Demographic Characteristics of Moderate to Severe Chronic Pain Study Population

Table 15 describes the baseline demographic (age, body mass index [BMI], sex, history of opioid use) and baseline chronic pain characteristics in the Phase 2 and Phase 3 ALO-01 Capsules chronic pain studies. In summary:

- The mean ages of the patients enrolled in the short-term efficacy studies (55.7 years in ALO-KNT-301 and 55.6 years ALO-KNT-202) were somewhat older than the patients enrolled in the long-term safety (51.6 years).
- The majority of patients in the two double-blind studies at randomization were women (ranging from 54.9-69.4%). In the long-term open-label study, there were similar percentages of women (52.7%) and men (47.3%).
- The mean BMI varied across the three studies from 30.2 to 33.2 kg/m² at start of treatment.
- The majority of patients had not previously used opioids in Study ALO-KNT-301 at randomization (75%) or in Study ALO-KNT-302 (52.9%).
- In Study ALO-KNT-202 the mean in-clinic numerical pain score at the start of open-label titration was 7.1 and at randomization baseline was 2.13, indicating the patients had been titrated to an effective dose for pain management. In Study ALO-KNT-301 the mean in-clinic pain scores at randomization baseline were similar in the ALO-01 (3.3) and placebo (3.2) treatment groups.

- In the double-blind studies (202 and 301), which had open-label titration to an effective dose, the mean weekly “average” pain scores at randomization baseline indicated effective pain management, with the overall mean score for “average pain in the last 24 hours” ranging from 2.15 to 2.71. In Study ALO-KNT-301 the mean weekly “average” pain scores at randomization baseline were similar in the ALO-01 and placebo groups.
- For Study ALO-KNT-302, the overall mean pain score at baseline for “average” pain in the last 24 hours was 6.0.
- In the double-blind studies (202 and 301) assessing chronic osteoarthritis pain, the most commonly reported areas of chronic pain at randomization baseline were the right knee (about 45-48% of patients) and left knee (about 29-36%), and fewer than 14% of patients reported chronic pain in either the right or left hip.
- In the open-label study (302) assessing chronic nonmalignant pain, the most commonly reported chronic pain history was pain in the lower back (57.0 % of patients overall). Fewer than 10% of patients reported chronic pain due to arthralgia (of the hip or knee).

Table 15: Summary of Baseline Characteristics: All Studies of Moderate to Severe Chronic Pain

Characteristic	ALO-KNT-202		ALO-KNT-301			ALO-KNT-302
	Open-label KADIAN® N=111	Total Randomized N=72	Open-label ALO-01 N=547	ALO-01 N=171	Placebo N=173	Open-label ALO-01 N=465
Gender [n (%)]						
Male	35 (31.5)	22 (30.6)	215 (39.3)	65 (38.0)	78 (45.1)	220 (47.3)
Female	76 (68.5)	50 (69.4)	332 (60.7)	106 (62.0)	95 (54.9)	245 (52.7)
Age (years)						
Mean (SD)	56.8 (11.1)	55.6 (10.5)	55.7 (12.3)	54.2 (11.6)	54.7 (12.9)	51.7 (10.6)
BMI (kg/m²)						
N	N=111	N=72	N=530	N=167	N=167	N=465
Mean (SD)	32.4 (6.0)	33.2 (6.2)	32.1 (6.4)	32.5 (6.9)	31.8 (6.4)	30.2 (3.0)
Opioid History [n (%)]						
Naive	79 (71.2%)	52 (72.2%)	407 (75.4%)	125 (74.9%)	129 (75.4%)	168 (36.1%)
Experienced	32(28.8%)	20 (27.8%)	133 (24.6%)	42 (25.1%)	42 (24.6%)	297 (63.9%)
In-clinic BPI Pain Score[†]						
Mean (SD)	7.1 (1.5)	2.1 (1.0)	NA	3.3 (1.3)	3.2 (1.1)	NA*
BPI [mean (SD)]						
Worst	NA*	3.2 (1.6)	6.8 (1.7) [#]	3.7 (1.7)	3.3 (1.6)	7.5 (1.5)
Least	NA*	1.6 (1.2)	5.3 (2.2) [#]	2.1 (1.4)	1.9 (1.3)	4.5 (2.0)
Average	NA*	2.2 (1.2)	6.1 (1.9) [#]	2.7 (1.3)	2.5 (1.2)	6.0 (1.7)
Current	NA*	2.1 (1.5)	5.9 (2.1) [#]	2.6 (1.6)	2.3 (1.5)	5.9 (2.1)

NA=not assessed; BPI=Brief Pain Inventory,

* All BPI data collected at in-clinic visits for Study ALO-KNT-302; BPI worst, least, average and current pain data from patient diary in Studies ALO-KNT-202 and ALO-KNT-301

† Average pain score on the BPI recorded in-clinic at study visits

For this assessment, n=341; includes only patients with a titration baseline and final baseline

Source: ISS, Study 302, Study 301, Study 202

6.3.3. Overview of Efficacy Assessments

A summary of the efficacy assessments in the studies of moderate to severe chronic pain are presented in Table 16.

Table 16: Major Efficacy Assessments in Studies of Moderate to Severe Chronic Pain

Efficacy Assessment	Phase 3 Efficacy ALO-KNT-301	Phase 2 PK ALO-KNT-202*	Phase 3 Safety ALO-KNT-302*
Primary Efficacy			
Diary BPI average pain intensity over entire double-blind period	X		
Secondary Efficacy			
Diary BPI worst, least, average, and current pain intensity	X	X	
In-clinic BPI average pain intensity	X		X
Proportion of responders	X		
In-clinic worst, least, average, and current pain intensity (mean)			X
WOMAC Osteoarthritis Index	X	X	
Pain, stiffness, physical function, composite scores			
MOS Sleep Scale	X		
7 subscale and overall scores			
Beck Depression Inventory	X		
Rescue medication usage	X	X	X

WOMAC=Western Ontario and McMaster Universities, MOS=Medical Outcomes Study, BPI=Brief Pain Inventory

* All efficacy assessments were considered secondary to the primary PK objective or safety objective

6.3.3.1. Brief Pain Intensity Short Form Questionnaire

In Studies ALO-KNT-202, ALO-KNT-301 and ALO-KNT-302, pain intensity was assessed using the Brief Pain Inventory (or BPI) Short Form questionnaire. The BPI scores were recorded on an 11-point scale (0 = no pain to 10 = pain as bad as you could imagine). In Studies ALO-KNT-202 and ALO-KNT-301, the BPI scores were recorded daily in the subject electronic diary and recorded at in-clinic visits. Diary BPI assessed worst pain in the last 24 hours, least pain in the last 24 hours, the average pain over 24 hours, and current pain at the time of the assessment, with the daily scores averaged over 7-day intervals to obtain weekly scores. The in-clinic BPI assessed average pain within the past 24 hours at the times of the scheduled visits. In Study ALO-KNT-302, worst, least, average and current pain scores were recorded at in-clinic visits.

6.3.3.2. Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index

Studies ALO-KNT-202 and ALO-KNT-301 used the WOMAC Osteoarthritis Index, an instrument designed to measure impact of intervention on osteoarthritis. The WOMAC Osteoarthritis Index had 3 subscales (pain, stiffness, and physical function) and a composite score. In both studies, higher scores indicated greater severity of symptoms. However, the 2 studies used different methodology in obtaining the scores. In Study ALO-KNT-202 patients responded to each question on the 3 subscales using a 100 mm Visual Analog Scale (VAS), where 0 = none and 100 = extreme pain/stiffness/difficulty. The composite score was the sum of the subscale scores. The total possible scores for WOMAC Osteoarthritis Index in Study ALO-KNT-202 are presented in Table 17.

Table 17: WOMAC Osteoarthritis Index in Study ALO-KNT-202

Scale (100 mm VAS)	Number of Questions	Total Possible Score
Pain	5	500
Stiffness	2	200
Physical Function	17	1700
Composite	24	2400

VAS=Visual Analog Scale; WOMAC=Western Ontario and McMaster Universities

In Study ALO-KNT-301, patients filled out a questionnaire with a 5 point scale, where 0 = none and 4 = extreme pain/stiffness/difficulty. Scores were summed within each subscale and overall in the composite score, and were then normalized such that the maximum score was 100 for each of the subscales and for the composite score.

6.3.3.3. Global Assessments

Study ALO-KNT-301 used the PGIC, which assessed the patient's global assessment of the change in their condition from baseline using a 7-point scale, ranging from 1 (very much improved) to 7 (very much worse).

Studies ALO-KNT-202 and ALO-KNT-302 used the Subject's Global Impression of Study Medication rating. Patients rated the medication on a 5-point scale ranging from 1 (poor) to 5 (excellent).

6.3.3.4. Other Efficacy Assessments

Study ALO-KNT-301 assessed the effect of analgesia on sleep and depression. The MOS Sleep Scale has 7 subscales (sleep disturbance, snoring, awaken short of breath or with a headache, quantity of sleep, optimal sleep, sleep adequacy, and somnolence), with higher scores indicating more impairment in all subscales except for sleep adequacy, where a higher score indicated less impairment. The Beck Depression Inventory evaluated the presence and degree of depression (<15 = mild depression, 15 to 30 = moderate depression, and >30 = severe depression).

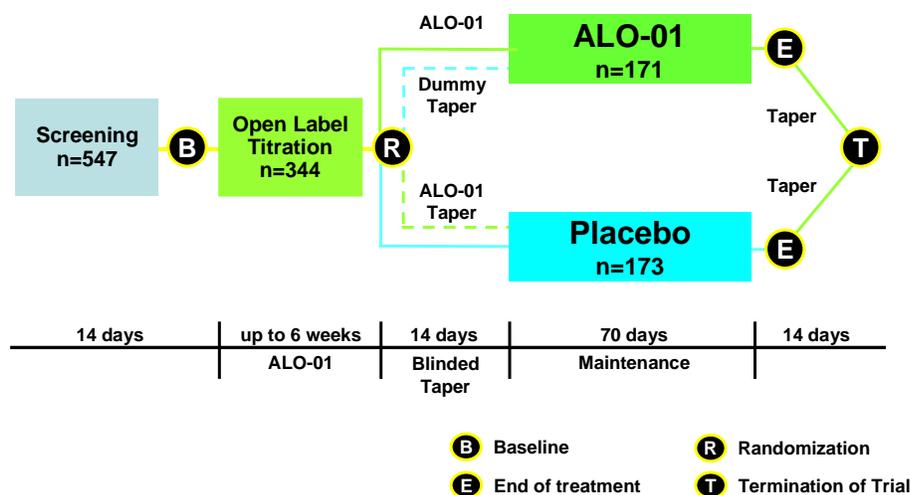
6.3.3.5. Rescue Medication Usage

Patients were asked to report all rescue medication use, which was provided by the study site as up to 2 g/day OTC-formulated acetaminophen. In Study ALO-KNT-202, the proportion of patients who used rescue medication was assessed. In Studies ALO-KNT-301, the mean number of tablets used per week was determined, while in ALO-KNT-302, the average daily dose in mg was calculated.

6.3.4. Study ALO-KNT-301

6.3.4.1. Study Design

Figure 27: Study ALO-KNT-301 Design: Enriched Enrollment, Randomized Withdrawal



Subjects with osteoarthritis of the hip or knee

After Screening and a washout interval, patients entered an open-label Titration Phase where they received ALO-01 BID. During titration, each subject's dose was adjusted to the optimal level required for pain management.

Patients who completed the open-label Titration Phase entered the double-blind Maintenance Phase and were randomized to receive either the same effective dose of ALO-01 achieved in the Titration Phase or placebo. Randomized patients were tapered gradually (in a blinded fashion, using a double-dummy design) to achieve the assigned treatment and all patients, whether receiving ALO-01 or placebo, were assessed for signs of withdrawal during the taper.

Baseline efficacy data were recorded at the start of the open-label (screening baseline, Visit X) and at randomization to the double-blind phase (randomization baseline, Visit Y). During the 12-week double-blind treatment, efficacy data were collected at clinic visits at Weeks 1, 2, 4, 6, 8, 10, and 12.

The primary efficacy measure was the change from randomization baseline (Visit Y) to the end of the double-blind Maintenance Phase (Visit Y+12 Weeks) on the Brief Pain Inventory (BPI) average pain score (daily scores of the BPI average pain evaluation were averaged for each patient over a 7-day interval to obtain a weekly score), recorded in the patient diary. For patients who completed the study, the final 7-day interval on study was used.

The following imputation rules were used for patients who discontinued early from the study:

- Screening baseline was imputed for discontinuations due to adverse events; this rule assigned no efficacy benefit to study drug if the patient discontinued due to an AE.
- If the results of the Clinical Opiate Withdrawal Scale (COWS) questionnaire at discontinuation were worse than at randomization baseline (Visit Y) and indicated at least a moderate (score ≥ 13) level of withdrawal symptoms, the following imputation rules were used:
 - For placebo, the randomization baseline value (Visit Y) was imputed for the Maintenance Week Y+12 value; this rule applied regardless of discontinuation reason and assigned full efficacy benefit.
 - For ALO-01, the weekly diary BPI average pain score during the last 7 days on study was imputed for discontinuations in the group due to lack of efficacy or administrative reasons; screening baseline was imputed for discontinuations due to AEs; this rule assigned a score that was worse than the randomization baseline score for patients who reported at least moderate levels of withdrawal symptoms.

The weekly diary BPI average pain score during the last 7 days on study was imputed for discontinuations due to lack of efficacy or administrative reasons; this rule assigned the actual pain reported at discontinuation, which was expected to be worse than randomization baseline but less severe than screening baseline, regardless of treatment.

Where the average of the last 7 days of Maintenance Phase was used for imputation, it included the last 7 days of diary data up to and including the Termination Visit (if applicable). Missing values were imputed with Last Observation Carried Forward (LOCF).

6.3.4.2. Primary Efficacy Measure: Change from Baseline in Diary BPI Average Pain Over the Entire Maintenance Phase

- All protocol-specified sensitivity analyses supported and were directionally consistent with the primary efficacy endpoint results. The observed pattern of statistically significant treatment group differences is a consequence of group differences in discontinuations due to lack of efficacy (3.5% for ALO-01 vs 18.5% for placebo).

The mean change from randomization baseline (Visit Y) to the Visit Y+12 Weeks weekly diary BPI average pain score was statistically significantly superior for the ALO-01 treatment group (-0.2) compared to the placebo group (0.3) (Table 18).

Table 18: Mean Change in BPI Average Pain Intensity from Baseline to 12 Weeks

Average Pain Assessment	Treatment Group				P-value
	Placebo		ALO-01		
	N	Mean (SD)	N	Mean (SD)	
Primary Imputation Method					
Baseline	173	3.2 (1.07)	170	3.3 (1.30)	
Visit Y+12 Weeks [†]	173	3.5 (2.13)	170	3.1 (1.99)	
Change from Baseline to Visit Y+12 Weeks	173	0.3 (2.05)	170	-0.2 (1.94)	0.045*
Protocol-specified Sensitivity Analyses					
Randomization Baseline [1]					
Visit Y+12 Weeks	173	3.1 (1.58)	170	2.9 (1.59)	
Change from Baseline to Visit Y+12 Weeks	173	-0.2 (1.32)	170	-0.4 (1.34)	0.122
Screening or Randomization Baseline [2]					
Visit Y+12 Weeks	173	3.9 (2.38)	170	3.3 (2.13)	
Change from Baseline to Visit Y+12 Weeks	173	0.7 (2.17)	170	0.0 (1.91)	0.005
Screening Baseline[3]					
Visit Y+12 Weeks	173	4.3 (2.49)	170	3.9 (2.54)	
Change from Baseline to Visit Y+12 Weeks	173	1.1 (2.37)	170	0.6 (2.31)	0.049

Pain intensity scale=11-point scale, where 0 = no pain and 10 = worst pain (“pain as bad as you can imagine”)

Visit Y=randomization baseline (following screening, titration, baseline, and open-label titration)

* Means and standard deviations from ANCOVA model with treatment as categorical factor and randomization baseline score as a covariate

† Primary imputation method

[1] Discontinuation were imputed with randomization baseline

[2] Discontinuations due to AE or loss of efficacy were imputed with screening baseline, and discontinuation due to other reasons were imputed with randomization baseline

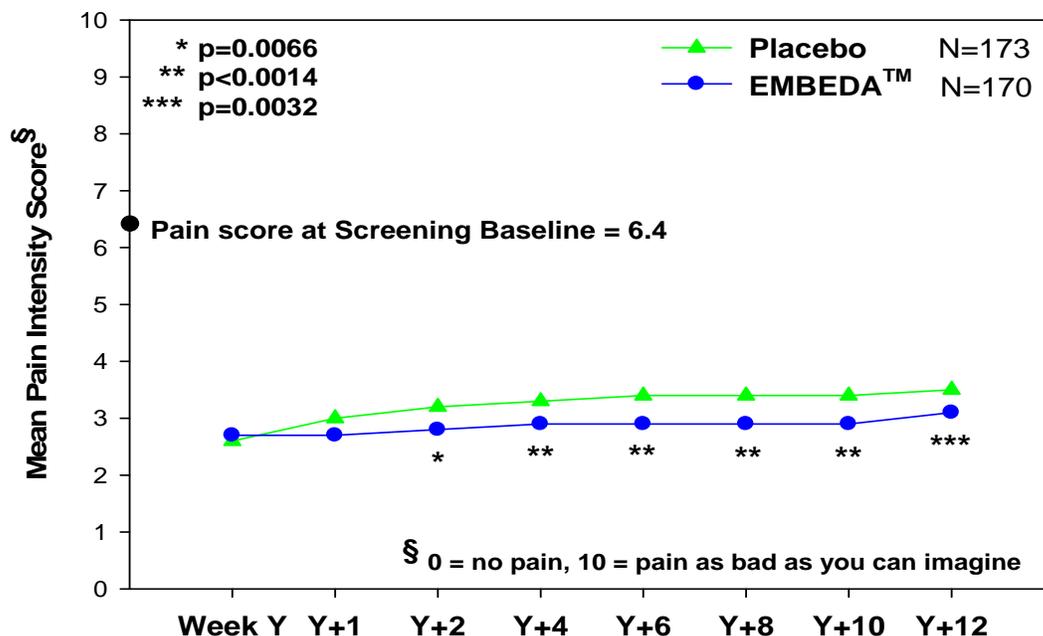
[3] Discontinuations were imputed with screening baseline.

6.3.4.3. Secondary and Other Efficacy Measures

The mean change from Baseline in worst, least, average and current pain was statistically significantly smaller in the ALO-01 treatment group compared to placebo throughout the Maintenance Phase when analyzed using the repeated measures model. This indicates a lesser pain increase after the end of open-label ALO-01 treatment.

Figure 28 shows the mean daily average pain for patients on Study ALO-KNT-301 within the intent-to-treat (ITT) Population, demonstrating statistical significance from Week Y+2 through the study endpoint, Week Y+12, between ALO-01 and placebo treatment groups.

Figure 28: Daily Average Pain: Study ALO-KNT-301 (ITT Population)



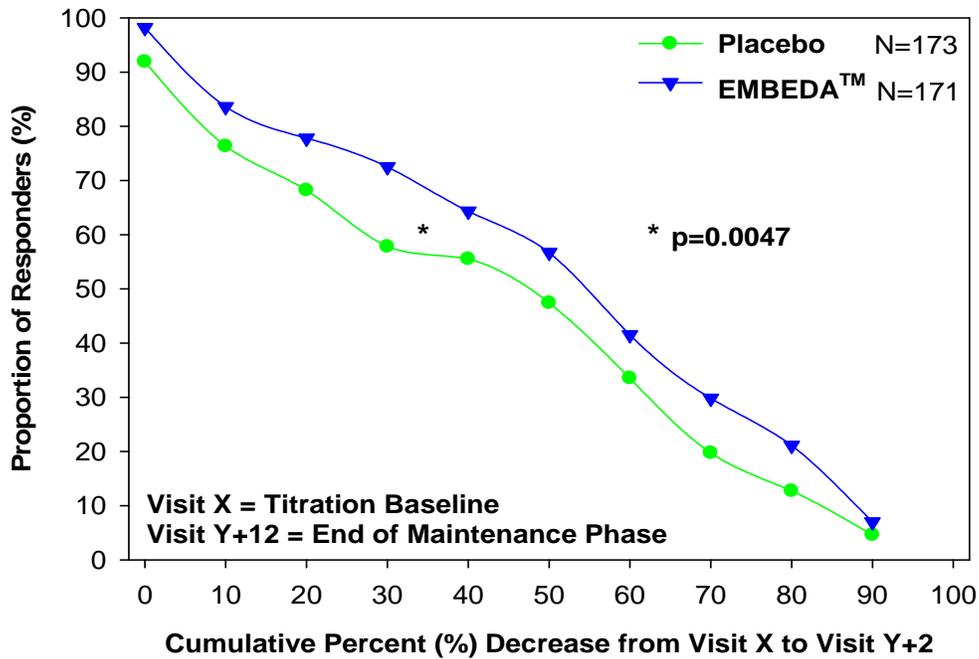
The proprietary name of ALO-01, EMBEDA™, is under FDA review at time of issuing this document.

6.3.4.4. Proportion of Responders Based on In-Clinic Average BPI

Patients were defined as responders by the percent decrease from screening baseline to week 12 of the maintenance phase on the in-clinic 24-hour pain assessment. Patients who discontinued from the study before week 12 were imputed with the LOCF.

- A greater proportion of patients in the ALO-01 treatment group compared to the placebo group reported at least 20%, 30%, 40%, and 50% improvement from screening baseline to endpoint. The proportion of patients who reported $\geq 30\%$ improvement was statistically significantly greater in the ALO-01 treatment group (72.5%) compared to placebo (57.8%) (P=0.0047) (Figure 29).

Figure 29: Proportion of Responders: Study ALO-KNT-301 (ITT Population)

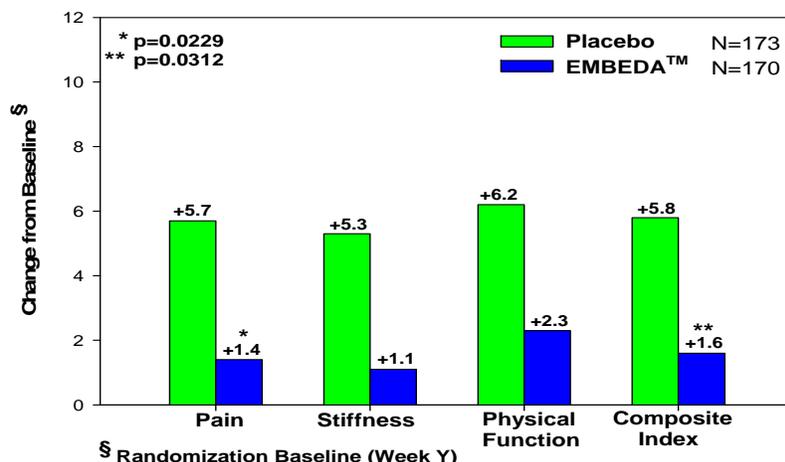


The proprietary name of ALO-01, EMBEDA™, is under FDA review at time of issuing this document.

6.3.4.5. WOMAC Osteoarthritis Index Scores

In Study ALO-KNT-301, the changes from baseline in WOMAC Osteoarthritis Index composite and subscale scores showed smaller increases in severity of scores for the ALO-01 treatment group compared to placebo. The treatment difference was statistically significant for the pain subscale and the composite scale. (Figure 30)

Figure 30: Change from Baseline on WOMAC Osteoarthritis Index Scores: Study ALO-KNT-301 (ITT Population)



The proprietary name of ALO-01, EMBEDA™, is under FDA review at time of issuing this document.

6.3.4.6. Patient Global Impression of Change

At the end of the double-blind treatment period, the proportion of patients who assessed their impression of change favorably (very much improved or much improved) was 44.4% and 38.2% in the ALO-01 and placebo groups, respectively, but the treatment difference was not statistically significant.

6.3.4.7. MOS Sleep Scale

For the MOS Sleep scale, higher scores reflected more impairment in all subscales except for sleep adequacy and sleep quality, where a higher score reflects less impairment.

No statistically significant treatment group differences were observed; however, there was numerically less impairment for patients in the ALO-01 treatment group compared to placebo for the sleep disturbance, sleep adequacy and somnolence subscales.

6.3.4.8. Beck Depression Inventory

In this study, patients with Beck Depression score ≥ 18 at Baseline were excluded from the study, and the mean baseline scores indicated only mild (< 15) depression in the ALO-01 (5.5) and the placebo (4.7) groups. Consequently, it would have been difficult to demonstrate significant improvement.

- The mean decrease from baseline to Week 12 was greater for patients in the ALO-01 (-1.4) treatment group compared to placebo (-0.9), indicating a greater reduction in depression, although the difference was not statistically significant.

6.3.4.9. Use of Paracetamol as Rescue Medication

Seventy-five percent (75%) ALO-01 group patients received at least one dose of rescue medication from breakthrough pain during double-blind treatment compared to 72% placebo group patients. Among patients who used rescue medication, the overall usage was lower in the ALO-01 treatment group compared to placebo (median: 2.4 and 4.4 tablets/week, respectively).

6.3.5. Study ALO-KNT-202

See Section 6.1.5 for details on the study design.

Baseline efficacy data were recorded at randomization to the initial double-blind treatment (randomization baseline); this was considered the baseline for the second double-blind treatment as well. During each 14-day double-blind period, efficacy data were collected at clinic visits on Days 1, 7, and 14.

6.3.5.1. Secondary Efficacy and Other Efficacy Measures

For the ITT population, the in-clinic pain assessment mean scores at double-blind Days 7 and 14 were similar for ALO-01 and KADIAN[®] treatment, and the treatment difference (ALO-01 treatment – KADIAN[®] treatment) was 0.0 on Day 7 and -0.2 on Day 14 (Table 19). The mean changes from baseline (Period 2, Day 1) for the in-clinic pain scores were small for each treatment, and no statistically significant difference was noted between the treatments ($p = 0.69$ for Day 7; $p = 0.31$ for Day 14).

In-clinic pain scores are summarized by treatment for the ITT population in Table 19.

Table 19: Summary of In-clinic Pain (LOCF), Study ALO-KNT-202 ITT Population

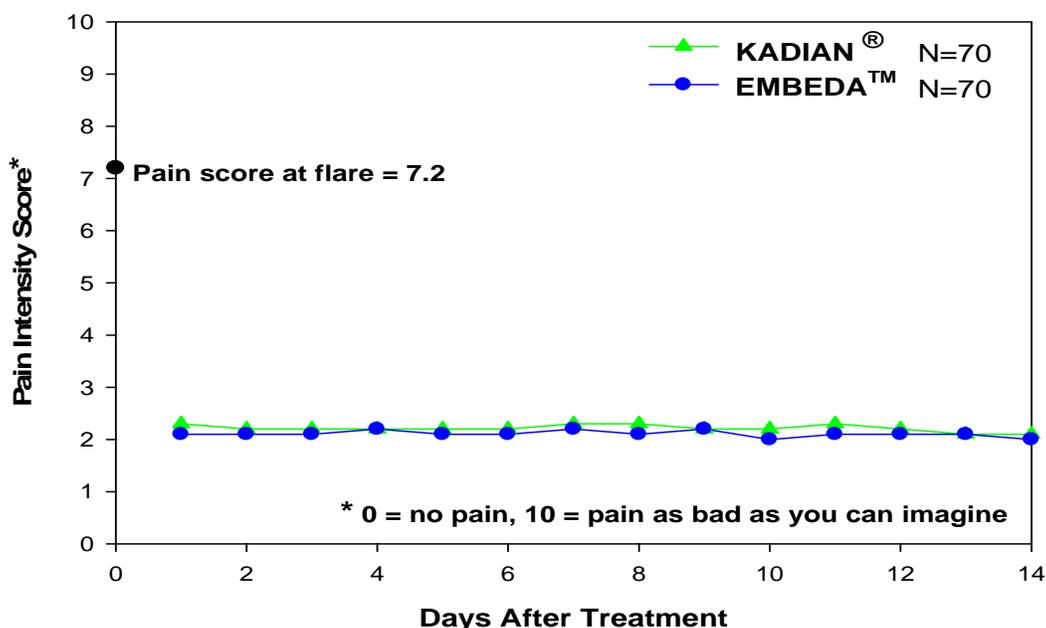
Time point Statistic	KADIAN [®]		ALO-01		Treatment Difference ^d	p-value ^e Treatment
	Baseline ^a	Observed ^b	CFB ^c	Observed ^b		
Day 7						
N	71	71	70	70	69	0.69
Mean	2.1	2.3	0.2	2.4	0.3	0.0
SD	1.03	1.26	1.15	1.60	1.46	1.36
Minimum	0	0	-3	0	-2	-3
Median	2.0	2.0	0.0	2.0	0.0	0.0
Maximum	4	5	3	8	5	4
95% CI ^e						(-0.27, 0.41)
Day 14						
N		71	70	71	70	0.31
Mean		2.4	0.3	2.3	0.1	-0.2
SD		1.27	1.26	1.52	1.51	1.42
Minimum		0	-2	0	-3	-4
Median		2.0	0.0	2.0	0.0	0.0
Maximum		6	3	8	5	4
95% CI ^e						(-0.54, 0.17)

Abbreviations: CI = Confidence interval; CFB = Change from baseline; ITT = intent-to-treat; LOCF = last observation carried forward; SD = standard deviation.

- a Baseline is Period 2, Day 1.
- b Higher scores indicate greater severity of symptoms.
- c CFB = the observed value at the current time point – the observed value at baseline. CFB was calculated on an individual patient basis, and then summary statistics were calculated. Results in this column cannot be obtained by subtracting the summary results of the observed value at baseline from the summary results of the value at the current time point.
- d Treatment difference (ALO-01 – KADIAN[®]) was calculated on an individual patient basis, and then summary statistics were calculated. Results in this column cannot be obtained by subtracting the summary results for KADIAN[®] from the summary results for ALO-01.
- e ANOVA model with CFB as response; Sequence, Period, and Treatment as fixed effects; Patientwithin Sequence as random effect; Day 0 and Baseline in-clinic pain as covariates.

Figure 31 shows the mean daily average pain for patients on Study ALO-KNT-202 within the ITT Population; there was no statistically significant difference between pain intensity scores for ALO-01 and KADIAN[®] treatments.

Figure 31: Daily Average Pain: Study ALO-KNT-202 (ITT Population, LOCF)



The proprietary name of ALO-01, EMBEDA[™], is under FDA review at time of issuing this document.

WOMAC Osteoarthritis Index Scores

The changes from baseline in WOMAC Osteoarthritis Index composite and subscale scores showed increases in severity of scores for both treatments, with smaller changes from baseline seen for the ALO-01 treatment; none of the changes were statistically significant.

Patient's Global Assessment of Study Medication

A higher percentage of patients rated the study medication positively (good, very good, or excellent) in the ALO-01 treatment group (65/71, 91.5%) compared to placebo (56/71, 78.9%)

Use of Paracetamol as Rescue Medication

The majority of patients used rescue medication during double-blind treatment, with a higher proportion of patients using rescue medication during KADIAN[®] treatment (41/71 patients, 57.7%) compared to ALO-01 treatment (36/71 patients, 50.7%).

6.3.6. Study ALO-KNT-302

See Section 6.1.6 for details on the study design.

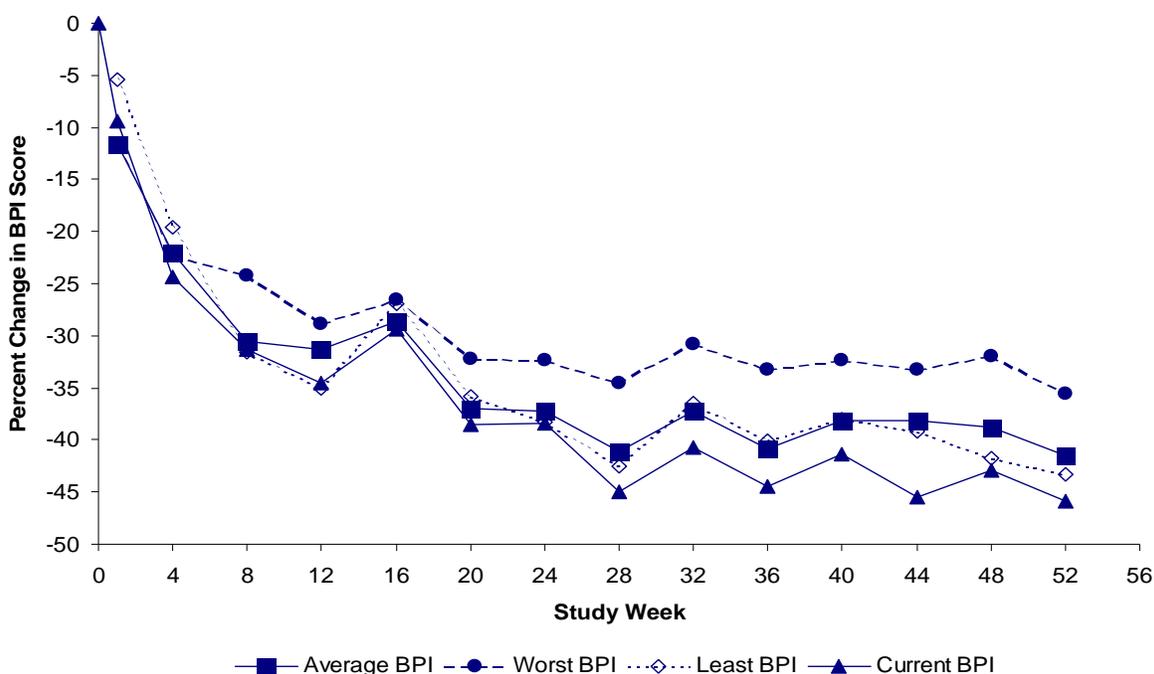
Efficacy data were collected at Baseline and at clinic visits in Weeks 1 and 4, then monthly up to Month 12.

6.3.6.1. Secondary Efficacy and Other Efficacy Measures

There were statistically significant mean percent decreases from baseline among all patients in average, worst, current, and least pain. The mean percent decreases for some parameters occurred as early as Week 1 and at each assessment up to 1 year. Among the patients who remained on the study, the magnitude of the mean improvement tended to increase over time through week 28 and stabilized thereafter through week 52, indicating the persistence of efficacy up to 1 year.

Mean percent changes in the BPI for average pain, worst pain, least pain, and current pain are summarized in Figure 32.

Figure 32: Percent Change in BPI Average, Worst, Current, and Least Pain at Each Visit in Study ALO-KNT-302 (ITT Population)



6.4. SUMMARY OF SAFETY DATA

Twelve studies contributed information regarding the safety of ALO-01 Capsules. These studies enrolled a total of 1253 patients, 1251 of whom received at least 1 dose of ALO-01.

Safety data from Phase 1 Studies ALO-KNT-201, ALO-01-07-106, and ALO-01-07-107 are not included in this document, as none of these studies evaluated the proposed commercial formulation (see section 4.5 Clinical Development Program). Safety data of other studies performed with healthy volunteers are briefly summarized in the section herein.

The overall conclusions about the safety data are:

- ALO-01 appeared to be safe and well tolerated in patients who were treated for moderate or severe pain for up to 12 months.
- Adverse events reported in $\geq 5.0\%$ of all ALO-01 patients in the clinical program were consistent with the well-known adverse reactions associated with morphine, including constipation, nausea, vomiting, somnolence, headache, diarrhea, and pruritus.
- The incidence of Serious Adverse Events (SAE) was low, and there was no trend for any specific adverse event. Three patients (1 placebo and 2 ALO-01) experienced SAEs considered possibly or probably related to study drug. In Study ALO-KNT-301, 1 ALO-01 subject experienced severe hypotension (probably related) during the Titration Phase and 1 placebo patient experienced severe abdominal pain (possibly related) during the Maintenance Phase. In Study ALO-KNT-302, 1 ALO-01 patient reported severe, (possibly related) SAEs of gastrointestinal inflammation and colitis.
- Evaluations of safety laboratory tests, vital signs, and ECGs revealed no clinically significant findings.
- There was no evidence of withdrawal symptoms resulting from the negligible exposure of sequestered naltrexone in subjects exposed to ALO-01 throughout the clinical program.

6.4.1. Statistical Methodology

Data are summarized and presented side by side for the studies. Limited pooling across studies is provided where appropriate. The method of pooling is provided in the footnote of the pooled table. All patients who received at least 1 dose of study medication in any of the 3 studies were included in the analysis population.

6.4.2. Exposure to the Drug

A total of 1253 subjects/patients were enrolled in the ALO-01 clinical program; 1251 received at least 1 dose of study drug and were included in the safety population.

Table 20: Number of Unique Subjects/Patients Exposed to ALO-01 in the Clinical Development Program - Safety Population

Study	Number of Subjects/Patients Exposed
Phase 1	
20-903-AU	8
ALO-01-07-101	36
ALO-01-07-102	36
ALO-01-07-103	32
ALO-01-07-104	24
ALO-01-07-205	32
Phase 2/3	
ALO-KNT-202	71 ^b
ALO-KNT-301	547
ALO-KNT-302	465 ^a
Total	1251

- a. A total of 467 patients were enrolled in Study ALO-KNT-302. Two of the 467 patients were not dosed.
 b. A total of 72 patients were randomized in Study ALO-KNT-202. One of the patients was not dosed with ALO-01.

The number of patients exposed to ALO-01, KADIAN[®], and placebo in the Phase 2/3 studies is presented in Table 21.

Table 21: Enumeration of Patients- All Phase 2/3 Studies - Safety Population

Protocol	Double-Blind ^a			Open ^b	
	ALO-01	KADIAN [®]	Placebo	ALO-01	KADIAN [®]
ALO-KNT-202	71	71			111
ALO-KNT-301	171		173	547	
ALO-KNT-302				465 ^c	
Total	242	71	173	1012	111

- a. Includes only the double-blind data from each study.
 b. Includes open KADIAN[®] periods from Study ALO-KNT-202 and open ALO-01 periods from Studies ALO-KNT-301 and ALO-KNT-302.
 c. Two additional patients were enrolled and not dosed.

Each of the blinded, short-term studies utilized enriched enrollment designs in which each patient was individually titrated to identify an effective dose providing adequate analgesia without intolerable side effects. The similarity in the Titration Phases of the studies was evident based upon median duration of exposure to open label study drug in Study ALO-KNT-202 (KADIAN[®]; 11.0 days) and in Study ALO-KNT-301 (ALO-01; 15.0 days).

6.4.3. Number of Patients Exposed to Various Doses for Defined Periods

Of the 1251 patients/patients included in this safety summary, 11 patients in Study 301 and 9 patients in Study 302 did not have enough dosing information to categorize total cumulative dose or exposure time. Eight subjects enrolled in Phase 1 Study 20-903-AU were not included because no electronic database existed for the study. These subjects were to receive a single dose of 60 mg.

Among the 1223 subjects/patients with ALO-01 dosing information in the clinical program, the total cumulative dose was ≤ 0.5 g for 347 subjects/patients. For the majority of subjects/patients (779/1223; 63.7%), the total cumulative dose was ≤ 5.0 g. The total number of subjects exposed to ALO-01 in Phase 2/3 studies (202, 301, 302) was 1083. When the 20 subjects without adequate dosing information are removed the total is 1063. A summary of duration of exposure to ALO-01 in the Phase 2/3 clinical program by total cumulative dose is presented in Table 22.

Table 22: Summary of ALO-01 Dose and Exposure, Phase 2/3 Studies (Safety Population)

	Total Dose (mg) Received								Subtotal
	≤ 0.5	$>0.5-1.0$	$>1.0-5.0$	$>5.0-10$	$>10-20$	$>20-50$	$>50-100$	>100	
Duration (days) of Exposure									
1	12	1							13
2-10	138	7	3						148
11-30	33	75	114	2	1				225
31-90	2	12	144	27	9				194
91-180	2		75	119	70	8	1		275
181-360			1	4	31	39	6	3	84
≥ 361				3	36	63	19	3	124
Subtotal	187	95	337	155	147	110	26	6	1063

Note: Including Studies 202, 301, and 302.

Eleven subjects from Study 301 and 9 subjects from Study 302 are excluded due to incomplete dosing information.

6.4.4. Disposition of Subjects

6.4.4.1. Healthy Volunteer Studies

Two subjects prematurely discontinued from study drug due to an AE across the five Phase 1 studies.

6.4.4.2. Blinded, Short-Term (2- to 12- Week Studies (Study ALO-KNT-202 and Study ALO-KNT-301))

A total of 113 patients were enrolled in Study 202 and 111 patients received at least 1 dose of study drug (either KADIAN[®] or ALO-01). A total of 547 patients were enrolled in the Titration Phase of Study 301 and received at least 1 dose of study drug. The similarity in the Titration Phase of the studies was evident based upon the proportions of patients who completed the Titration Phase of Study 202 (61.1%; 69/111) and Study 301 (62.9%; 344/547). In both studies, the most common reason for discontinuation from the Titration Phase was adverse events (25.7% and 22.7%, respectively) (Table 23).

A total of 72 patients were randomized and received at least 1 dose of randomized study drug in Study 202. Of the 72 randomized patients, 35 were randomized to KADIAN[®] followed by ALO-01 and 37 were randomized to ALO-01 followed by KADIAN[®].

Three patients discontinued the study after randomization. One patient (202-004-9419) discontinued following dosing with KADIAN[®], due to constipation. One patient (202-005-9521) discontinued following dosing with ALO-01 due to fatigue, crying, headache, somnolence, asthenia, and vomiting. One patient (202-008-9808) discontinued after receiving both ALO-01 and KADIAN[®] (titration) due to a family emergency. Two overlapping groups of 71 patients each received at least 1 dose of ALO-01 and at least 1 dose of KADIAN[®] during the double-blind phase.

A total of 344 patients (173 placebo and 171 ALO-01) were enrolled in the Maintenance Phase of Study 301 and received at least 1 dose of study drug (Table 23). A total of 56.6% (98/173) of patients in the placebo treatment group and 64.3% (110/171) of patients in the ALO-01 treatment group completed the Maintenance Phase. The most common reasons for discontinuation were lack of efficacy (18.5% placebo, 3.5% ALO-01), adverse events (7.5% placebo, 10.5% ALO-01), and patient withdrew from study (6.9% placebo, 8.8% ALO-01).

Table 23: Patient Disposition – Discontinuation of Study Drug Blinded, Short-Term Studies 202 and 301

	Double-Blind ^a (Maintenance Phase)				Open-label (Titration Phase)	
	Study ALO-KNT-202		Study ALO-KNT-301		Study ALO-KNT-301	Study ALO-KNT-202
	ALO-01	KADIAN [®]	ALO-01	Placebo	ALO-01	KADIAN [®]
Number of Patients Enrolled	72 (100)	72 (100)	171 (100)	173 (100)	547 (100)	113 (100)
Number of Patients in Safety Population	71 (98.6)	71 (98.6)	171 (100)	173 (100)	547 (100)	111 (98.2)
Number of Patients Completing Study	69 (95.8)		110 (64.3)	98 (56.6)	344 (62.9)	69 (61.1)
Reasons for Discontinuation	1 (1.4)	2 (2.8)	61 (35.7)	75 (43.4)	203 (37.1)	44 (38.9)
Adverse Event	1 (1.4)	1 (1.4)	18 (10.5)	13 (7.5)	124 (22.7)	29 (25.7)
Death	0	0	0	0	0	0
Did not Meet Inclusion/Exclusion Criteria	0	0	1 (0.6)	2 (1.2)	14 (2.6)	2 (1.8)
Investigator’s Discretion	0	0	3 (1.8)	0	4 (0.7)	1 (0.9)
Lack of Efficacy	0	0	6 (3.5)	32 (18.5)	22 (4.0)	0
Lost to Follow-Up	0	0	3 (1.8)	2 (1.2)	4 (0.7)	2 (1.8)
Non-Compliance	0	1 (1.4)	9 (5.3)	6 (3.5)	9 (1.6)	2 (1.8)
Pregnancy	0	0	0	0	0	0
Patient Withdrew from Study	0	0	15 (8.8)	12 (6.9)	21 (3.8)	0
Patient Withdrew Consent	0	0	0	0	0	3 (2.7)
Termination of Study or Withdrawal of Patient by the Sponsor	0	0	0	0	0	1 (0.9)
Other	0	0	6 (3.5)	8 (4.6)	5 (0.9)	4 (3.5)

a. Includes only the double-blind data from each study.

Source: ISS

6.4.4.3. Long-Term, Open-Label Safety Study (Study ALO-KNT-302)

There were 467 patients enrolled in long-term, safety Study 302. There were 465 patients included in the evaluation of results. Two patients were enrolled and not dosed. Disposition of patients is summarized in Table 24.

Disposition was evaluated by average daily dose (<80 mg/day, 80-120 mg/day, and >120 mg/day). It should be noted that, of the 465 treated patients, 9 did not have sufficient dosing information to calculate an average daily dose or exposure time leaving 456 for analysis. The disposition of these 456 patients was evaluated by dose group as well as opioid status. Of these 456 patients, the majority (299 patients) were in the <80 mg/day dose group, with smaller

numbers of patients in the 80-120 mg/day dose group (79 patients) and >120 mg/day dose group (78 patients).

Of the 467 enrolled patients, 307 discontinued from the study. The most common reasons for discontinuation were adverse events (23.7%), non-compliance (13.7%), and patient withdrew from study (11.1%). The percentage of patients who discontinued was highest in the <80 mg/day dose group (71.2%), intermediate in the >120 mg/day dose group (55.1%) and lowest in the 80-120 mg/day dose group (50.6%).

As evaluated by reason for discontinuations, discontinuation due to AEs and discontinuation due to patient withdrew from study were more common in the <80 mg/day dose group than in the higher dose groups. It is possible that patients in the <80 mg/day dose group (who did not titrate to higher levels) could not tolerate the effects of opioid treatment.

Withdrawal due to noncompliance was more common in the 80-120 mg/day and >120 mg/day dose groups than in the <80 mg/day dose group. Discontinuations due to lack of efficacy were similar across dose groups.

Table 24: Patient Disposition – Discontinuation of Study Drug Long-Term, Open Label Safety Study ALO-KNT-302 - Safety Population

	n (%)			
	Average Daily Dose of ALO-01			Overall
	< 80 mg	80-120 mg	>120 mg	
Patients Enrolled	299 (100.0)	79 (100.0)	78 (100.0)	467 ^a
Patients in Safety Population	299	79	78	465 ^b
Discontinuations from Study	213 (71.2)	40 (50.6)	43 (55.1)	307 (65.7)
Reasons for Discontinuation				
Adverse Event ^c	94 (31.4)	8 (10.1)	7 (9.0)	110 (23.7)
Lack of Efficacy	29 (9.7)	4 (5.1)	6 (7.7)	39 (8.4)
Noncompliance	28 (9.4)	18 (22.8)	18 (23.1)	64 (13.7)
Investigator’s Discretion	2 (0.7)	1 (1.3)	0	3 (0.6)
Patient Withdrew from Study	40 (13.4)	3 (3.8)	6 (7.7)	52 (11.1)
Lost to Follow-Up	15 (5.0)	4 (5.1)	4 (5.1)	28 (6.0)
Did not Meet Inclusion/Exclusion Criteria	1 (0.3)	0	1 (1.3)	4 (0.9)
Other Reason	4 (1.3)	2 (2.5)	1 (1.3)	7 (1.5)

Note: A patient was considered to be discontinued from the study if there was a negative response for “Did patient complete study?” on End of Study CRF.

Note: Other reasons for discontinuation included hospital admission for hip replacement infection (1 patient) and sponsor decision (6 patients).

- a. There were 2 patients who were not treated with study drug.
- b. There were 9 patients who did not have enough dosing information to categorize average daily dose. Therefore, the total number of patients dosed (N = 465) exceeds the sum of the number of patients presented by dose group (N = 456).
- c. One patient was erroneously included in the listing of AEs leading to study drug discontinuation; however, this patient completed the study.

Source: Study 302

6.4.5. Demographic and Other Characteristics of Study Population

See section 6.3.2.

6.4.6. Adverse Events

6.4.6.1. Safety of ALO-01

Table 25 and Table 26 summarize the common adverse events categorized by severity across the three studies. Please note that the titration periods for these studies are of different duration, thus, direct comparisons are complicated.

Assuming however that adverse events accumulated over the time of titration one would expect the KADIAN[®] period of 2 weeks in study 202 to have lowest adverse events rate compared to study 301 where ALO-01 was titrated over 7 weeks or study 302 where ALO-01 was not time or

dose limited. The data for study 302 are presented separately for the initial 12 weeks of maintenance and for the full 48 weeks of maintenance to facilitate limited comparisons across studies. This display of the data is potentially less favorable to ALO-01 when assessing the overall adverse events profile across the Phase 2/Phase 3 studies.

Open-Label Titration Phase

Of the 111 patients who received at least 1 dose of open-label KADIAN[®] during the Titration Phase of Study ALO-KNT-202, AEs were reported by 93 (83.8%) patients. Of the 547 patients who received at least 1 dose of open-label ALO-01 during the Titration Phase of Study ALO-KNT-301 or in the first 4 weeks of study 302, AEs were reported by 347 (63.4%) and 303 (65.2%) respectively.

The most frequently reported ($\geq 5.0\%$ of all patients) AEs during the Titration Phase of these studies included constipation, nausea, dry mouth, vomiting, dizziness, headache, somnolence, and pruritus. The overall safety profile in the Titration Phases of these studies was consistent with opioid therapy. The vast majority of adverse events were mild to moderate in all studies.

Maintenance Phase

The adverse event rate was similar in patients who received double blind KADIAN[®] and double blind ALO-01 (45.1% and 46.5%, respectively) in Study ALO-KNT-202 and in patients who received placebo and ALO-01 (48.6% and 53.2%, respectively) in the Maintenance Phase of Study ALO-KNT-301.

The most frequently reported ($\geq 5.0\%$ of ALO-01 subjects) AEs during the Maintenance Phase of both blinded, short-term studies included constipation, nausea, and vomiting. A similar profile was observed in patients who received double blind KADIAN[®]. Other frequently reported AEs among ALO-01 patients included somnolence (9.9%) in Study ALO-KNT-202 and headache (7.0%) in Study ALO-KNT-301. Frequently reported AEs among placebo patients included nausea (7.5%) and rhinorrhoea (6.9%).

Of the 465 patients who received at least 1 dose of study drug in long-term safety Study ALO-KNT-302, AEs were reported by 378 (81.3%) patients.

Treatment related AEs were reported as possibly, probably, or definitely related to ALO-01 by 288 (61.9%) patients. The most common AEs were typical opioid-related events of constipation, nausea, headache, and vomiting similar to the double blind studies..

The most frequently reported ($\geq 5.0\%$ of patients) treatment-related AEs included constipation (31.2%), nausea (22.2%), vomiting (8.0%), somnolence (7.3%), headache (6.9%), and pruritus (5.6%).

Treatment-related AEs were more common in the <80 mg dose group and 80-120 mg dose group than in the >120 mg dose group. The increased incidence of AEs in patients taking lower doses is likely to be a consequence of the manner in which patients were up-titrated. The decision to increase the dose was based on both pain response and the occurrence of AEs. Therefore, patients who had AEs were less likely to be up-titrated, and more likely to remain at dose levels <120 mg.

**Table 25: Common Adverse Events by Severity
 (Reported by > 5% of ALO-01 Treated Patients), Titration Phase**

System Organ Class / Preferred Term	Study ALO-KNT-301 ALO-01 (N=547) n (%)	Study ALO-KNT-302 ALO-01 (N=465) n (%)	Study ALO-KNT-202 KADIAN® (N=111) n (%)
Patients Reporting at least 1 Adverse Event	347 (63.4%)	303 (65.2%)	92 (82.9%)
Mild	149 (27.2%)	141 (30.3%)	44 (39.6%)
Moderate	160 (29.3%)	129 (27.7%)	35 (31.5%)
Severe	38 (6.9%)	33 (7.1%)	13 (11.7%)
Constipation	169 (30.9%)	111 (23.9%)	51 (45.9%)
Mild	92 (16.8%)	60 (12.9%)	29 (26.1%)
Moderate	67 (12.2%)	41 (8.8%)	18 (16.2%)
Severe	10 (1.8%)	10 (2.2%)	4 (3.6%)
Nausea	115 (21.0%)	81 (17.4%)	43 (38.7%)
Mild	72 (13.2%)	44 (9.5%)	26 (23.4%)
Moderate	39 (7.1%)	34 (7.3%)	13 (11.7%)
Severe	4 (0.7%)	3 (0.6%)	4 (3.6%)
Dry mouth	32 (5.9%)	13 (2.8%)	17 (15.3%)
Mild	24 (4.4%)	12 (2.6%)	15 (13.5%)
Moderate	8 (1.5%)	1 (0.2%)	2 (1.8%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)
Somnolence	78 (14.3%)	28 (6.0%)	31 (27.9%)
Mild	46 (8.4%)	17 (3.7%)	23 (20.7%)
Moderate	24 (4.4%)	10 (2.2%)	5 (4.5%)
Severe	8 (1.5%)	1 (0.2%)	3 (2.7%)
Vomiting	50 (9.1%)	33 (7.1%)	25 (22.5%)
Mild	18 (3.3%)	16 (3.4%)	15 (13.5%)
Moderate	28 (5.1%)	16 (3.4%)	5 (4.5%)
Severe	4 (0.7%)	1 (0.2%)	5 (4.5%)
Dizziness	47 (8.6%)	13 (2.8%)	21 (18.9%)
Mild	31 (5.7%)	8 (1.7%)	19 (17.1%)
Moderate	12 (2.2%)	4 (0.9%)	0 (0.0%)
Severe	4 (0.7%)	1 (0.2%)	2 (1.8%)
Pruritus	38 (6.9%)	22 (4.7%)	16 (14.4%)
Mild	21 (3.8%)	11 (2.4%)	14 (12.6%)
Moderate	16 (2.9%)	10 (2.2%)	2 (1.8%)
Severe	1 (0.2%)	1 (0.2%)	0 (0.0%)
Headache	33 (6.0%)	37 (8.0%)	14 (12.6%)
Mild	20 (3.7%)	14 (3.0%)	9 (8.1%)
Moderate	12 (2.2%)	18 (3.9%)	4 (3.6%)
Severe	1 (0.2%)	5 (1.1%)	1 (0.9%)

202/301 – Includes AEs with onset during the open label titration phase (~4 and 6 wks, respectively)

302 – Includes AEs with onset during the first 4 wks of study

Source: ISS

Table 26: Common Adverse Events by Severity (Reported by >5% of ALO-01 Treated Patients), Maintenance Phase

System Organ Class / Preferred Term	Double Blind				Weeks	
	Study 202		Study 301		5 – 16	5 – 52
	ALO-01 (N=71) n (%)	KADIAN [®] (N=71) n (%)	ALO-01 (N=171) n (%)	Placebo (N=173) n (%)	ALO-01 (N=322) n (%)	ALO-01 (N=322) n (%)
Patients Reporting at Least One Adverse Event	33 (46.5%)	32 (45.1%)	91 (53.2%)	84 (48.6%)	178 (55.3%)	243 (75.5%)
Mild	26 (36.6%)	26 (36.6%)	34 (19.9%)	46 (26.6%)	72 (22.4%)	71 (22.0%)
Moderate	7 (9.9%)	5 (7.0%)	48 (28.1%)	27 (15.6%)	77 (23.9%)	120 (37.3%)
Severe	0 (0.0%)	1 (1.4%)	9 (5.3%)	11 (6.4%)	29 (9.0%)	52 (16.1%)
Constipation	11 (15.5%)	9 (12.7%)	12 (7.0%)	7 (4.0%)	33 (10.2%)	48 (14.9%)
Mild	9 (12.7%)	6 (8.5%)	7 (4.1%)	5 (2.9%)	17 (5.3%)	23 (7.1%)
Moderate	2 (2.8%)	2 (2.8%)	5 (2.9%)	2 (1.2%)	13 (4.0%)	20 (6.2%)
Severe	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	3 (0.9%)	5 (1.6%)
Diarrhea	2 (2.8%)	2 (2.8%)	21 (12.3%)	21 (12.1%)	14 (4.3%)	23 (7.1%)
Mild	2 (2.8%)	2 (2.8%)	9 (5.3%)	9 (5.2%)	4 (1.2%)	6 (1.9%)
Moderate	0 (0.0%)	0 (0.0%)	11 (6.4%)	10 (5.8%)	9 (2.8%)	14 (4.3%)
Severe	0 (0.0%)	0 (0.0%)	1 (0.6%)	2 (1.2%)	1 (0.3%)	3 (0.9%)
Nausea	7 (9.9%)	6 (8.5%)	20 (11.7%)	13 (7.5%)	30 (9.3%)	51 (15.8%)
Mild	5 (7.0%)	5 (7.0%)	13 (7.6%)	3 (1.7%)	20 (6.2%)	31 (9.6%)
Moderate	2 (2.8%)	1 (1.4%)	7 (4.1%)	7 (4.0%)	8 (2.5%)	16 (5.0%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.7%)	2 (0.6%)	4 (1.2%)
Vomiting	6 (8.5%)	3 (4.2%)	12 (7.0%)	4 (2.3%)	13 (4.0%)	28 (8.7%)
Mild	5 (7.0%)	2 (2.8%)	8 (4.7%)	2 (1.2%)	8 (2.5%)	14 (4.3%)
Moderate	1 (1.4%)	1 (1.4%)	4 (2.3%)	2 (1.2%)	3 (0.9%)	11 (3.4%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)	3 (0.9%)
Headache	3 (4.2%)	6 (8.5%)	12 (7.0%)	6 (3.5%)	11 (3.4%)	26 (8.1%)
Mild	2 (2.8%)	6 (8.5%)	5 (2.9%)	3 (1.7%)	9 (2.8%)	17 (5.3%)
Moderate	1 (1.4%)	0 (0.0%)	7 (4.1%)	3 (1.7%)	0 (0.0%)	4 (1.2%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)	5 (1.6%)
Somnolence	7 (9.9%)	6 (8.5%)	2 (1.2%)	5 (2.9%)	7 (2.2%)	10 (3.1%)
Mild	6 (8.5%)	6 (8.5%)	1 (0.6%)	5 (2.9%)	3 (0.9%)	5 (1.6%)
Moderate	1 (1.4%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	4 (1.2%)	4 (1.2%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Fatigue	2 (2.8%)	0 (0.0%)	2 (1.2%)	2 (1.2%)	7 (2.2%)	18 (5.6%)
Mild	2 (2.8%)	0 (0.0%)	1 (0.6%)	2 (1.2%)	2 (0.6%)	5 (1.6%)
Moderate	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	4 (1.2%)	11 (3.4%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	2 (0.6%)
Insomnia	0 (0.0%)	1 (1.4%)	6 (3.5%)	4 (2.3%)	9 (2.8%)	18 (5.6%)
Mild	0 (0.0%)	1 (1.4%)	1 (0.6%)	1 (0.6%)	4 (1.2%)	0 (0.0%)
Moderate	0 (0.0%)	0 (0.0%)	3 (1.8%)	3 (1.7%)	5 (1.6%)	1 (0.3%)
Severe	0 (0.0%)	0 (0.0%)	2 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 26: Common Adverse Events by Severity (Reported by >5% of ALO-01 Treated Patients), Maintenance Phase (Continued)

System Organ Class / Preferred Term	Double Blind				Weeks	
	Study 202		Study 301		5 – 16	5 – 52
	ALO-01 (N=71)	KADIAN® (N=71)	ALO-01 (N=171)	Placebo (N=173)	ALO-01 (N=322)	ALO-01 (N=322)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Urinary tract Infection	1 (1.4%)	0 (0.0%)	1 (0.6%)	1 (0.6%)	7 (2.2%)	19 (5.9%)
Mild	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.6%)	5 (1.6%)	12 (3.7%)
Moderate	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)	7 (2.2%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Study 202, Study 302, ISS

6.4.6.2. ALO-01 Capsule Severe Adverse Events by Dose in the Long Term Study ALO-KNT-302

During the 52-week safety Study ALO-KNT-302, severe AEs were reported by 16.6% of subjects. A summary of severe AEs by dose are reported by ≥1.0% of subjects in Table 27. Note that these AEs are similar to the other studies but are increased in severity over time.

Table 27: Severe Adverse Events by Dose Reported by ≥1.0% of Subjects in Long-Term, Safety Study ALO-KNT-302 - Safety Population

Preferred Term	Average Daily Dose of ALO-01			Overall N = 465 n (%)
	< 80 mg N = 299 n (%)	80-120 mg N = 79 n (%)	>120 mg N = 78 n (%)	
Any Adverse Event	48 (16.1)	18 (22.8)	11 (14.1)	77 (16.6)
Constipation	8 (2.7)	3 (3.8)	3 (3.8)	14 (3.0)
Nausea	5 (1.7)	1 (1.3)	1 (1.3)	7 (1.5)
Headache	6 (2.0)	2 (2.5)	1 (1.3)	9 (1.9)

Note: As 9 subjects are missing dosing information, the subtotals in the by-dose columns do not add to the total presented in Overall column.

Source: Study 302

6.4.6.3. Deaths, Other Serious Adverse Events, Adverse Events Associated with Discontinuation of ALO-01 Capsules, and Other Significant Events

In summary:

- There were no deaths reported in the clinical program
- No SAEs were reported in healthy volunteer Studies 20-903-AU, ALO-01-07-101, ALO-01-07-102, ALO-01-07-103, ALO-01-07-104, and ALO-01-07-205.

Blinded, short-term (2- to 12-Week) studies ALO-KNT-202 and ALO-KNT-301:

- In Study ALO-KNT-202 one subject (202-003-9309) was randomized to KADIAN[®] - ALO-01 treatment sequence, experienced a SAE of chest pain, after completing the open-label KADIAN[®] treatment in period 5. This subject was a 51-year-old white male with a medical history of myopia/hyperopia, bilateral tinnitus, pneumonia, occasional chest discomfort, occasional irregular heart beat, GERD, Barrett's esophagus, occasional stomach pain, erectile dysfunction, sleep disturbance, right and left shoulder surgeries, left inguinal hernia repair, left ear hearing loss, right knee arthroscopic surgery, left foot fracture, right hand and wrist fracture, and hypercholesterolemia. Concomitant medications at the time of the event included oral treatment with Nexium 40 mg QD, propranolol 40 mg BID, and Celebrex 200 mg QD.

On [REDACTED], the subject (202-003-9309) presented to the emergency department with complaints of chest pain, headache, and nausea, and was hospitalized. Laboratory results for cardiac enzymes were negative, and a heart attack was ruled out. The subject was discharged from the hospital on [REDACTED], and the event was considered resolved. The Investigator determined the intensity of the chest pain to be moderate and its relationship to study drug as unlikely. The subject withdrew from the study due to the SAE.

- No SAEs were reported during the double-blind portion of Study ALO-KNT-202.
- Of the 547 subjects who received at least 1 dose of study drug during the Titration Phase of Study ALO-KNT-301, SAEs were reported by 3 (0.5%) subjects. Of the 3 subjects reporting a SAE during the Titration Phase, 1 subject (301-122-0003) experienced severe hypotension that was considered by the Investigator to be probably related to study drug.
- Of the 344 subjects who received at least 1 dose of study drug during the Maintenance Phase of Study ALO-KNT-301, SAEs were reported by 3 (1.7%) placebo subjects and 6 (3.5%) ALO-01 subjects. Of the 9 subjects reporting a SAE during the Maintenance Phase, 1 placebo subject (301-142-0013) experienced severe abdominal pain that was considered by the Investigator to be possibly related to study drug.

Long-Term, Safety Study (ALO-KNT-302)

- Of the 465 subjects who received at least 1 dose of study drug in long-term, safety Study ALO KNT 302, 33 subjects (7.1%) reported 1 or more SAEs. The most

common individual SAEs were colitis, chest pain, arthritis bacterial, osteoarthritis, and deep vein thrombosis (2 subjects each). No other individual SAE was reported by >1 subject.

- There were 14 subjects who discontinued due to a SAE. No individual SAE led to the discontinuation of more than 1 subject. One additional subject (302-216-005) discontinued the study with SAE onset 32 days after the last dose. This SAE (gastroenteritis) was rated moderate and possibly related to the study drug by the investigator.
- One subject (302-223-2009) had SAEs of severe gastrointestinal inflammation and severe colitis categorized by the Investigator as possibly related to study drug. No other SAE was categorized as related to study drug.
- There were no notable dose-related trends by Preferred Term.

6.4.6.3.1. Discontinuations of Study Medications Due to Adverse Events: Studies ALO-KNT-202 and ALO-KNT-301, Study ALO-KNT-302

Because of the enriched enrollment design, subjects who were unable to be titrated to effect due to opioid-related AEs were to be prematurely discontinued, which accounts for the greater number of subjects discontinuing during the Open-label Titration Phase.

Study ALO-KNT-202

Source: Study 202 and ISS

During open-label titration:

- 28 of 111 subjects discontinued open-label KADIAN[®] due to non-serious AEs.
- The most common ($\geq 5\%$ of all subjects) AEs that led to premature discontinuation were somnolence (9.0%), vomiting (8.1%), constipation (7.2%), and nausea (6.3%).

During double-blind treatment:

- 2 subjects discontinued due to AEs:
 - 1 KADIAN[®]-treated subject (202-004-9419) due to constipation, and
 - 1 ALO-01-treated subject (202-005-9521) due to crying, fatigue, vomiting, and asthenia. Note this subject reported fatigue, crying, headache, and somnolence that resulted in discontinuation of the open-label KADIAN[®] medication during the open-label titration phase, but did not discontinue the study. She continued onto the double-blind phase and discontinued the study after receiving a single dose of ALO-01 medication.

Study ALO-KNT-301

Source: ISS

During open-label titration:

- 130 of 547 (23.8%) subjects discontinued due to AEs.

- Nausea, constipation, somnolence, and vomiting were the AEs that most frequently led to premature discontinuation ($\geq 2\%$ of all subjects).

During double-blind treatment:

- 6.4% of placebo-treated and 8.2% of ALO-01 treated subjects had 1 or more AEs that started in the double-blind phase and led to discontinuation.
- Adverse events that led to premature discontinuation in ≥ 2 subjects in either treatment group included nausea (1 placebo, 2 ALO-01), hyperhidrosis (2 placebo, 0 ALO-01), and diarrhea (2 placebo, 0 ALO-01).

Study ALO-KNT-302

Source: ISS

- 115 of 465 subjects (24.7%) had 1 or more AEs that led to discontinuation. Two additional subjects discontinued from the study due to multiple events but are not included in the total due to the manner in which the early termination was documented.
- The AEs that most frequently ($\geq 2\%$ of subjects) led to discontinuation were nausea (5.6%), constipation (3.4%), and vomiting (2.8%).

Table 28 and Table 29 summarized the AEs resulting in discontinuation of the study medications.

Table 28: Adverse Events Leading to Study Drug Discontinuation - Titration Phase (>2 subjects in ALO-01 group)

Preferred Term	Study 301	Study 302	Study 202
	ALO-01 [1] (N=547) n (%)	ALO-01 [2] (N=465) n (%)	KADIAN [3] (N=111) n (%)
Patients Reporting at Least One Adverse Event	130 (23.8%)	82 (17.6%)	28 (25.2%)
Nausea	24 (4.4%)	22 (4.7%)	7 (6.3%)
Constipation	19 (3.5%)	12 (2.6%)	8 (7.2%)
Vomiting	15 (2.7%)	11 (2.4%)	9 (8.1%)
Somnolence	15 (2.7%)	7 (1.5%)	10 (9.0%)
Dizziness	8 (1.5%)	5 (1.1%)	5 (4.5%)
Pruritus	5 (0.9%)	6 (1.3%)	3 (2.7%)
Headache	2 (0.4%)	8 (1.7%)	4 (3.6%)
Fatigue	4 (0.7%)	4 (0.9%)	3 (2.7%)
Lethargy	3 (0.5%)	4 (0.9%)	0 (0.0%)
Diarrhea	1 (0.2%)	3 (0.6%)	0 (0.0%)
Sedation	2 (0.4%)	2 (0.4%)	0 (0.0%)
Abdominal pain	1 (0.2%)	2 (0.4%)	0 (0.0%)
Chills	0 (0.0%)	3 (0.6%)	0 (0.0%)
Tremor	1 (0.2%)	2 (0.4%)	1 (0.9%)
Depression	1 (0.2%)	2 (0.4%)	1 (0.9%)
Disorientation	3 (0.5%)	0 (0.0%)	0 (0.0%)

Insomnia	2 (0.4%)	1 (0.2%)	0 (0.0%)
Hyperhidrosis	1 (0.2%)	2 (0.4%)	0 (0.0%)

Table 28: Adverse Events Leading to Study Drug Discontinuation - Titration Phase (>2 subjects in ALO-01 group) (Continued)

Preferred Term	Study 301	Study 302	Study 202
	ALO-01 [1] (N=547) n (%)	ALO-01 [2] (N=465) n (%)	KADIAN [3] (N=111) n (%)
Rash	1 (0.2%)	2 (0.4%)	0 (0.0%)
Vertigo	2 (0.4%)	0 (0.0%)	0 (0.0%)
Dry mouth	0 (0.0%)	2 (0.4%)	1 (0.9%)
Chest discomfort	0 (0.0%)	2 (0.4%)	0 (0.0%)
Anxiety	2 (0.4%)	0 (0.0%)	0 (0.0%)
Confusional state	2 (0.4%)	0 (0.0%)	0 (0.0%)
Dyspnoea	0 (0.0%)	2 (0.4%)	0 (0.0%)

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

[1] Includes AEs with onset during 6 week ALO-01 titration phase of study 301 for all patients.

[2] Includes AEs with onset during the first 4 weeks ALO-01 treatment in study 302.

[3] Includes AEs with onset during 4 week KADIAN titration phase of study 202.

Table 29: Adverse Events Leading to Study Drug Discontinuation- Maintenance Phase (≥2 events in ALO-01 group)

Preferred Term	Double Blind				Weeks	
	Study 202		Study 301		5 – 16	5 – 52
	ALO-01 (N=71) n (%)	KADIAN [®] (N=71) n (%)	ALO-01 (N=171) n (%)	Placebo (N=173) n (%)	ALO-01 (N=322) n (%)	ALO-01 (N=322) n (%)
Patients Reporting at Least One Adverse Event	1 (1.4%)	1 (1.4%)	17 (9.9%)	11 (6.4%)	20 (6.2%)	35 (10.9%)
Nausea	0 (0.0%)	0 (0.0%)	2 (1.2%)	1 (0.6%)	3 (0.9%)	4 (1.2%)
Vomiting	1 (1.4%)	0 (0.0%)	1 (0.6%)	1 (0.6%)	1 (0.3%)	2 (0.6%)
Constipation	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	2 (0.6%)	4 (1.2%)
Stomach Discomfort	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)	3 (0.9%)
Abdominal Pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	2 (0.6%)
Diarrhea	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.2%)	0 (0.0%)	0 (0.0%)
Hyperhidrosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.2%)	0 (0.0%)	0 (0.0%)

6.4.7. Clinical Laboratory Assessments and Other Safety in the Double-Blind and Long-Term Studies

6.4.7.1. Clinical Laboratory Evaluations

In general, in the clinical program, the laboratory findings were mild to moderate in nature, consistent with the subject's condition(s), and were spurious, or transient. There were 3 AEs associated with laboratory findings in the long-term safety study. One subject (302-233-2004) had a mild elevation of cholesterol that was reported as a hepatic enzyme elevation. Liver function tests for this subject were within normal limits at all visits. Two (302-202-2004 and 302-216-2001) subjects had a mild increase in alanine aminotransferase. Each of these events resolved within approximately 1 week and the final value was <2 times the upper limit of normal.

6.4.7.2. Other Safety Evaluations

Analyses of potentially clinically significant vital signs and shifts from normal to abnormal were

- not performed (Study ALO-KNT-202),
- showed similar percentages of subjects with elevations of laboratory values in the placebo and EMBEDA™ treatment groups (Study ALO-KNT-301),
- or showed no notable changes in the percent change from baseline (Study ALO-KNT-302).

In the long-term Study ALO-KNT-302, 62 subjects (30.8%) at Visit 8 had electrocardiogram (ECG) tracings that changed from baseline; no change was reported as clinically significant. At the Final Treatment Visit, there were 79 subjects (20.5%) whose ECG had changed from baseline. Only one change was reported as clinically significant in one subject who was diagnosed with an incomplete right bundle branch.

6.4.8. Withdrawal Assessments in the Double-Blind and Long-Term Studies

Measures of opioid withdrawal were assessed in Studies ALO-KNT-301 and ALO-KNT-302. Study ALO-KNT-301 included 2 measures of opioid withdrawal: the COWS and the Subjective Opiate Withdrawal Scale (SOWS); Study ALO-KNT-302 used the COWS assessment tool only.

The COWS assessment tool asked the clinician to complete an 11-item questionnaire to assess the level of the patient's opioid dependence and addresses common opiate withdrawal signs and symptoms (eg, resting pulse rate, sweating, pupil size). The clinician scored each of the 11-items using an intensity rating scale of 0 (none/normal) to 4 or 5 (severe). Higher scores reflected greater withdrawal severity with a maximal possible score of 48.

The occurrence of withdrawal symptoms as assessed by the COWS in Study ALO-KNT-301 is presented in Table 30. Among the 253 patients (126 placebo and 127 ALO-01 with an ALO-01 randomization dose of ≤80 mg, the mean COWS value at randomization baseline (Visit Y) was 0.7 in the placebo group and 0.5 in the ALO-01 group. At Visit Y+12 Weeks, the mean change

from Visit Y was smaller in the ALO-01 treatment group (0.1) compared to the placebo group (0.3). Among the 91 subjects (47 placebo and 44 ALO-01) with an ALO-01 randomization dose of >80 mg, the mean COWS value at randomization baseline was 0.6 in the placebo group and 0.4 in the ALO-01 group. At Visit Y+12 Weeks, the mean change from Visit Y was 0.2 in the ALO-01 treatment group and 0.1 in the placebo group.

Three patients (2 placebo and 1 ALO - 01) had a COWS value of ≥ 23 (moderate withdrawal) during the study (Source: Study 301).

Placebo patient 301-121-0016 is a 45 year old opioid experienced male. He had COWS values of 0, 0, and 23, at Randomization Baseline, Weeks 1, and 2, respectively. This opioid-experienced patient was taking 120 mg total daily dose prior to the Taper Period at the beginning of the Maintenance Phase. The patient was tapered over 11 days prior to Week 2. At time of discontinuation from the study Week 6, the patient's COWS value was 1. The patient was prematurely discontinued from the study due to lack of efficacy on Maintenance Day 42.

Placebo patient 301-173-0004 is a 56 years old opioid naïve female. She had COWS values of 0 and 23 at Randomization Baseline and Week 1, respectively. This opioid-naïve patient was taking 60 mg total daily dose prior to the Taper Period at the beginning of the Maintenance Phase. The patient was tapered over 4 days prior to Week 1. The patient was prematurely discontinued from the study due to lack of efficacy on Maintenance Day 7.

ALO-01 patient 301-126-0026 is a 51 year old opioid naïve female. She had COWS values of 1, 0, 0, and 28 at Randomization Baseline, Weeks 1, 2, and follow-up, respectively. This opioid-naïve patient was randomized to 120 mg total daily dose. The patient received the last dose of study drug on Maintenance Day 49. The patient was never tapered from study drug. On Maintenance Day 52, the patient experienced drug withdrawal syndrome and was prematurely discontinued from the study. The patient was treated with lorazepam and the event resolved the same day without sequelae.

Patient 301-160-0010 is a 58 year old opioid naïve male. He had a single COWS assessment with a value of 16 at Early Term Visit prior to randomization due to AE of severe worsening of anxiety. Study Drug Accountability indicates the patient was compliant with study drug dosing until Titration Week 5 then took only 5 capsules in 10 days between Visit X+5 and Early Term Visit.

Placebo Patient 301-150-0008 is a 42 year old opioid naïve male. He had a COWS value of 3 at randomization baseline, 13 at Week 1, 8 at Week 2 and 1 at Week 12. Study Drug Accountability appears to indicate patient was compliant with study drug dosing and no overuse of rescue APAP. This patient completed the study. This patient was stabilized to 80 mg dose prior to randomization.

Table 30: Clinical Opiate Withdrawal Scale (COWS): Study ALO-KNT-301

Dose / Treatment Group	Baseline Score*	Mean (SD) Change from Baseline to Study Endpoint†
Among 253 patients taking ≤80 mg at randomization		
Placebo (N=126)	0.7	-0.3 (1.2)
ALO-01 (N=127)	0.5	-0.1 (0.9)
Among 91 patients taking >80 mg at randomization		
Placebo (N=47)	0.6	-0.1 (1.0)
ALO-01 (N=44)	0.4	0.2 (0.6)

* Scale=0 (none/normal) to 4 or 5 (severe).

† Randomization Baseline (Week Y) to Week Y+12 of double-blind treatment in Study ALO-KNT-301

In Study ALO-KNT-302, there were no consistent trends in mean values by dose group or study visit. Five patients had moderate symptoms of withdrawal during their study participation: 1 at Visit 2, 1 at Visit 7 and all 5 at the Early Termination Visit. Two patients were reported as noncompliant; 1 patient was discontinued from study due to discrepancies with study medication (site was using improper dosing); 1 patient was discontinued prematurely from study and was not taking medication as prescribed; and 1 patient was prematurely discontinued due to an AE of lethargy and was suspected of not taking medication as prescribed. Data are presented in Table 31.

Patient 206-2001 is a 50 year old opioid experienced male. He had COWS values of 19 and 23, was non-compliant, adjusted his own dosage, and lost 2 bottles of study drug. This patient dropped out of the study. It was suspected that the patient had not taken study medication as indicated. This patient's urine drug screen (UDS) was positive for hydrocodone (not study medication).

Patient 206-2005 is a 50 year old opioid experienced male. He had COWS values of 17 and 13. This patient was non-compliant and only took study drug for 7 days. This patient's UDS was positive for oxycodone (not study medication).

Patient 228-2002 is a 56 year old opioid experienced female. She had a COWS value of 14 at the final treatment visit. This patient was prematurely discontinued per the Investigator due to discrepancies with study medication (site was using improper dosing). All of the patient's UDS were positive for study medication; however, some UDS were missed at unscheduled visits. The patient was not tapered from study medication and only 2 follow-up telephone contacts were done, with a total SOWS value of 0.

Patient 248-2007 is a 38 year old opioid naïve female. She had a COWS value of 18 at the final treatment visit. This patient informed the site that she lost one bottle of study medication and ran out of study medication prior to her next visit. This patient was positive for prohibited medication, did not take study medication as prescribed, and was prematurely discontinued from the study.

Patient 256-2008 is a 54 year old opioid experienced male. He had a COWS value of 13 at the final treatment visit. This patient prematurely discontinued from the study due to an AE of lethargy. The patient returned 30 capsules in 1 bottle and 1 bottle was never returned. It was suspected that the patient was not taking study medication as prescribed due to the AE.

The results from both studies support the observation that the safety profile of ALO-01 did not show an increased risk of opioid withdrawal syndrome for patients taking ALO-01 compared to placebo (ALO-KNT-301) or for patients taking open-label ALO-01 for long-term use (ALO-KNT-302). The results indicated that the mean change from baseline in both studies was <2 (no sign of withdrawal). More specific potential withdrawal signs and symptoms assessments are discussed in section 6.4.9.

Table 31: Clinical Opiate Withdrawal Scale (COWS): Study ALO-KNT-302[#]

Dose / Treatment Group	Baseline Score*	Mean (SD) Change from Baseline to Study Endpoint [†]
Among 177 subjects taking ALO-01 Overall	1.2	-0.4 (1.58)
Among 100 subjects taking ALO-01 <80 mg at Visit 15 (Month 13)	1.2	-0.5 (1.51)
Among 41 subjects taking ALO-01 80-120 mg at Visit 15 (Month 13)	1.0	-0.2 (1.38)
Among 36 subjects taking ALO-01 >120 mg at Visit 15 (Month 13)	1.5	-0.3 (1.97)

* Scale=0 (none/normal) to 4 or 5 (severe).

[†] Baseline is defined as the first COWS assessment conducted.

[#] Source: Study 302

6.4.9. Assessment of Potential Naltrexone Associated Safety Risks

6.4.9.1. Potential Naltrexone-Related Adverse Events including Opioid Withdrawal.

Typical naltrexone adverse events reported as greater than 10% incidence and those associated with the signs and symptoms of opioid withdrawal syndrome are listed below. (ReVia Package Insert (Dupont – US) 2003), Goodman & Gilman's Handbook 1996)

While nausea and vomiting are associated with withdrawal syndrome, they are not specific since they are seen with opioid agonist administration as well. The more specific findings are diarrhea, increased lacrimation, rhinorrhea, piloerection, tachycardia, anxiety, hyperhidrosis and abdominal cramping. (Adam and Victor's Neurology (online))

- Vital Signs: Tachycardia, hypertension, fever, chills
- Skin: Increased perspiration (hyperhidrosis), piloerection
- Eyes and Nose: Increased lacrimation, rhinorrhea
- Gastrointestinal System: Abdominal pain, cramping, diarrhea, nausea, vomiting
- Musculoskeletal system: Muscle pain, myalgia, muscle cramps, joint pain, arthralgia,
- Central Nervous System: Yawning, anxiety, restlessness, nervousness, irritability, insomnia, headache

The safety database for the Clinical Program, which encompasses all patients treated with a least one dose of ALO-01 Capsule, was filtered to identify those adverse events associated with naltrexone or with withdrawal and the adverse events occurring in 2 or more patients in the pooled ALO-01 population are listed in Table 32.

Table 32: All Associated Naltrexone Potential Adverse Events, All Studies: Safety Population

Term ³	Double-Blind ¹				ALO-01 (N=1012)	Open ² KADIAN [®] (N=111)	Pooled ALO-01 (N=1083)
	Study 202 ALO-01 (N=71)	Study 202 KADIAN [®] (N=71)	Study 301 ALO-01 (N=171)	Study 301 Placebo (N=173)			
Any Adverse Event	13 (18.3%)	13 (18.3%)	33 (19.3%)	33 (19.1%)	214 (21.1%)	26 (23.4%)	240 (22.2%)
Lacrimation	0 (0%)	0 (0%)	1 (0.6%)	7 (4.0%)	6 (0.6%)	0 (0%)	7 (0.6%)
Increased Nausea	7 (9.9%)	6 (8.5%)	20 (11.7%)	13 (7.5%)	232 (22.9%)	45 (40.5%)	256 (23.6%)
Vomiting	6 (8.5%)	3 (4.2%)	12 (7.0%)	4 (2.3%)	105 (10.4%)	27 (24.3%)	123 (11.4%)
Diarrhea	2 (2.8%)	2 (2.8%)	21 (12.3%)	21 (12.1%)	50 (4.9%)	11 (9.9%)	73 (6.7%)
Abdominal Pain	2 (2.8%)	5 (7.0%)	9 (5.3%)	8 (4.6%)	41 (4.1%)	8 (7.2%)	52 (4.8%)
Chills	0 (0%)	2 (2.8%)	4 (2.3%)	6 (3.5%)	17 (1.7%)	2 (1.8%)	21 (1.9%)
Pyrexia	0 (0%)	2 (2.8%)	2 (1.2%)	1 (0.6%)	19 (1.9%)	2 (1.8%)	21 (1.9%)
Muscle	5 (7.0%)	5 (7.0%)	8 (4.7%)	8 (4.6%)	43 (4.2%)	11 (9.9%)	54 (5.0%)
Pain/Stiffness Joint	2 (2.8%)	4 (5.6%)	2 (1.2%)	6 (3.5%)	24 (2.4%)	7 (6.3%)	28 (2.6%)
Pain/Stiffness Headache	3 (4.2%)	6 (8.5%)	12 (7.0%)	6 (3.5%)	89 (8.8%)	18 (16.2%)	103 (9.5%)
	2 (2.8%)	2 (2.8%)	9 (5.3%)	8 (4.6%)	60 (5.9%)	8 (7.2%)	71 (6.6%)
Anxiety/Irritability Insomnia	0 (0%)	1 (1.4%)	6 (3.5%)	4 (2.3%)	34 (3.4%)	1 (0.9%)	40 (3.7%)
Nightmare	0 (0.0%)	0 (0.0%)	2 (1.2%)	1 (0.6%)	7 (0.7%)	0 (0.0%)	9 (0.8%)
Rhinorrhoea/Nasal Congestion	0 (0.0%)	0 (0.0%)	6 (3.5%)	13 (7.5%)	18 (1.8%)	1 (0.9%)	24 (2.2%)
Increased Sweating	1 (1.4%)	1 (1.4%)	7 (4.1%)	6 (3.5%)	38 (3.8%)	3 (2.7%)	46 (4.2%)
Piloerection	0 (0%)	0 (0%)	1 (0.6%)	1 (0.6%)	1 (0.1%)	0 (0%)	2 (0.2%)
Hypertension	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)	10 (1.0%)	0 (0%)	11 (1.0%)

¹ Includes only the double-blind data from each study.

² Includes open label KADIAN[®] periods from 202, open label ALO-01 periods from 301 and study 302

³ If a patient has more than one AE that codes to the same Preferred Term, the patient will be counted only once for that Preferred term.

Examination of the filtered data do not reveal a pattern of opioid withdrawal syndrome but rather a collection of scattered elements that may be associated with naltrexone or withdrawal. Within study 202 only nausea and vomiting had a higher incidence in the ALO-01 group compared to KADIAN[®]. In the open label data, even with ALO-01 data drawn from 10 times as many patients as KADIAN[®], the only notable imbalances were insomnia, increased sweating and rhinorrhea/nasal congestion. Diarrhea, abdominal pain and anxiety/irritability were lower in the ALO-01 group compared to KADIAN[®]. Overall these data are consistent with the low observed

plasma levels of naltrexone and 6-β-naltrexol and the low scores for the COWS assessment in those patients taking ALO-01 as directed.

6.4.9.2. Hepatic Enzyme Elevations with ALO-01 Capsules

The origin of the concern about hepatotoxicity comes from one study of high dose oral naltrexone (300 mg/day) in obese patients (ReVia Package Insert 2007). Subsequent published studies, many in alcoholic patients, failed to observe clinically relevant hepatotoxicity with naltrexone. In fact, studies report a reduction in transaminase levels with naltrexone at oral doses of 50 mg/day - much higher than the exposure in our clinical program. (AGA 2002, Volpicelli et al. 1992)

- There were no notable treatment-emergent elevations of hepatic transaminases in our short and medium-term, double-blind studies – 202 and 301. No patient had a treatment emergent elevation of ALT or of AST greater than 3 times the upper limit of normal.
- In Study 302, where patients had longer ALO-01 exposure, at higher average doses, the hepatic transaminase elevations observed were primarily minor.
- Of over 400 patients enrolled, only 4 patients accounted for 5 values of ALT and AST in the moderate range, or greater than 3x ULN. These subject data are unclear in their association with ALO-01 dose, and they have medical histories, therapies and/or conditions that have been associated with elevations of transaminases. The details of these 4 patients are outlined in Table 33. The liver function results of two patients with significant clinical values are detailed in Table 34 and Table 35.
 - The first case was a 51 year old obese, opioid naïve female (302-233-2005) with a history of cholecystectomy, who terminated from the study early after less than 4 days on 20mg/day of ALO-01, due to nausea.
 - The second case was a 34 year old obese, opioid-naïve female (302-202-2004) with a history of cholecystectomy, and an upper respiratory viral infection at enrollment. She terminated study enrollment due to worsening chest pressure, shortness of breath and nausea, after 6 days on 40 mg/day ALO-01. She had isolated elevation of ALT, which normalized by the follow-up visit.
 - The third case is a 61 year old obese, opioid-experienced female (302-216-2001), also with a history of cholecystectomy, as well as a seizure disorder. Her medications on enrollment included dilantin. She completed the study with minor adverse events of nausea and gastroenteritis. Abnormal alkaline phosphatase levels on entry increased, along with modest elevations of ALT and AST, nearly 3 months after a dose increase in ALO-01 from 60 mg/day to 80 mg/day, and quickly returned to normal after reduction in dose to 40 mg/day, but continued to fluctuate.
 - The fourth case is a 61 year old non-obese, opioid-experienced female (302-251-2014) with a history of alcohol abuse, seizure disorder and a complicated concomitant medication list, including phenobarbital, and lovastatin. She

terminated early from the study for a positive alcohol screen, nearly 1 year after enrollment. She had fluctuating, elevated levels of ALT, AST and Alkaline phosphatase, without clear association with ALO-01 dose, but possibly related to alcohol abuse.

- Our observations suggest that the very low level of exposure to naltrexone was unlikely to have played a significant role in the elevations of hepatic transaminases.

Table 33: Study ALO-KNT-302: Clinical Details of Patients with significant ALT and AST values.

Patient Identification	Clinical Details
Patient 302-233-2005	Demographic: 49-year-old female, BMI 42.3, opioid-naïve Past Medical History: Cholecystectomy 1993, migraine headache, contact dermatitis Medications: < 4 days on ALO-01 @ 20 mg/day Study Status: Terminated early due to nausea which started on drug day 2 ALT:19 – 161; AST: 19 – 181
Patient 302-202-2004	Demographic: 34-year-old female, BMI 41.3, opioid-naïve Past Medical History: Cholecystectomy 1996, upper-respiratory virus @ enrollment Medications: 6 days on ALO-01 @ 40mg/day Study Status: Terminated early due to increasing Chest pressure, SOB, nausea ALT history: 33 - 184 – 69
Patient 302-216-2001	Demographic: 60 years old female, BMI 31, opioid-experienced Past Medical History: Cholecystectomy, seizures, Mitral Valve Prolapse Concomitant Medications: erapamil, toprolol, Dilantin, Lyrica Adverse Events: Sleepiness, nausea, gastroenteritis Study Status: Completed study

Table 33: Study ALO-KNT-302: Clinical Details of Subjects with significant ALT and AST values. (Continued)

Patient Identification	Clinical Details
Patient 302-251-2014	Demographic: 59 years old Female, BMI 21, opioid-experienced Past-Medical History: Alcohol Abuse, Seizures, GERD, hypercholesterolemia, ADD, tachycardia Concomitant Medications: Phenobarbitol, metoprolol, lovastatin, prilosec, xanax, tylenol, celexa, remeron, methyphenidate Adverse Events: Anorexia, nausea, tiredness Study Status: Terminated early for positive alcohol screen

Table 34: Liver Function Test Results for Patient 302-216-2001

Dose ALO-01	BSL	40	60	80	80	40	40	0
Date	1/10/07	4/13/07	4/23/07	7/9/07	9/28/07	10/17/07	1/16/08	1/30/08
ALT	38	63	26	22	159	31	80	25
AST	33	58	30	22	75	26	43	20
Alk Phos	163	175	143	163	209	176	188	174

Values above the upper limit of normal are indicated in green.

Table 35: Liver Function Test Results for Patient 302-251-2014

Dose	BSL	60	100	160	120
Date	2/22/07	5/25/07	8/17/07	11/12/07	1/7/08
ALT	30	82	37	51	29
AST	21	151	53	45	35
Alk Phos	125	155	189	155	150

Values above the upper limit of normal are indicated in green.

In addition 6 patients (302-217-2007, 302-231-2009, 302-232-2008, 302-232-2015, 302-247-2002, 302-251-2002) entered the study with ALT elevations greater than 2 times the upper limit of normal. (Patients were excluded from enrollment for greater than 3 times the upper limit of normal for any transaminase elevation.) All of these patients had decreases in their transaminase

levels to the normal range on ALO-01. Data for these patients are displayed in Figure 33 and Figure 34.

Figure 33: AST Elevations at Baseline for Patients 302-217-2007, 302-231-2009, 302-232-2008, 302-232-2015, 302-247-2002, 302-251-2002

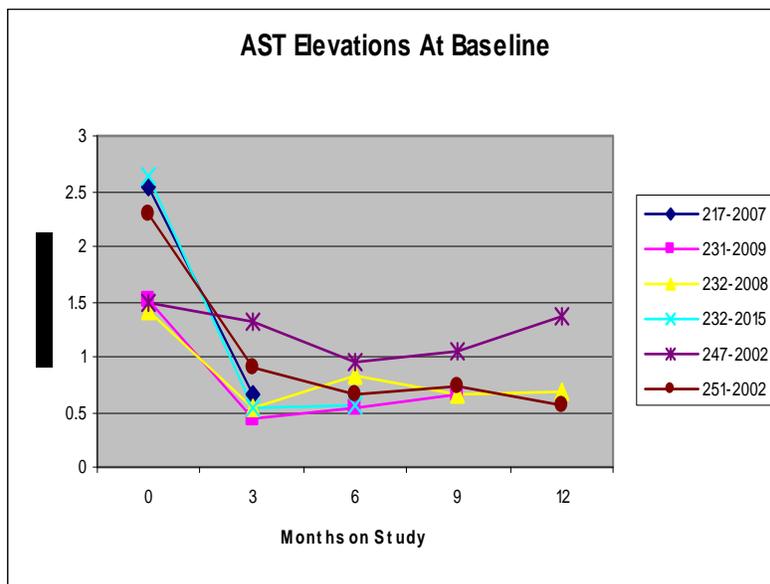
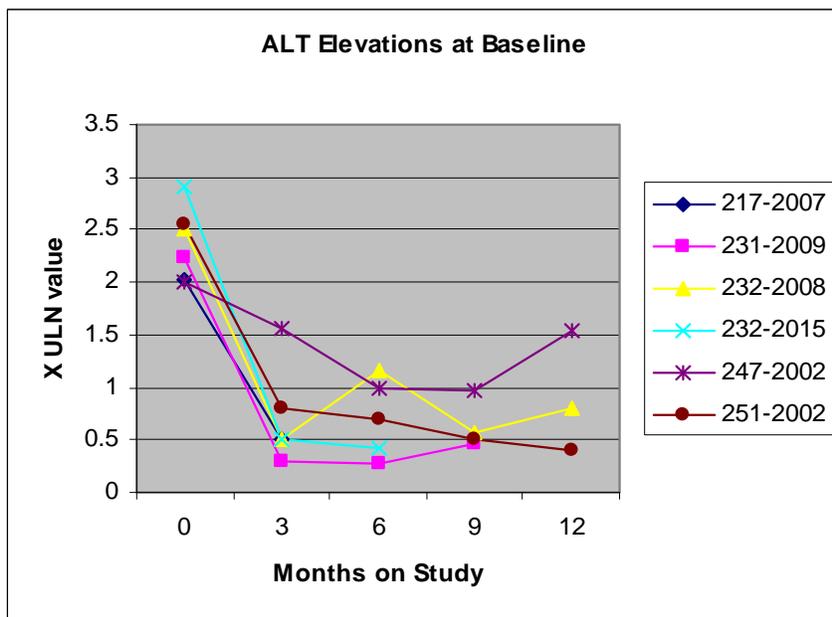


Figure 34: ALT Elevations at Baseline for Patients 302-217-2007, 302-231-2009, 302-232-2008, 302-232-2015, 302-247-2002, 302-251-2002.



In summary, very few patients had transaminase elevations, and those reported were minor and either transient, or attributable to concomitant medical conditions or therapies. It is unlikely that the very low levels of naltrexone or 6-β-naltrexol observed in these studies contributed to the

transaminase elevations. The exposure to naltrexone from ALO-01 does not appear to pose a hepatic risk.

6.4.10. Conclusions

- ALO-01 was well tolerated in short and long-term studies with an adverse event profile attributable to the sustained release morphine component which was not compromised by the addition of sequestered naltrexone.
- There was no notable pattern to SAEs and few were even possibly attributable to ALO-01.
- No evidence of precipitated opioid withdrawal was evident from either COWS or focused examination of withdrawal-associated adverse events. The withdrawal events reported were primarily due to placebo assignment or non-compliance with ALO-01 regimen.
- No evidence of hepatotoxicity with ALO-01 treatment was evident in the laboratory data. Especially notable is the reduction in transaminase levels with ALO-01 treated patients. This is consistent with the negligible plasma levels of naltrexone observed.
- ALO-01 is safe and well tolerated for extended duration treatment of chronic pain.

7. RISK MANAGEMENT PLAN

Alpharma has conducted extensive pre-marketing risk assessment to develop the ALO-01 Risk Management Plan, and to contribute to the post-marketing risk planning framework. The Risk Management Plan (RMP) encompasses both the Pharmacovigilance program and the Risk Evaluation and Mitigation Strategies (REMS) plan, which define elements to mitigate specific risks identified in the proposed labeling of ALO-01.

7.1. Risk Characterization

The medical risks associated with tampering with ALO-01 Capsules pellets were identified for opioid-naive and opioid-tolerant individuals. When crushing, chewing, or dissolving the pellets, the resulting morphine dose may be fatal, particularly in opioid-naive individuals. In contrast, when crushing, chewing or dissolving the pellets, liberating the naltrexone from its sequestered core, may result in the absorption of naltrexone and increase the risk of precipitating withdrawal symptoms in opioid-tolerant individuals.

The ALO-01 Capsule is classified as an extended-release opiate analgesic and is subject to the standard class labeling for contraindications, warnings, and precautions (see USPI). The black box statement for the proposed Full Prescribing Information submitted in the NDA of ALO-01 Capsules is presented in Figure 35.

Figure 35: Proposed Labeling-Boxed Warning

WARNING: ALO-01 capsules are an extended-release oral formulation containing pellets of morphine sulfate, an opioid receptor agonist with a sequestered core of naltrexone hydrochloride, an opioid receptor antagonist. ALO-01 is indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. When ALO-01 capsule contents are crushed, dissolved or chewed, both morphine and naltrexone are released and rapidly absorbed. The absorbed naltrexone mitigates the effects of the morphine.

ALO-01 capsules are to be swallowed whole or the contents of the capsules sprinkled on applesauce. The pellets in the capsules are not to be crushed, dissolved, or chewed. Misuse or abuse of ALO-01 by tampering with the formulation, crushing, dissolving, or chewing the pellets, causes the rapid release and absorption of both morphine and naltrexone. The resulting morphine dose may be fatal, particularly in opioid-naïve individuals. In opioid-tolerant individuals, the absorption of naltrexone may increase the risk of precipitating withdrawal.

ALO-01 capsules are a Schedule II controlled product which if taken intact can be misused or abused as can other extended-release opioid receptor agonists, legal or illicit.

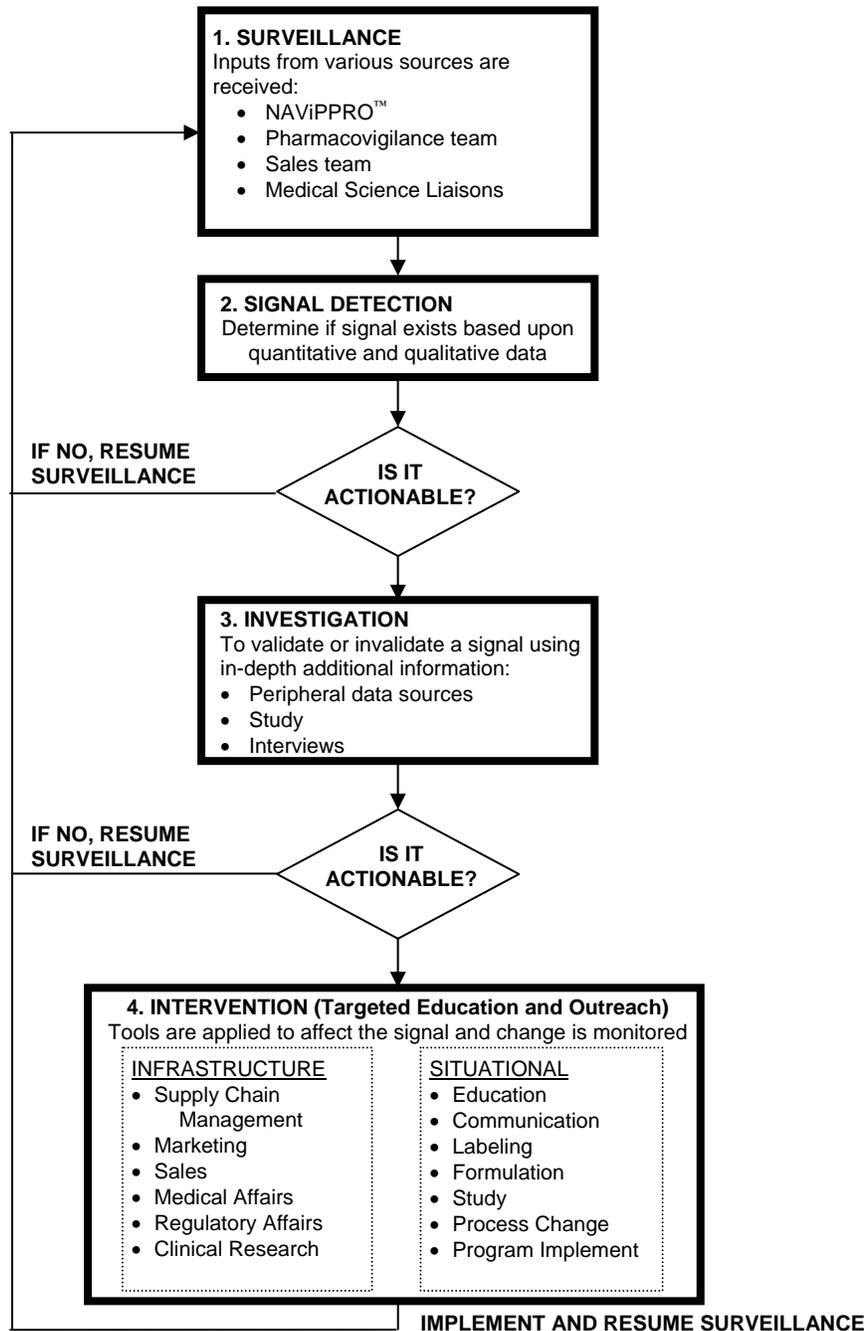
ALO-01 capsules are NOT intended for use as a prn analgesic.

Patients should not consume alcoholic beverages while on ALO-01 therapy. The co-ingestion of alcohol with ALO-01 may result in an increase of plasma levels and potentially fatal overdose of morphine.

7.2. Risk Management Process

Figure 36 presents the process used by Alpharma's Risk Management Committee to define, decide and implement corrective actions and to assess the performance of any RMP or product-specific REMS plan.

Figure 36: Risk Management Process Flow Diagram



7.3. REMS Plan

Goals and objectives are defined below:

- Goal #1: To minimize the potential for misuse, abuse, and diversion of ALO-01 Capsules.

- Objective #1: To minimize the potential misuse of the drug resulting in life-threatening events, such as respiratory depression leading to death
- Objective #2: To minimize the potential misuse, abuse, and diversion of drugs, in the pediatric population (less than 18 years of age)
- Objective #3: To minimize the potential diversion of drug from patients with moderate-to-severe chronic pain and assure appropriate management of pain
- Goal #2: To minimize the potential for appropriately prescribed patients to undergo withdrawal symptoms from the unintentional misuse of ALO-01 Capsules:
 - Objective #1: To minimize the potential for the drug to be inappropriately prescribed by qualified medical professionals
 - Objective #2: To minimize the potential for the drug to be inappropriately used by patients with chronic moderate-to-severe pain, resulting in precipitated withdrawal
 - Objective #3: To recognize and report the occurrence of withdrawal symptoms

7.3.1. Communication Plan

Alpharma will communicate the benefits and risks of ALO-01 Capsules to prescribers and pharmacists with a comprehensive communication plan that educates patients on the appropriate use of opioids, and their associated risks when treating their pain.

The REMS Communication Plan provides a comprehensive scientific and medical profile of the risks and benefits of the product in the Full Prescribing Information made available to the Health Care Professionals and, a Medication Guide to help them answer questions from patients regarding the appropriate use of the product.

Direct education is an important risk mitigation component for healthcare professionals. As such, these risks will be communicated via an ongoing national educational campaign that was initiated in 2007. PainBalance™ (“Maximize Relief. Minimize Abuse.”) is an Alpharma educational initiative and public awareness campaign, that explains the necessary “balance” between appropriate opioid prescribing and the precautions needed to prevent misuse, abuse, and diversion.

The initiative includes a multitude of programs including support of relevant continuing medical education and scientific symposia, and collaborations with scientific and government/regulatory organizations.

Education materials for stakeholders will emphasize appropriate storage of opioids, to minimize misuse, abuse, and diversion. In addition, Alpharma is sponsoring the National Family Partnership’s national “Lock Your Meds” campaign. This campaign, works with families and schools, to help minimize accidental exposure to opioids in homes where children live.

7.3.2. Elements of Safe Use

7.3.2.1. Healthcare providers who prescribe have particular training or experience, or are specially certified.

All medical professionals who are prescribers (considered pre-certified by their state medical board), have a DEA registration, and are called upon by Alpharma's field representatives will be provided with ALO-01 Capsules Medical Risk Management Kit. Prescribers may also request the kit through an Alpharma website.

Alpharma will support continuing education programs in related educational topics. Prescribers will receive brochures or other awareness communications from third-party medical education companies or organizations. Such programs, which may be supported by Alpharma educational grants, are intended to fulfill unmet educational needs. Topics will include:

- Appropriate prescribing of opioids
- Misuse, abuse, and diversion of opioids
- Withdrawal syndrome associated with opioids
- Urine drug testing and applications
- Lawful prescribing and prevention of diversion

Additionally, for clinicians who are DEA-registrants but may not have access to other educational offerings and cannot be reached by Alpharma representatives through its proactive communication plan, Alpharma will partner with a well-respected, professional medical association to support the development of a national "opioid safety course" for prescriber audiences in conjunction with a well-respected, professional medical association.

7.3.2.2. Pharmacies, practitioners, or healthcare settings that dispense ALO-01 Capsules are specially certified.

All pharmacies that have a DEA registration and are provided a license to dispense medications by their state board of pharmacy (considered to be pre-certified by the state), who may dispense ALO-01 Capsules, will be provided the following:

- Full Prescribing Information
- Medication Guide (physical and/or electronic formats)
- Katz N. Ed. "Tips, Photographs, & Explanations. A Practical Guide for Prescribing Controlled Substances". PharmaCom Group (Stamford). 2007. (handbook)

Alpharma will support continuing education programs in related educational topics. Pharmacists will receive brochures or other awareness communications from third-party medical education companies or organizations. Such programs, which may be supported by Alpharma educational grants, are intended to address unmet educational needs. Topics will include:

- Appropriate prescribing of opioids
- Misuse, abuse, and diversion of opioids

- Withdrawal syndrome associated with opioids
- Urine drug testing and applications
- Lawful prescribing and prevention of diversion

7.3.2.3. ALO-01 Capsules may be dispensed to patients with documentation of safe-use conditions;

In order to document safe-use conditions, prescribers who are contacted by Alpharma field sales representatives will be provided copies of the ALO-01 Capsules Medication Guide, and copies of:

- a standard patient opioid agreement,
- a screening tool,
- instructions for performing a urine drug test.

In addition these materials will be available to all prescribers and pharmacists by request through an Alpharma website. Proper use instructions will accompany the tools to give prescribers directions for incorporating them into practice including the recommendation that all documents be kept in the patient's medical chart for permanent record. As an example of its utility, an opioid agreement enables a commitment between the prescriber and the patient to treat pain appropriately while handling opioid medicines with care. Documentation of a patient screening and results from a urine drug test provide prescriber with guidance on whether patients may need additional provisions when prescribed opioids.

7.3.2.4. Each patient using ALO-01 Capsules is subject to certain monitoring

To enable basic monitoring of patients on ALO-01 Capsule treatment therapy, prescribers who are visited by Alpharma representatives, will be provided copies of a standard patient opioid agreement.

The opioid agreement is a mechanism to ensure compliance with drug therapy. It encourages patients to accept responsibility for and commit to responsible management of their opioid therapy. For example, a typical patient opioid agreement will have a clause that limits fulfillment of a patient's prescription to only one pharmacy. During follow-up visits, the prescriber is responsible for monitoring the patient's compliance with the agreement, using clinical judgment. Opioid agreements are signed between the prescriber and the patient; they require a mutual commitment to appropriate use of opioids for pain treatment, and are kept in the patient's medical chart.

Urine drug tests requirements are typically as part of a standard prescriber-patient opioid agreement. Targeted prescribers of ALO-01 Capsules will be provided instructional material on how to perform a urine drug test and interpret the results. These tests will be used to determine patients' compliance with prescribed opioids and identify non-prescribed substances. For example, for a patient taking ALO-01 Capsules, a urine drug test should show a positive morphine sample. Its absence could mean that the prescription was not filled or that the patient has been diverting the substance, possibly for profit and falsifying adequate opioid therapy.

Recommendations on the use of urine drug tests will be based upon individual clinician discretion (compulsory or random) and based upon a well-accepted and referenced medical guideline standard.

7.3.3. Implementation System

The deliverables of the REMS will be implemented in the following manner:

7.3.3.1. ALO-01 Capsules Medical Risk Management Kit (for Prescribers)

Material: The physical elements for prescribers will be packaged as a single “ALO-01 Capsules Medical Risk Management Kit” as part of a responsible-use campaign and will contain the following items:

- Full Prescribing Information
- Medication Guide
- Fishman SM. Responsible Opioid Prescribing: A Physician’s Guide. Federation of State Medical Boards. 2007. (handbook)
- Katz N. Ed. “Tips, Photographs, & Explanations. A Practical Guide for Prescribing Controlled Substances”. PharmaCom Group (Stamford). 2007
- Standard patient screening opioid risk tool
- Standard patient opioid agreement
- Instructional material on performing and interpreting urine drug tests

Route of Dissemination: The kit will be mailed to Alpharma-visited prescribers directly by a third-party vendor. It may be requested by visiting an Alpharma educational website or by contacting the toll-free call center. Requests for additional standard forms will be made available during the initial mailing and on the web.

Timeframe: Materials will be available for dissemination by the date of the product launch. Permission is currently being requested for materials provided by external sources. On a trimester basis, the list of prescribers currently being visited by Alpharma representatives will be reviewed and any new prescribers will also be sent the kit.

7.3.3.2. Product Education (for Pharmacists)

Materials:

- Full Prescribing Information
- Medication Guide
- Katz N. Ed. “Tips, Photographs, & Explanations. A Practical Guide for Prescribing Controlled Substances”. PharmaCom Group (Stamford). 2007. (handbook) (See Appendix G, Proposed REMS Supporting Document)

Route of dissemination: Pharmacists may receive items through a third-party mailing, and may request information and tools via an Alpharma educational website or by contacting the toll-free call center.

Timeframe: Materials will be available for dissemination by the date of the product launch.

7.3.3.3. Support the development of a national opioid safety course for health professionals, specifically those who are DEA registrants:

Materials: On-line responsible opioid use course

Route of dissemination: Alpharma will work with a well respected medical association to develop a program designed to educate clinicians on the appropriate prescribing of opioids.

Timeframe: Course would be available to health professionals, who are also DEA registrants, within 12 months of the date of the product launch.

7.3.3.4. Full Prescribing Information and Medication Guide:

Materials:

Full prescribing information

Medication Guide

Route of dissemination: Prescribing information and Medication Guides will be packaged with the stock bottle of drugs that is shipped to wholesalers for distribution to pharmacies.

Timeframe: Materials will be ready for dissemination by date of product launch.

7.3.4. Timetable for the Assessment of the REMS

Alpharma will submit REMS assessments according to the required reporting schedule of 18 months, 3 years, and 7 years of the anniversary of the approval date of ALO-01.

In addition to the regulatory requirements outlined in 21CFR314.80 for post marketing safety reporting requirements, early notification of adverse events set on a 15-day reporting schedule will allow the FDA to more quickly detect an emerging signal than if submitted in the periodic safety reports. In this case, the 15-day timeframe for reporting serious and unexpected adverse events associated with this product would be broadened to include the following adverse event case reports as “Important Medical Events”:

- Cases of drug-related misuse, abuse, and diversion
- Cases of drug-related pediatric exposure 18 years and under
- Cases of drug-related withdrawal syndrome
- Cases of overdose and medication errors
- Cases of death as an outcome

7.3.5. Information Needed for Assessments

In order to determine the performance and to enable continuous enhancements of the REMS, various surveillance data streams will be monitored to identify trends and potential signals.

All the data from the surveillance systems will be reviewed in aggregate on a routine basis to help identify trends that may be signals of abuse, misuse or medication errors.

Internal Sources of Information

POST-MARKETING PHARMACOVIGILANCE

Data obtained from post-marketing pharmacovigilance will include adverse events that will be deemed medically important such as: medication errors, accidental ingestions, exposure in adolescents, opioid withdrawal, death, respiratory depression, misuse, abuse, and diversion.

MEDICAL INFORMATION REQUESTS

Alpharma will track the number of requests for medical information and review the quantitative and qualitative patterns of medical information requests.

PRESCRIPTION VOLUME

Data from an industry standard vendor will be used to express the population exposure of ALO-01 Capsules. Evaluating general prescription volume information would also provide insight on the impact of ALO-01 on total use of long-acting opioids and localized adoption or rejection of abuse-deterrent technologies in geographical areas that are historically high in opioid abuse.

External Sources of Information

SUBSTANCE TREATMENT CENTERS (NAVIPPRO™)

ALO-01 Capsules–specific data collected from substance abuse treatment center patients during admission. These data are obtained from the NAVIPPRO™ System’s Addiction Severity Index (ASI-MV) Connect, and include: number of admissions noting ALO-01 Capsules as product of abuse, how drug was obtained and misused, geographical locations, other concomitant medications, and routes of administration.

INTERNET MESSAGE BOARDS (NAVIPPRO™ - WIS)

ALO-01 Capsules–specific data from the NAVIPPRO™ internet surveillance and survey systems, called Web Informed Services (WIS), provides insight on trends through substance-abuse related message boards. This Internet “chatter” can provide both qualitative and quantitative data on ALO-01 Capsules, specifically whether they’re being misused and/or if naltrexone as an abuse deterrent is a topic of discussion.

NATIONAL DRUG ABUSE DATABASES:

- DRUG ABUSE WARNING NETWORK (DAWN) which collects data of emergency departments visits
- NATIONAL SURVEY ON DRUG USE AND HEALTH (NSDUH), a population survey.

POISON CONTROL DATABASES

Data from the American Association of Poison Control Centers' National Poison Data Systems (NPDS) provide insight into all the toxicological information on the poison exposures reported to the US poison control centers.

MEDIA

Information from media surveillance including: quantitative increases in articles or news clips noting ALO-01 Capsules and geographical or behavioral trends.

FDA ADVERSE EVENT REPORTING SYSTEM (AERS)

Data from AERS will permit the comparison of reporting rates of ALO-01 Capsules to other opioids, with regards to misuse, abuse, overdose, and withdrawal.

8. ASSESSMENT OF BENEFIT/RISK RATIO

As mentioned in section 5, chronic pain is a significant health problem in the US and is often best treated with long-term prescription pain relievers. However, abuse and diversion of opioid prescription pain relievers is a public health problem extending beyond risks to the patient. The current challenge is maintaining patient access to opioids for legitimate pain management while minimizing potential for drug diversion and societal abuse.

In addition to regulation and education, decreasing abuse potential with innovative opioid formulations such as ALO-01 Capsules may curb opioid prescription diversion and illicit use.

Alpharma conducted a comprehensive pre-marketing risk assessment which guided the development and the design of ALO-01 to optimize its capability:

- To offer a safe, well-tolerated, efficacious alternative to patients with chronic pain without the societal prejudice often associated with the medical use of opioids.
- To mitigate the potential for abuse by the patient themselves or by non-patient population.

Table 36 provides a listing of the background, potential risks mitigated by the design of ALO-01 and the outcomes of the supporting clinical studies.

Other residual risks and new risks that may develop during the commercialization of ALO-01 will be addressed by Alpharma's Risk Management Plan and the supporting REMS and Pharmacovigilance plans.

Table 36: Summary of Potential Risks Mitigated and Outcomes of Clinical Studies

Background/Rationale	Potential Risks	Clinical Study	Outcome
Recreational users of this product who attempt to tamper with this product can be deterred if sufficient naltrexone abates the euphoric drive for misuse.	Ratio of morphine to naltrexone is insufficient to abate euphoria and drug liking while minimizing systemic exposure to naltrexone	ALO-KNT-201	Ratio to reduce drug liking and euphoria is optimally defined with minimal naltrexone PK profile.
Patients with chronic pain who are on long-term opioids and exposed to ALO-01 will not experience withdrawal symptoms.	Naltrexone absorption results in withdrawal syndrome.	ALO-KNT-302	The negligible levels of naltrexone absorption observed in the clinical program do not induce withdrawal syndrome.

**Table 36: Summary of Potential Risks Mitigated and Outcomes of Clinical Studies
 (Continued)**

Background/Rationale	Potential Risks	Clinical Study	Outcome
From a pharmacokinetic perspective, if ALO-01 and KADIAN [®] are bioequivalent, basic pharmacokinetic and pharmacologic studies do not need to be repeated.	ALO-01 is not bioequivalent to KADIAN [®] and studies will need to be initiated to better understand the product profile.	ALO-01-07-101	ALO-01 was found to be bioequivalent to KADIAN [®] by C _{max} and AUC.
Patients with chronic pain who need the flexibility to dose ALO-01 in various routes of administration (whole oral capsule or content sprinkled) or conditions (fasted or fed) can do so without compromise of drug efficacy or safety.	(1) ALO-01 sprinkled on apple sauce product is not bioequivalent to intact oral ALO-01 capsule given under fasted conditions; (2) ALO-01 given under fed conditions is not bioequivalent to intact ALO-01 given under fasted conditions.	ALO-01-07-102	(1) ALO-01 sprinkled on apple sauce was bioequivalent to ALO-01 given under fasted conditions. (2) ALO-01 given under fed conditions showed lower C _{max} but AUC was the same as ALO-01 given under fasted conditions.
1) Co-ingestion of extended-release opioid formulations with alcohol has been reported to cause the immediate release of the full, potentially lethal, dose of opioid (dose-dumping). 2) If ALO-01 is co-administered with alcohol despite general warnings; the full opioid dose will not be released. The effect of alcohol on ALO-01 needs to be defined to address unintended dose-dumping of the opioid.	ALO-01 co-administered with alcohol would induce dose-dumping.	ALO-01-07-103	(1) Overall exposure (AUC) at 4%, 20%, and 40% alcohol co-administered with ALO-01 was not different from ALO-01 administered with water. (2) At 4% and 20% alcohol co-administered with ALO-01, the rate and extent of absorption was not different from ALO-01 co-administered with water. At 40% alcohol co-administered with ALO-01, C _{max} was 2-fold greater and T _{max} was 5 hours earlier than other treatment arms.

**Table 36: Summary of Potential Risks Mitigated and Outcomes of Clinical Studies
 (Continued)**

Background/Rationale	Potential Risks	Clinical Study	Outcome
If a recreational user misuses ALO-01, sufficient naltrexone needs to be released to abate the euphoria associated with abuse.	If ALO-01 is crushed, the released naltrexone is not sufficient to deter abuse via abatement of euphoria.	ALO-01-07-104	When ALO-01 was crushed, naltrexone release was complete and bioequivalent to naltrexone oral solution of the same dose sequestered in the core.
If recreational abusers crush and inject contents of ALO-01, the exact amounts of naltrexone and morphine must abate euphoria to achieve the abuse-deterrent effect.	Plasma levels of naltrexone and morphine do not abate euphoria.	ALO-01-07-106	Intravenous study shows that the current ratio of morphine to naltrexone in ALO-01 is appropriate and significantly abates euphoria.
Patients who are on a stable dose of chronic opioids, and take ALO-01 will not experience opioid withdrawal syndrome if there is an incomplete sequestration of naltrexone. The amount of naltrexone that is needed to precipitate withdrawal symptoms needs to be quantified.	Plasma naltrexone levels observed in intact, multi-dose ALO-01 are near the threshold for precipitating withdrawal symptoms in patients on long-acting opioids.	ALO-01-07-107	Bolus Intravenous dosing of naltrexone lead to plasma concentrations much higher and with different pharmacokinetics than that observed with oral dosing of ALO-01. This study is being re-designed to employ much lower given orally naltrexone starting doses in view of actual naltrexone plasma concentrations observed in study 302.

**Table 36: Summary of Potential Risks Mitigated and Outcomes of Clinical Studies
 (Continued)**

Background/Rationale	Potential Risks	Clinical Study	Outcome
If used as intended, patients with chronic pain on ALO-01 should not have a clinically significant naltrexone effect. ALO-01 should have a similar efficacy and safety profile to an existing sustained-release opioid product.	(1) Significant naltrexone levels are measured at high levels in multi-dose, steady state; (2) ALO-01 is inferior to a currently marketed analgesic in efficacy and safety in pain patients.	ALO-KNT-202	(1) Steady state plasma morphine exposure (AUC) for ALO-01 was bioequivalent to KADIAN [®] and mean concentration profiles were similar. (2) Negligible levels of naltrexone detected from ALO-01 in some patients had no clinical affect on pain scores. (3) ALO-01 was found to be similar to a currently marketed long-acting opioid in efficacy and safety.
If ALO-01 is crushed the morphine and naltrexone should be released in the appropriate consistent ratio to be abuse deterrent.	(1) Morphine is fully released but naltrexone is inadequately released when ALO-01 is crushed; (2) Crushing ALO-01 does not abate euphoria.	ALO-01-07-205	(1) Both morphine and naltrexone are completely released in the appropriate ratio when ALO-01 is crushed. (2) Crushing ALO-01 significantly abates drug liking compared to IR morphine.
For patients with chronic pain, ALO-01 needs to demonstrate its efficacy in a larger population size of patients.	ALO-01 is not efficacious in a larger population of real patients.	ALO-KNT-301	ALO-01 was found to be efficacious for patients with chronic pain based upon the data.
For patients with chronic pain, ALO-01 needs to demonstrate its safety in a larger population size of patients.	ALO-01 is not safe in a larger population of real patients.	ALO-KNT-302	ALO-01 was found to be safe and well tolerated in 467 patients up to 12 months of therapy. This clinical study result is the primary contributor to the product's safety database.

9. CONCLUSION

Pain is one of the most common reasons to consult a physician, yet it is often inadequately treated, leading to needless suffering. Although morphine is recommended for the treatment of moderate-to-severe chronic pain, there are numerous impediments to its use. Barriers include concerns about addiction, respiratory depression, tolerance, diversion, abuse and fear of regulatory action. In an effort to provide a suitable morphine formulation to minimize abuse associated with opioid therapy, Alpharma has developed a product employing a pharmacologic core technology- ALO-01. This document presented a summary of the clinical data supporting the efficacy, safety and tolerability of ALO-01 Capsules. Clinical pharmacokinetic data confirmed that the naltrexone remains sequestered in the core technology when ALO-01 is used as directed. Clinical safety data were assessed to identify the potential adverse events associated with the negligible level of naltrexone detected. While ALO-01 could provide benefits to patients, the possible risks associated with its commercialization also need to be addressed. Strategies to mitigate the residual or new risks were proposed in the REMS.

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