

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-321

MEDICAL REVIEW(S)

CLINICAL REVIEW TEMPLATE

Application Type	NDA
Submission Number	22-321
Submission Code	RS-000
Letter Date	July 29, 2008 <i>June 30</i>
Stamp Date	July 30, 2008 <i>June 30</i>
PDUFA Goal Date	December 30, 2008
Reviewer Name	Jin Chen, MD, PhD
Review Completion Date	Nov 25, 2008
Established Name	Morphine sulfate extended-release with naltrexone HCl
(Proposed) Trade Name	EMBEDA
Therapeutic Class	Opioid analgesic
Applicant	Alpharma Pharmaceuticals
Priority Designation	P
Formulation	Capsule
Dosing Regimen	Once or Twice a day
Indication	Management of moderate-to-severe chronic pain
Intended Population	Adults

TABLE OF CONTENTS

1. RECOMMENDATIONS/RISK BENEFIT ANALYSIS.....	4
1.1 RECOMMENDATION ON REGULATORY ACTION	4
1.2 RISK BENEFIT ANALYSIS.....	4
1.3 RECOMMENDATIONS FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES	6
1.4 RECOMMENDATION FOR OTHER POSTMARKETING STUDY COMMITMENTS	7
2. INTRODUCTION AND REGULATORY BACKGROUND	7
2.1 PRODUCT INFORMATION	7
2.2 TABLE OF CURRENTLY AVAILABLE TREATMENT(S) FOR PROPOSED INDICATION	8
2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES	9
2.4 IMPORTANT ISSUES WITH CONSIDERATION TO RELATED DRUGS	9
2.5 SUMMARY OF PRESUBMISSION REGULATORY ACTIVITY RELATED TO THIS SUBMISSION	10
2.6 OTHER RELEVANT BACKGROUND INFORMATION.....	11
3. ETHICS AND GOOD CLINICAL PRACTICES.....	11
3.1 SUBMISSION QUALITY AND INTEGRITY	11
3.2 COMPLIANCE WITH GOOD CLINICAL PRACTICES	11
3.3 FINANCIAL DISCLOSURES	11
4. SIGNIFICANT EFFICACY OR SAFETY FINDINGS RELATED TO OTHER REVIEW DISCIPLINES.....	11
4.1 CHEMISTRY MANUFACTURING AND CONTROLS (CMC).....	11
4.2 CLINICAL MICROBIOLOGY (IF APPLICABLE).....	15
4.3 PRECLINICAL PHARMACOLOGY/TOXICOLOGY	15
4.4 CLINICAL PHARMACOLOGY	15
4.4.1 Mechanism of Action	15
4.4.2 Pharmacodynamics.....	17
4.4.3 Pharmacokinetics.....	22
5. SOURCES OF CLINICAL DATA AND REVIEW STRATEGY	28
5.1 TABLES OF CLINICAL STUDIES	28
5.2 REVIEW STRATEGY	31
5.3 DISCUSSION OF INDIVIDUAL STUDIES	31
6. INTEGRATED REVIEW OF EFFICACY	32
SUMMARY OF EFFICACY RESULTS AND CONCLUSIONS	32
6.1 PROPOSED INDICATION	33
6.2 METHODS/STUDY DESIGN.....	33
6.3 DEMOGRAPHICS	34
6.4 PATIENT DISPOSITION	36
6.5 ANALYSIS OF THE PRIMARY ENDPOINT(S)	36
6.6 SECONDARY ENDPOINT(S).....	39
6.7 SUBPOPULATIONS	41
6.8 ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS	41
6.9 DISCUSSION OF PERSISTENCE OF EFFICACY AND/OR TOLERANCE EFFECTS	42
6.10 ADDITIONAL EFFICACY ISSUES/ANALYSES.....	44
7. INTEGRATED REVIEW OF SAFETY	46
SUMMARY OF SAFETY RESULTS AND CONCLUSIONS.....	46
7.1 METHODS.....	47
7.1.1 Discussion of Clinical Studies Used to Evaluate Safety	47
7.1.2 Adequacy of Data	48

7.1.3	Pooling Data Across Studies to Estimate and Compare Incidence.....	48
7.2	ADEQUACY OF SAFETY ASSESSMENTS.....	49
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations 49	
7.2.2	Explorations for Dose Response.....	56
7.2.3	Special Animal and/or In Vitro Testing.....	56
7.2.4	Routine Clinical Testing.....	56
7.2.5	Metabolic, Clearance, and Interaction Workup.....	56
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class.....	57
7.3	MAJOR SAFETY RESULTS AND DISCUSSION.....	57
7.3.2	Nonfatal Serious Adverse Events.....	57
7.3.3	Dropouts and/or Discontinuations.....	59
7.3.4	Significant Adverse Events.....	62
7.4	SUPPORTIVE SAFETY RESULTS AND DISCUSSION.....	62
7.4.1	Common Adverse Events.....	62
7.4.3	Laboratory Findings.....	69
7.4.4	Vital Signs.....	73
7.4.5	Electrocardiograms (ECGs).....	73
7.4.6	Special Safety Studies.....	74
7.4.7	Immunogenicity.....	74
7.5	OTHER SAFETY EXPLORATIONS.....	74
7.5.1	Dose Dependency for Adverse Findings.....	74
7.5.2	Time Dependency for Adverse Findings.....	75
7.5.3	Drug-Demographic Interactions (gender, race).....	76
7.5.4	Drug Disease Interactions.....	76
7.5.5	Drug-Drug Interactions.....	76
7.6	ADDITIONAL SAFETY EVALUATIONS.....	77
7.6.1	Human Carcinogenicity.....	77
7.6.2	Human Reproduction and Pregnancy Data.....	77
7.6.3	Pediatrics and Assessment and/or Effects on Growth.....	77
7.6.4	Overdose, Drug Abuse Potential/ Withdrawal and Rebound.....	77
7.7	ADDITIONAL SUBMISSIONS.....	91
8.	POSTMARKETING EXPERIENCE.....	91
9.	APPENDICES.....	91
9.1	LITERATURE REVIEW AND OTHER IMPORTANT RELEVANT MATERIALS/REFERENCES.....	91
9.2	LABELING RECOMMENDATIONS.....	91
9.3	ADVISORY COMMITTEE MEETING.....	92
9.4	INDIVIDUAL STUDY REVIEWS.....	93
9.4.1	Study ALO-KNT-301.....	93
9.4.2	Study ALO-KNT-202.....	122
9.4.3	Study ALO-KNT-302.....	137

1. RECOMMENDATIONS/RISK BENEFIT ANALYSIS

1.1 Recommendation on Regulatory Action

The proposed morphine/naltrexone combination product, Kadian NT Capsule (ALO-01 or EMBEDA)¹ is recommended for *approval* for the proposed indication according to my review of clinical data submitted in this NDA:

- Kadian NT Capsule was statistically superior to placebo in analgesia in chronic pain patients.
- Kadian NT Capsule was bioequivalent to the reference drug, Kadian capsules, in the PK profile of morphine.
- There were no new safety signals associated with Kadian NT capsules based on the submitted safety database as compared to safety profile of other drugs in the opioid class.
- No apparent opiate withdrawal syndrome was associated with naltrexone release. Although plasma naltrexone and 6- β -naltrexol (a weak active metabolite) were detectable in some patients during the 12-month open-label Kadian NT treatment, the levels were very low and the possible minimal impact on opiate withdrawal and/or efficacy of morphine is acceptable with the appropriate labeling (titration to effect regimen and warnings).

1.2 Risk Benefit Analysis

The proposed formulation, Kadian NT capsules containing extended-release morphine pellets sequestered with naltrexone cores (the ratio of morphine to naltrexone: 25:1) was found efficacious and no new safety signals were detected in clinical trials in patients with chronic pain. The benefit/risk analysis is shown below.

Benefits:

- Kadian NT efficacy was established with one adequate and well-controlled clinical trial in chronic pain patients.
- No new safety signals were detected during the clinical trials compared to other drugs in the opioid class.
- The naltrexone sequestered in the Kadian NT pellet core released when the pellets were physically manipulated (b) (4) and showed abuse deterrence potential in the *in vivo* crushed study.
- Kadian NT was bioequivalent in its plasma morphine profile to Kadian and maintained the similar morphine extended-release profile, suggesting no PK interaction with naltrexone.

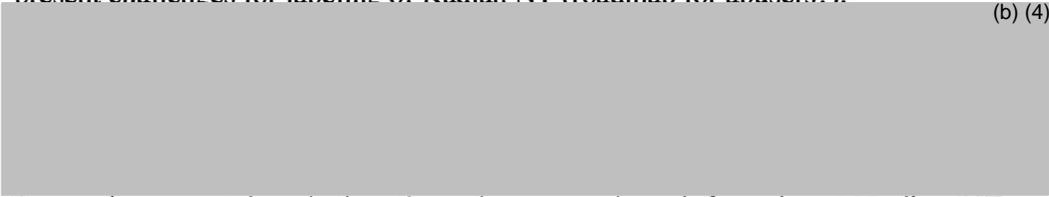
Risks:

- Exposure of intact Kadian NT to 40% alcohol *in vivo* selectively dose-dumps morphine but not naltrexone, however, no *in vivo* dose-dumping occurred with

¹ Kadian NT, ALO-01 and EMBEDA are synonymous and refer to the same product. For consistency in this review, Kadian NT capsule is used; ALO-01 may be shown in some tables and figures which are copied and pasted from the Applicant's original documents in the NDA submission.

Kadian under the same conditions (NDA 20-616), suggesting Kadian NT may be more risky in terms of misuse/abuse. The selective dose-dumping may also present challenges for labeling of Kadian NT (roadman for abusers?).

(b) (4)

- 
- 
- It remains uncertain whether the naltrexone released from intact Kadian NT pellets (for on-label use) compromises efficacy of morphine and/or precipitates opiate withdrawal syndrome in opiate-dependent patients due to the inadequate design of the clinical trials in terms of the assessment of withdrawal. However, there were no documented cases of withdrawal syndrome during the clinical trials.

Naltrexone release from intact Kadian NT pellets: In the 12-month open-label trial (Study ALO-KNT-302), plasma naltrexone and its metabolite, 6- β -naltrexol, were detectable in 23% and 80% patients, respectively, across 12 months. The highest plasma levels were 0.145 ng/ml for naltrexone and 3.72 ng/ml for 6- β -naltrexol from trough blood sampling (at around 12 hours post dosing). There appears to be no accumulation of either naltrexone or 6- β -naltrexol based on the trough blood samples. As compared to published studies, the plasma naltrexone and 6- β -naltrexol levels were low and may not result in significant pharmacological effects.

- Publication #1²: In opiate-experienced/nondependent healthy subjects treated with an oral daily dose naltrexone 25 mg for five days, plasma naltrexone and 6- β -naltrexol were approximately 3 ng/ml and 18 ng/ml, respectively at trough blood sampling (5.5 hours post dosing).
- Publication #2³: In opiate-naïve healthy subjects treated with oral daily dose of naltrexone 16, 32 or 48 mg, the plasma concentration of naltrexone to occupy half opiate receptors in the brain was 1.6 ng/ml based on a positron emission tomography (PET) scan.

Kadian NT treatment (with flexible dosing regimen over 12 months) resulted in 10-20 times less for plasma naltrexone and 5 times less for 6- β -naltrexol than the literature reports. Effects on analgesic efficacy of morphine or precipitation of opiate withdrawal would be likely minimal. However, the clinical trials submitted in the NDA provided limited values to assess the naltrexone-associated effects:

- The study population was not opiate-dependent patients (the susceptible population)
- Subjects were titrated Kadian NT but not Kadian
- Kadian was not included a reference (comparator).

² Schuh KJ, et al: Onset, magnitude and duration of opioid blockade products by buprenorphine and naltrexone in humans. *Psychopharmacology* 145: 162-174, 1999.

³ Wong DF et al: In vivo human opiate receptor occupancy of naltrexone: A dose-response analysis (Abstract); *Society for Neuroscience* 2006

Both studies were cited by the Applicant to support assessment of low plasma naltrexone levels resulted from Kadian NT capsules in the NDA submission.

Although the individual titration regimen to effect as labeled for all opiate products may potentially justify the antagonistic effects of naltrexone, a further study conducted during the post-marketing period may be useful to address both potential impact on efficacy and opiate withdrawal associated naltrexone released from Kadian NT.

Naltrexone release from manipulated Kadian NT pellets: the unique property of the Kadian NT pellet is the sequestered naltrexone core and when the pellet is physically manipulated, naltrexone releases in order to prevent the drug liking and euphoric effects of morphine. Both *in vitro* (extraction) and *in vivo* (PK/PD) studies in the NDA demonstrated some potential advantage of the abuse deterrence (such as the *in vivo* crushed PK/PD studies and the *in vitro* extraction of both morphine and naltrexone with (b) (4)). However, the following concerns may limit the values of the abuse deterrence potential:

- Under certain *in vitro* conditions (b) (4) morphine can be selectively extracted from Kadian NT and easily separated from naltrexone. Thus, IV abuse of Kadian NT can not be mitigated.
- The morphine, but not naltrexone, can be selectively dumped from Kadian NT *in vivo* by 40% alcohol. The C_{max} of plasma morphine was double and the T_{max} was 5 hours shorter, when compared to administration of Kadian NT with water. The C_{max} was 60% C_{max} from the crushed Kadian NT. Under the 40% alcohol, the plasma naltrexone was undetectable in most subjects and plasma 6-β-naltrexol was detected in all subjects but was low. The highest plasma levels were 2.6% C_{max} for naltrexone and 6.3% C_{max} for 6-β-naltrexol when compared with the crushed Kadian NT. Opiates are commonly abused with alcohol; the presence of naltrexone in this formulation appears to have no effect when Kadian NT is abused or misused with alcohol.
- (b) (4)
- Kadian was not compared in the PK/PD study with crushed Kadian NT. It is unknown the actual advantage (magnitude) of naltrexone released from the crushed Kadian NT in mitigation of drug liking and euphoric effects.
- (b) (4)

1.3 Recommendations for Postmarketing Risk Management Activities

The proposed product, Kadian NT capsules, meets the requirements of the Risk Evaluation and Mitigation Strategy (REMS) (*Title IX, Subtitle A, Section 901 of FDAAA*). The Applicant has proposed REMS, which is under reviewing by the Office of Surveillance and Epidemiology (OSE).

1.4 Recommendation for other Postmarketing Study Commitments

The following post-marketing studies on Kadian NT are recommended if the product is approved:

- If a claim is sought by the Applicant regarding “abuse deterrence” for Kadian NT, epidemiology studies should be conducted in “actual” use setting to further assess the favorable benefit/risk ratio of Kadian NT over Kadian in terms of misuse/abuse.
- Potential precipitation of opiate withdrawal syndrome associated with naltrexone release from Kadian NT should be further assessed in opioid-dependent patients.

2. INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

Kadian NT capsules contain extended-release pellets of morphine sulfate with sequestered naltrexone hydrochloride. The pellets are spheroid in shape with diameters ranging from 1.0 mm to 1.7 mm. Each pellet consists of (b) (4)

The morphine sulfate to naltrexone hydrochloride ratio is fixed at 25:1 (4% naltrexone HCl). (b) (4)

(Figure 2.1).

Kadian NT pellet is designed to provide extended-release morphine sulfate while the naltrexone hydrochloride remains sequestered within the pellet. If the Kadian NT pellets are cracked or crushed, both morphine and naltrexone are released and the opportunity to abuse the immediately released morphine is offset by the opiate antagonistic effects of naltrexone. If Kadian NT pellets are subjected to some of the most common approaches to “extract” the morphine from the extended-release pellet, the naltrexone would likely be co-extracted with morphine and mitigate the liking and euphoric effects of the morphine in the drug abuser.

There are six dosage strengths of Kadian NT capsules based on the amount of morphine sulfate: 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg.

**Figure 2.1: A schematic representation and a cross-sectional SEM picture of Kadian NT (ALO-01) pellet
(From the Applicant's Figure 1 in Section 3.2.P.1 of the NDA submission)**

(b) (4)



2.2 Table of Currently Available Treatment(s) for Proposed Indication

The proposed indication of Kadian NT capsules is “*The management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time*”. The same treatment is indicated by six currently-marketed extended-release opioid oral products in US (Table 2.2).

There are two opiate agonist/antagonist combination oral products intended to mitigate IV abuse of the opiate agonists:

- **Talwin NX** (NDA 18-733, approved Dec 16, 1982): the pentazocine and naloxone combination oral tablets (0.5 mg and 50 mg) for the indication “**the relief of moderate to severe pain**”
- **Suboxone** (NDA 20-733, approved on Oct 8, 2002): the buprenorphine and naloxone combination oral tablets (2/0.5 mg and 8/2 mg) for indication “**the treatment of opioid dependence**”.

**Table 2.2: Currently available treatment for proposed indication of Kadian NT Capsules
(Extracted from the CDER's Orange Book, Nov 13, 2008)**

Drug Name	Active Ingredient	Dosage form	NDA #	Approved date	Inventor
Kadian	Morphine sulfate	Capsule 10, 20, 30, 50, 60, 80, 100, 200 mg	20-616	1996 2001 2006 2007	Alpharma Pharms
MS Contin	Morphine sulfate	Tablet 15, 30, 60, 100, 200 mg	19-516	1987 1988 1989 1990 1993	Purdue Pharma LP
Avinza	Morphine sulfate	Capsule 30, 60, 90, 120 mg	21-260	2002	King Pharms
Oramorph SR	Morphine sulfate	Tablet 15, 30, 60, 100 mg	19-977	1991 1994	Xanodyne Pharm
Opana ER	Oxymorphone HCl	Tablet 5, 7.5, 10, 15, 20, 30, 40 mg	21-610	2006 2008	Endo Pharms
OxyContin	Oxycodone HCl	Tablets 10, 15, 20, 30, 40, 60, 80 mg	20-553	1995, 1997, 2006	Purdue Pharma LP
Ultram ER	Tramadol HCl	Tablet 100, 200, 300 mg	21-692	2005	Biovail Labs

2.3 Availability of Proposed Active Ingredient in the United States

The two active ingredients, *morphine sulfate* and *naltrexone*, formulated in the proposed product are available in the United States. There are 15 morphine sulfate products and three naltrexone products, as a Reference Listed Drug (RLD), marketing in US (based on CDER's Orange Book, November 13, 2008)

2.4 Important Issues with Consideration to Related Drugs

Misuse and abuse of extended-release morphine products by crushing (then taken by oral and snorting) and extraction (followed by IV) is the important issue. Other risk associated with extended-release formulation of opiates is dose-dumping when the products are taken alcohol. Development of misuse/abuse deterrent formulations of morphine and other opiates is one of strategies to mitigate these risks.

2.5 Summary of Presubmission Regulatory Activity Related to this Submission

Meetings with the Applicant:

- On March 16, 2005, a pre-IND 70,853 meeting was held to discuss overall clinical development program.
- On Aug 30, 2005, the initial IND was submitted with a Phase 2 protocol (multiple-dose PK, efficacy/safety in chronic pain patients).
- On Aug 31, 2007, the Applicant requested a pre-NDA meeting and canceled the request later (on Oct 1, 2007) after received the **Division's written response**.

SPA agreements on the Phase 3 protocol ALO-KNT-301:

On July 11, 2006, the Applicant submitted a Phase 3 trial protocol (ALO-KNT-301) SPA review, and resubmitted **on Sep 8 and Oct 31, 2006 in response to Division's comments**. The following final agreements were reached on Dec 14, 2006:

- Randomized withdrawal approach
- Primary endpoints: The mean change of weekly BPI diary average pain score from the randomization baseline to Week 12 (the end of maintenance treatment)
- Primary efficacy analyses, including BOCF/LOCF mixed imputation method for dropouts and sensitivity analyses (three alternative imputation methods)

Refuse-to-filed the first NDA submission:

On Feb 28, 2008, the proposed product was submitted under NDA22-321. However, it was refused to file due to deficiencies in safety database. Subsequently, the Applicant withdrew the submission. The NDA was resubmitted on June 30, 2008 (fileable, under review now).

Guidance to the Applicant for clinical development

- One pivotal efficacy trial and one long-term safety trial
- Safety database: 500 patients exposed to the product, including 100 patients for 6 months and 50 patients for 12 months
- Superiority trial on Kadian NT (vs. placebo and/or active comparator) if there is any systemic naltrexone exposure.
- Clinical data are needed to support that the sequestered naltrexone in Kadian NT will deter abuse of morphine and not result in opiate withdrawal.
- Provide an integrated safety dataset for all phase 2 and 3 trials.
- **Difficult to establish labeling claim "reduce the abuse potential"**
- Need development of a post-marketing product to support an indication for reduced abuse potential
- Sequestered core of naltrexone in Kadian NT may deter crushing abuse (IV or oral), but not prevent abuse following oral intact pellets capsules.
- If the product is bioequivalent to Kadian, a similar labeling (to Kadian) would be acceptable

2.6 Other Relevant Background Information

The Applicant appears not to have submitted this product to other regulatory agencies outside US.

3. ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

All data and documents in this NDA were electronically submitted by following the **electronic submission and CTD's guidances**. The documents were well organized and linkable. The datasets in SAS format were also easily accessible with consistent variables.

3.2 Compliance with Good Clinical Practices

All clinical trials were conducted under Good Clinical Practice, as stated in the front page of the study reports.

Four study sites from Study ALO-KNT-301 and two study sites from Study ALO-KNT-302 were selected for inspection by the Division of Scientific Investigations (DSI). There are no outstanding issues based on the preliminary inspection result received two sites of each study. The final conclusion and results from the remaining two sites of Study 301 are pending.

3.3 Financial Disclosures

The Applicant submitted the Form FDA 3454 "**Certification: Financial Interests and Arrangements of Clinical Investigator**", attached with a list of all investigators of submitted clinical studies and checked the "1" as quoted below:

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

4. SIGNIFICANT EFFICACY OR SAFETY FINDINGS RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry Manufacturing and Controls (CMC)

As per the CMC reviewer, Dr. Elsbeth Chikhale, there are no outstanding issues with the CMC data submitted in the NDA, including impurity, stability and manufacturing. Of

five manufacturing sites selected for inspection, four were completed and the result for one site is pending. There are no outstanding issues with the four completed inspection sites based on preliminary results. See the CMC review for details.

In vitro extraction studies under different tampering conditions submitted under the CMC section were primarily reviewed by the Control Substance Staffs (CSS) of CDER. The review is pending. The following summary is based on the Applicant's background packager for the Close Session of the Advisory Committee meeting.

(b) (4)



2 Page(s) has been Withheld in Full immediately following this page as B4 (CCI/TS)

4.2 Clinical Microbiology (if applicable)

Not applicable for this product.

4.3 Preclinical Pharmacology/Toxicology

As per the Pharm/Tox reviewer, Dr. Elizabeth Bolan, no preclinical pharmacology/toxicology studies on Kadian NT were submitted to this NDA. There are no outstanding issues with the proposed product. The preclinical information in the proposed labeling is adapted from reference drugs, Kadian (NDA 20-616) and ReVia (b) (4) through 505(b)(2) regulation. See Pharm/Tox review for details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Morphine is a natural product that is the prototype for the class of natural and synthetic opioid analgesics. Opioids produce a wide spectrum of pharmacologic effects including analgesia, dysphoria, euphoria, somnolence, respiratory depression, diminished gastrointestinal motility, altered circulatory dynamics, histamine release and physical dependence.

Morphine produces both its therapeutic and its adverse effects by interaction with one or more classes of specific opioid receptors (μ , κ and δ) located throughout the body. Morphine acts as a pure agonist, binding with and activating opioid receptors at sites in the peri-aqueductal and peri-ventricular grey matter, the ventro-medial medulla and the spinal cord to produce analgesia.

Naltrexone is a potent, pure, centrally acting antagonist at opiate receptors μ , κ and δ that reverses the subjective and analgesic effects of opioid agonists by competitively binding at opiate receptors. Naltrexone can either displace opiate agonist (such as morphine) from binding at these receptors or prevent opiate binding. The elimination half-life of naltrexone is about 4 hours; however, the pharmacological effects of naltrexone may persist for up to 72 hours. It is also known that naltrexone has higher binding affinity than morphine to those opiate receptors.

Effects of morphine on the Central Nervous System (CNS): The principal actions of therapeutic value of morphine are analgesia and sedation (i.e., sleepiness and anxiolysis). Specific CNS opiate receptors and endogenous compounds with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression of analgesic effects. In addition, when morphine binds to μ -opioid receptors, it results in positive subjective effects, such as drug liking, euphoria, and high. Morphine produces respiratory depression by direct action on brainstem respiratory centers. The mechanism of respiratory depression involves a reduction in the responsiveness of the brainstem respiratory centers to increases in carbon dioxide tension, and to electrical stimulation. Morphine depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia. Morphine causes miosis, even in total darkness, and little tolerance develops to this effect. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen with worsening hypoxia in the setting of morphine overdose.

Effects of morphine on the Gastrointestinal Tract and Other Smooth Muscle: Gastric, biliary and pancreatic secretions are decreased by morphine. Morphine causes a reduction in motility associated with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm. The end result is constipation. Morphine can cause a marked increase in biliary tract pressure as a result of spasm of the sphincter of Oddi.

Effects of morphine on the Cardiovascular System: Morphine produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Release of histamine may be induced by morphine and can contribute to opioid-induced hypotension. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating.

The proposed product, Kadian NT pellet (filled into Capsules), is a fixed combination of morphine sulfate and naltrexone HCl at a ratio of 25 to 1. The naltrexone is sequestered in the core of extended-release pellet of morphine. Physical manipulation of the pellets (crushing or dissolution) would hypothetically present an effective antagonistic dose of naltrexone with morphine and mitigate the euphoric potential of morphine. If, however, Kadian NT pellets/Capsules are taken properly, the naltrexone would remain sequestered and less likely antagonize analgesic effects of morphine or precipitate opiate withdrawal syndrome in opiate-dependent patients.

4.4.2 Pharmacodynamics

The Applicant submitted four PD studies: three were single oral dose trials (ALO-KNT-201, ALO-01-07-106 and ALO-01-07-205) and one was IV dosing trial (ALO-01-07-107), to establish and confirm the optimal ratio of morphine and naltrexone in terms of drug liking and euphoric effects. These study reports were consulted to the Controlled Substance Staffs (CSS) in OND/CDER (see the CSS's review for details). **The following is summary based on the PK review performed by Dr. Srikanth Nallani, the Applicant's Summary of Clinical Pharmacology Studies and individual study reports submitted in the NDA:**

Study ALO-KNT-201 (morphine to naltrexone ratio): This was a randomized, double-blind, single-dose, crossover, placebo-controlled, PK and PD study to evaluate the most effective and appropriate amount of naltrexone required (naltrexone to morphine ratio) to abate the euphoric effect of morphine in nondependent, recreational opioid drug users. The subjects received a single oral dose of 120 mg morphine (immediately release) and varying dose of naltrexone in five different ratios of naltrexone to morphine from 1:50 to 1:3.125 followed by PD (drug liking and abuse potential) and PK (plasma morphine, naltrexone and 6- β -naltrexol) assessments. The results showed that

- Co-administration of an oral solution of naltrexone with morphine 120 mg dose dependently reduced the positive effects of morphine administration. Naltrexone 4.8 mg (25:1 morphine/naltrexone ratio) was the lowest naltrexone dose that reduced the morphine induced positive effects.
- Study medications were tolerated by the subjects (nondependent, recreational opioid drug users).
- Co-administration of most naltrexone doses with morphine 120 mg tended to increase C_{max} and decrease T_{max} (shorter) of morphine in a dose-dependent manner.
- The C_{max} and AUC of plasma naltrexone and 6- β -naltrexol was dose propositional.

Study ALO-01-07-205 (crushed vs. intact pellets): This was a randomized, placebo-controlled, double-blind, triple-dummy, sing-dose, 4-way crossover study in healthy opiate experienced but non-dependent adult subjects (n=32). The objective was to compare PD (drug liking, subjective drug values, Addiction Research Center Inventory and pullillometry) and PK (plasma morphine, naltrexone and 6- β -naltrexol) among whole

Kadian NT pellets, crushed Kadian NT pellets (b) (4), morphine oral solution (Statex Oral Drops, immediate-release) and placebo. The subjects received a single oral dose of 120 mg morphine of each testing agent with apple juice. The crushed Kadian NT pellets were dissolved in apple juice at room temperature before administration.

The results showed that average drug liking scores were lower in Kadian NT pellets intact and crushed when compared to morphine sulfate oral solution. There was statistical significance in the peak drug liking between intact or crushed Kadian NT and morphine oral solution or placebo but not between intact and crushed Kadian NT (Table 4.4.2).

The profile of drug liking scores over 12 hours post-dosing appears correlated with profile of plasma morphine and naltrexone, as shown in Figure 4.4.2a. There was high variability in the PD response noted in all treatment groups.

The responder analysis of the peak drug liking reduction compared to the morphine oral solution treatment showed that more subjects treated with crushed Kadian NT had the drug liking reduction 40-40% than with intact Kadian NT (Figure 4.4.2b).

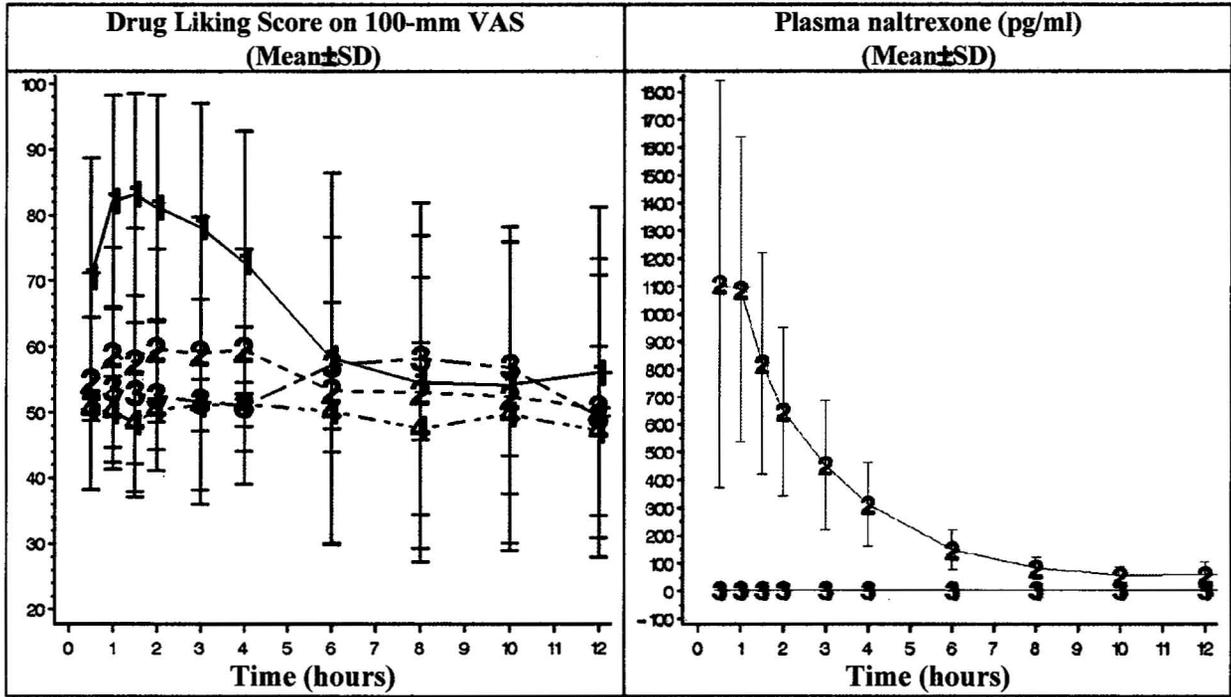
During the study, four subjects (Subject #9002, 9009, 9015, 9034) receiving the crushed Kadian NT demonstrated strong drug liking (VAS score = 100), despite the release of naltrexone from the sequestered pellets.

Table 4.4.2: Comparison of the peak drug liking (Emax) after single oral dose among crushed Kadian NT and intact Kadian NT, placebo, morphine oral solution (From the Applicant's Table 14.2.2.1.3 in the study ALO-01-07-205 report)

**Table 14.2.2.1.3 VAS: Drug Liking - Emax (Primary Endpoint)
Analysis of Variance - Per Protocol Population**

	Mean of Differences (95% CI)	F (df)	P-value	Adjusted P-value*
Key Components of Variance				
Treatment	----	62.05 (3, 90)	<.001	----
Period	----	3.55 (3, 90)	0.018	----
Treatment Sequence	----	1.82 (3, 28)	0.166	----
Contrasts				
Kadian NT 120 mg crushed - Placebo	15.9 (10.4, 21.3)	33.32 (1, 90)	<.001	<.001
Kadian NT 120 mg whole - Placebo	15.4 (9.9, 20.9)	31.38 (1, 90)	<.001	<.001
Morphine Sulfate IR 120 mg - Placebo	37.3 (31.8, 42.7)	183.74 (1, 90)	<.001	<.001
Morphine Sulfate IR 120 mg - Kadian NT 120 mg crushed	21.4 (15.9, 26.9)	60.58 (1, 90)	<.001	<.001
Morphine Sulfate IR 120 mg - Kadian NT 120 mg whole	21.9 (16.4, 27.3)	63.26 (1, 90)	<.001	<.001
Kadian NT 120 mg whole - Kadian NT 120 mg crushed	-0.5 (-5.9, 5.0)	0.03 (1, 90)	0.865	0.875

* P-values were adjusted using the Benjamini and Hochberg procedure to account for the effect of multiple testing of primary endpoints



Morphine Pharmacokinetics

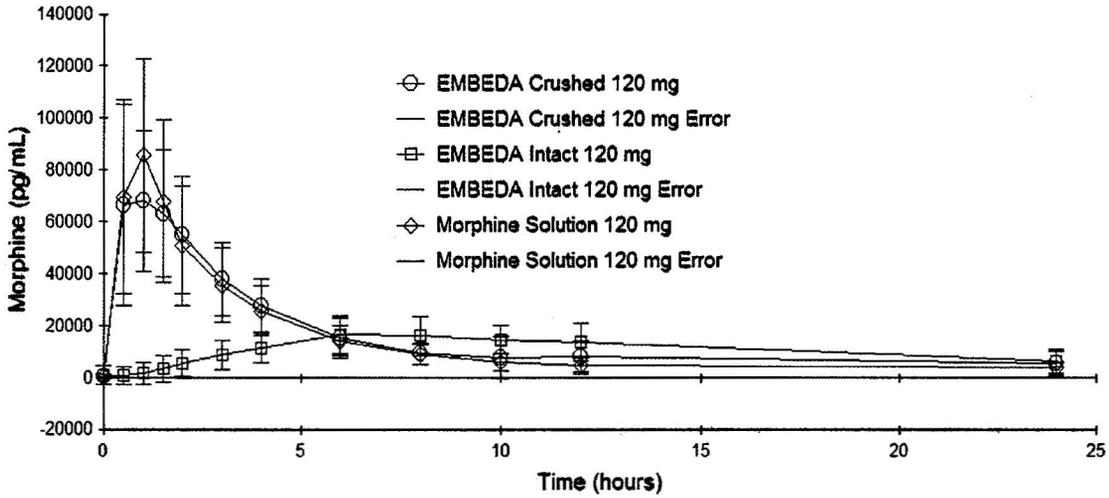


Figure 4.4.2a: Profile of drug liking (Left), plasma naltrexone (Right) and plasma morphine (Lower) in opiate-experienced but non-dependent healthy subjects (Study ALO-01-07-205). The subjects (n=32) were treated with a single oral dose of 120 mg morphine sulfate in the following preparations: morphine oral solution (1), crushed Kadian NT pellets (2) dissolved in

apple juice, and intact Kadian NT pellets (3) or placebo (4). From the PK review performed by Dr. Srikanth Nallani.

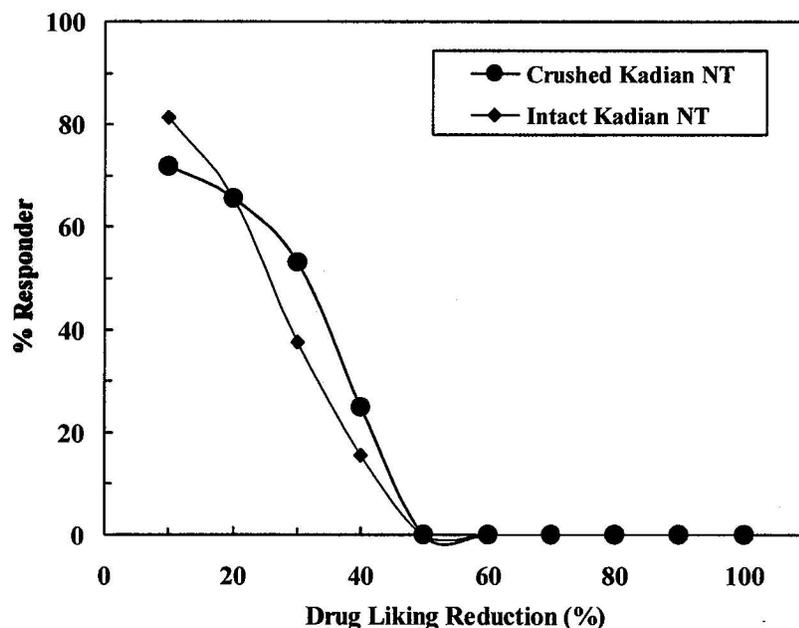


Figure 4.4.2b: Responder analysis of reduction of drug liking (peak effect, or Emax) in subjects treated with Kadian NT intact or crushed pellets compared to those treated with morphine oral solution (Study ALO-01-07-205). The figure was produced from the Applicant's Table 11 of Study ALO-01-07-205 report (the table was also included in the PK review performed by Dr. Srikanth Nallani).

Study ALO-01-07-106 (morphine vs. naltrexone by IV): This was a randomized, double-blind, placebo-controlled, cross-over trial in nondependent, recreational opioid drug users to evaluate drug liking and euphoric effects of naltrexone on IV morphine. The subjects (n=28) received a single IV bolus of 30 mg morphine (similar to 100 mg oral morphine), 30 mg morphine+1.2 mg naltrexone (similar to 4 mg oral naltrexone in Kadian NT). The drug liking and euphoric effects were assessed following each treatment. Time-matched blood samples were taken for plasma morphine, naltrexone and 6- β -naltrexol.

The results showed that the combination of morphine + naltrexone significantly reduced the drugliking/euphoric effects associated with morphine (Figure 4.4.2c).

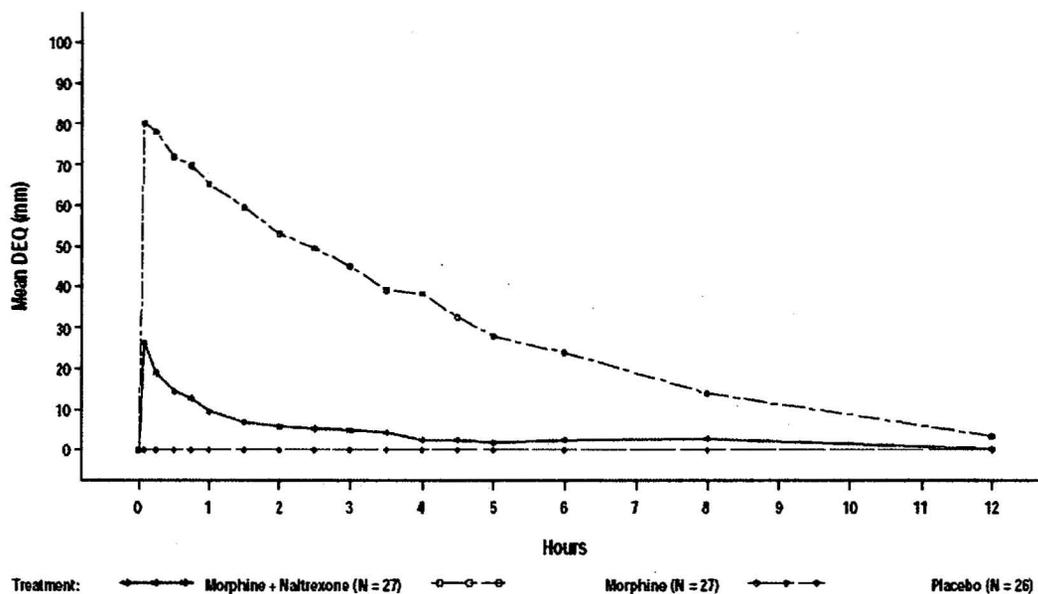


Figure 4.4.2c. Subjective drug effects of morphine in opiate-experienced non-dependent subjects treated with single IV bolus of morphine (30 mg), morphine+naltrexone (30 mg/1.2mg) or placebo. The mean DEQ (Drug Effects Questionnaire) was based on scores on Question #5 "How high are you now?". From the Applicant's Figure 6 in the Study ALO-01-07-106 report.

Study ALO-01-07-107 (Kadian vs. IV naltrexone): This was an open-label study in chronic pain patients on a stable dose of Kadian followed by serial intravenous boluses of naltrexone to assess opiate withdrawal. The subjects were 16 patients with chronic moderate to severe non-malignant pain and were on a stable dose of opioid equivalent to ≤ 390 mg morphine per day. After entering into the study, the subject switched to Kadian followed by titration. After Kadian dose became stable (based on analgesic response), naltrexone ≤ 3 mg was administered by IV every 10 minutes until the subject reached a score of ≥ 13 on the Clinical Opiate Withdrawal Scale (COWS). Blood samples were collected at time 0 (prior to dosing), 2 and 7 minutes post dosing for plasma naltrexone and 6- β -naltrexol; and time 0, 30 and 60 minutes for plasma morphine.

The study was inconclusive due to a flawed study design as per the Applicant. The following results were summarized from the Study ALO-01-07-107 report:

- The mean COWS score was 0.4 (0-12) at baseline, 6.9 (range 0-22, n = 13) after the first dose of naltrexone, 12.0 (1-20, n = 10) after the second dose, 8.0 (0-18, n = 5) after the third dose, and 10.5 (8-13, n = 2) after the fourth dose.
- There were no correlation between COWS scores and plasma naltrexone or 6- β -naltrexol.

4.4.3 Pharmacokinetics

As per the PK review team, the PK studies submitted in this NDA to support the proposed indication are acceptable and there are no outstanding issues with the proposed product. The following conclusions and summary are made according to the PK review performed by Dr. Srikanth Nallani:

- At a single oral dose, Kadian NT Capsule 100 mg was bioequivalent in plasma morphine profile to the reference drug, Kadian Capsules 100 mg, after single oral dose in healthy adult subjects.
- At multiple oral doses (40 mg bid to 160 mg bid), Kadian NT was comparable in profile of plasma morphine to Kadian Capsules in patients with moderate-to-severe pain due to osteoarthritis.
- Kadian NT strengths from 20 mg to 100 mg were compositionally proportional based on the dissolution profiles.
- Kadian NT Capsule 60 mg when administered with 40% alcohol, but not with 4% and 20% alcohol, in healthy adult subjects resulted in significantly dose-dumping of morphine *but not* naltrexone.

Single-dose bioequivalence of morphine to Kadian: the bioequivalence of morphine with Kadian NT capsules were assessed in single oral doses (Study ALO-01-07-101) in healthy adult subjects and in multiple oral doses in chronic patients, as compared to reference drug, Kadian capsule. The results showed Kadian NT was bioequivalent in PK profile of plasma morphine to Kadian in both single and multiple doses.

Study ALO-01-07-101 was an open-label, randomized, single-dose, 2-way cross over study in healthy adult subjects (n=34) under fasted condition to establish bioequivalence of morphine between Kadian NT 100 mg and reference drug Kadian 100 mg. Kadian NT Capsule 100 mg was bioequivalent in profile of plasma morphine to Kadian Capsule 100 mg (morphine sulfate extended-release), except had a shorter T_{max} of morphine (Table 4.4.3a)

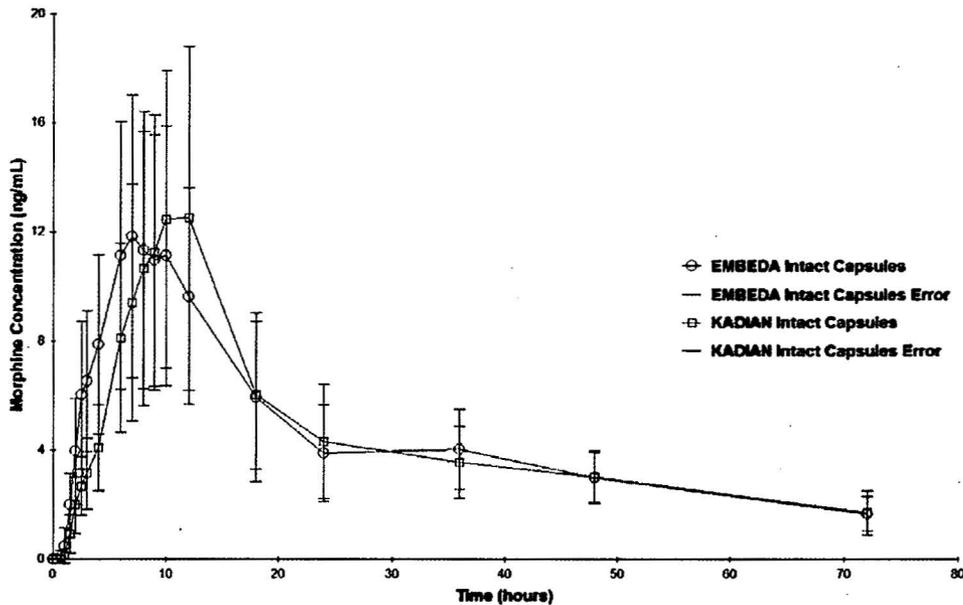
Table 4.4.3a: Comparison of PK profile of plasma morphine between Kadian NT 100 mg and Kadian 100 mg (Study ALO-01-07-101)
(From the PK review performed by Dr. Srikanth Nallani)

Parameter*	Kadian NT	Kadian
AUC0-t (ng.hr/mL)	310.9 (25.30%)	304.52 (25.8%)
AUCinf (ng.hr/mL)	384.01 (24.10%)	390.98 (29.90%)
Cmax (ng/mL)	12.31 (36.80%)	13.19 (45.70%)
Tmax (h)	7.5 (2.50-18.00)	10 (6.00-24.00)
Half-life (h)	28.8 (39.90%)	33.83 (34.60%)

*Geometric mean (CV%) is presented for AUC and Cmax, median (range) for Tmax and arithmetic mean (CV%) for half-life.

	Ratio of Least Square Means (%)	CI: Lower Limit (%)	CI: Upper Limit (%)	CV (%)
Including all completed subjects				
AUC0-t (ng.h/mL), N=34	102.2	98.6	105.9	8.6
AUCinf (ng.h/mL), N=30	97.4	91.2	104.1	13.9
Cmax (ng/mL), N=34	93.8	82.4	106.7	32.2

Plasma Profile of Morphine (EMBEDA vs KADIAN)



Multiple-dose comparison of plasma morphine with Kadian: Study ALO-KNT-202 was Phase 2 an active-controlled (Kadian), 2-week treatment, double-blind, cross-over trial in patients with moderate-to-severe pain due to osteoarthritis. The patients were titrated with open-label Kadian treatment at dose from 20 mg bid to 160 mg bid. The PK blood sampling included trough blood samples every 4 weeks for 52 weeks and 12 hours post dosing on Day 14 (the end of double-blind treatment) of period 2 (double-blind phase) for plasma morphine, naltrexone, and 6- β -naltrexol analysis.

Of 72 randomized patients, 67 were included in the PK analysis. Mean trough plasma morphine concentrations on Days 1, 7, and 14 were similar during Kadian NT treatment and Kadian treatment. Mean plasma morphine was slightly higher for Kadian NT as compared to Kadian across 12 hours post dosing at the end of treatment (Day 14) (Figure 4.4.3). The mean steady state C_{max} of plasma morphine was approximately 12% greater for Kadian NT compared with Kadian.

Average Morphine Levels (ng/mL) Over Time

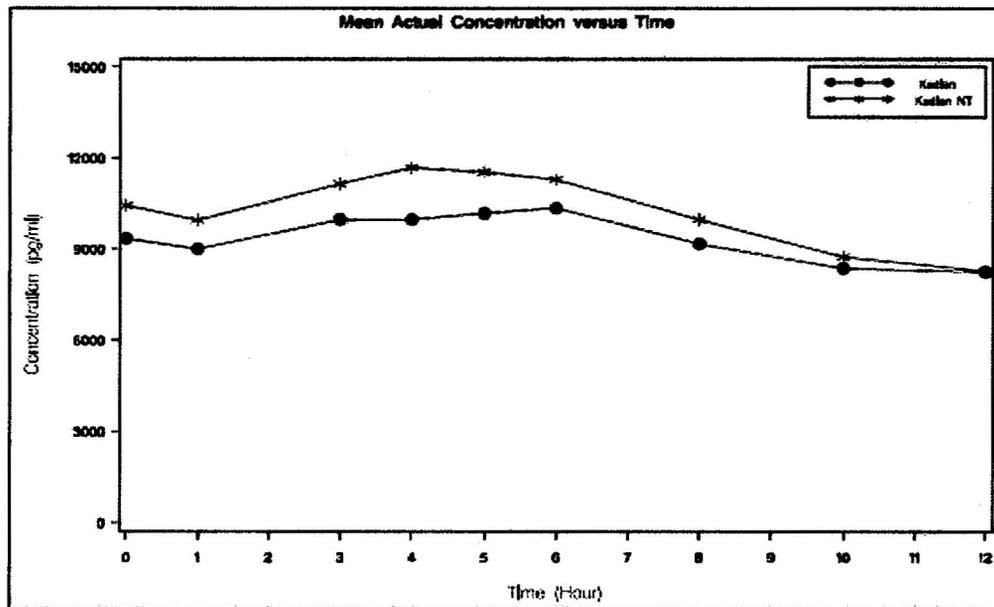


Figure 4.4.3a: Mean plasma morphine concentration during the 12 hours post dosing (Study ALO-KNT-202) on Day 14 (the end of double-blind treatment) of Period 2. (From the PK review performed by Dr. Srikanth Nallani)

Alcohol interaction study: Study ALO-01-07-103 was an open-label, randomized, single-dose, 4-way crossover, 4-sequence PK interaction study in health adults (n=32) treated with Kadian NT 60 mg capsule and alcohol (0%, 4%, 20%, or 40%) under fasting conditions. The profile of plasma morphine was similar between 4% or 20% alcohol and water, but not 40% alcohol (Figure 4.4.3b and Table 4.4.3b). The 40% alcohol taken with Kadian NT 60 mg resulted in dose-dumping of morphine but not naltrexone (Tables 4.4.3b and 4.4.3c).

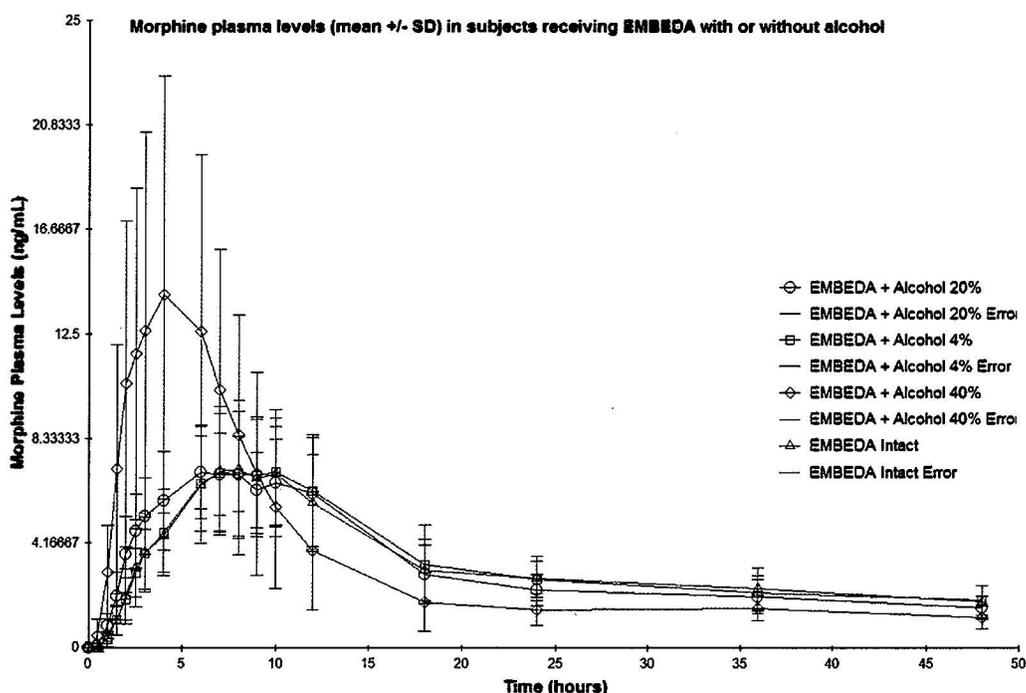


Figure 4.4.3b: Profile of plasma morphine in healthy adults treated with single oral dose of Kadian NT Capsule 60 mg and alcohol at 4%, 20% and 40% or water (Study ALO-01-07-103). Co-administration of Kadian NT with 40% alcohol resulted in significantly dose-dumping of morphine. (From the PK review performed by Dr. Srikanth Nallani)

Table 4.4.3b: PK parameters of morphine in healthy subjects after a single dose of Kadian NT 60 mg was administered with 0-40% alcohol (From the Applicant's Table 11.4.7.1:1 in the Study ALO-01-07-107 report)

Parameter*	ALO-01 + 4% alcohol (A) N=31	ALO-01 + 20% alcohol (B) N=31	ALO-01 + 40% alcohol (C) N=32	ALO-01 (D) N=32
AUC 0-t (ng·h/mL)	156.86 (21.3%)	152.80 (19.6%)	151.50 (45.7%)	155.78 (23.1%)
AUCinf** (ng·h/mL)	220.73 (25.7%)	212.88 (26.5%)	250.81 (50.9%)	227.28 (24.0%)
Cmax (ng/mL)	7.6915 (34.5%)	8.1233 (24.4%)	14.9817 (46.1%)	7.4972 (36.0%)
tmax (h)	8.00 (2.50-18.00)	8.00 (4.00-12.00)	4.00 (2.00-6.00)	9.00 (2.50-12.00)
Half-life** (h)	35.494 (45.6%)	29.759 (40.5%)	37.304 (55.9%)	31.133 (46.0%)
kel** (1/h)	0.02339 (42.4%)	0.02759 (43.9%)	0.02357 (45.4%)	0.02828 (59.1%)

*Geometric mean (CV%) is presented for AUC and Cmax, median (range) for tmax and arithmetic mean (CV%) for half-life and kel. **For these parameters, N=14, 18, 13 & 17 for A, B, C & D, respectively.

- Plasma morphine was on average 2-fold higher in C_{max} (ranged from 1.4 to 5 fold increase) and 5 hours earlier in T_{max} when Kadian NT was administered with 40% alcohol instead of water, although the AUC was comparable between the 40% alcohol and water (Table 4.4.3b). Compared with the PK parameters of morphine with crushed Kadian NT 60 mg (Study ALO-01-07-104, PK study in healthy subjects treated with a single-dose of crushed or intact Kadian NT 60 mg), the C_{max} was 60% of the crushed Kadian NT (Table 4.4.3d).
- Plasma naltrexone levels were below the detection limits in most subjects and plasma 6-β-naltrexol was detectable in all subjects during the study. The highest detectable plasma naltrexone and 6-β-naltrexol in those subjects were 15 pg/ml (with 20% alcohol) and 221 pg/ml (with 40% alcohol), respectively (Table 4.4.3c), which was 2.6% and 6.3% C_{max} of the crushed Kadian NT 60 mg resulted from Study ALO-01-07-104 (C_{max} =579 pg/ml for naltrexone and 3530 pg/ml for 6-β-naltrexol).

The 40%-alcohol morphine dose dumping was not observed with the approved product, Kadian (see the PK review on NDA 20-616 performed by Dr. David Lee on 12/22/2006).

Table 4.4.3c: Plasma levels of naltrexone and 6-β-naltrexol in the detectable subjects after a single dose of Kadian NT 60 mg was administered with 0-40% alcohol (Extracted from the Applicant's the Study ALO-01-07-107 report)

Treatment	Plasma Naltrexone		Plasma 6-β-naltrexol	
	Detectable Subject (n)	pg/ml	Detectable Subject (n)	pg/ml
Kadian NT+Water	4	6.8-9.0	32	0.5-106
Kadian NT+4% Alcohol	5	4.4-7.7	32	0.62-71.1
Kadian NT+20% Alcohol	7	5.1-14.6	32	0.5-131
Kadian NT+40% Alcohol	3	4.5-11.6	32	0.52-221

Table 4.4.3d: PK parameters of morphine in healthy subjects after a single dose of the crushed or intact Kadian NT 60 mg (Extracted from the Applicant's Table 11.4.3.4 in the Study ALO-01-07-104 report)

PK Parameter	Crushed Kadian NT 60 mg N=23	Intact Kadian NT 60 mg N=23
	Mean (CV%)	Mean (CV%)
T _{max} (hr)*	2.00 [2.00-2.10]	7.03 [6.00-12.00]
C _{max} (ng/mL)†	24.5 (34.99)	7.73 (42.36)
AUC _{0-t} (hr*ng/mL)†	162.6 (33.10)	173.7 (31.40)
AUC _{inf} (hr*ng/mL)†	177.4 (29.30)	201.8 (37.53)

* median and range; † geometric mean

In vitro alcohol dissolution:

(b) (4)



(b) (4)



Food interaction: Study ALO-01-07-102 was an open-label, randomized, single-dose (Kadian NT Capsule 100 mg), 3-way crossover/6-sequence, comparative bioavailability study in healthy adult subjects (n=36) under fed and fasting conditions, and sprinkled on applesauce. Dr. Nallani concluded that Kadian NT capsules may be administered without regard for food consumption. Patients who are unable to take whole Kadian NT capsules may consume it by sprinkling the pellets on applesauce. Consumption of Kadian NT capsule with food decreased the C_{max} of morphine by 22% without a significant change in the AUC compared to fasting condition. Additionally, Kadian NT pellets sprinkled over applesauce was bioequivalent to fasting condition.

Plasma naltrexone and 6-β-naltrexol: Plasma naltrexone and 6-β-naltrexol were analyzed in several single and multiple dose PK studies with Kadian NT. Since naltrexone has a shorter half life (4 hours), its longer half-life metabolite, 6-β-naltrexol, levels may also be a marker of overall naltrexone exposure. Overall plasma levels were

low and highly variable. The following cases were summarized from the Dr. Nallani's PK review draft:

In Study ALO-01-07-104, one subject had detectable plasma naltrexone level (5 pg/ml) upon receiving intact Kadian NT (Morphine 60 mg, Sequestered naltrexone 2.4 mg).

In Study # 102, under fasting condition for intact capsule formulation, plasma naltrexone concentrations (fasting: range 4.46 to 20.8 pg/ml) were detected in 11 samples from three subjects; while the rest of the subjects (n=31) had plasma naltrexone levels below the detection limit (4.0 pg/ml) at all time points. Five subjects receiving capsule contents sprinkled over applesauce had fifteen samples with plasma naltrexone levels in the range of 5.74 to 64.5 pg/ml, while the rest (n=27) were below the detection level of naltrexone. In fifteen subjects (out of n = 34) receiving Kadian NT with high fat meal, plasma naltrexone levels were in the range of 4.05 - 132 pg/ml) at different time points.

In Study # 202, trough blood samples were analyzed for plasma morphine, naltrexone, and 6- β -naltrexol approximately every 4 weeks for 52 weeks in selected subjects who gave consent to participate in the PK sub-study. Trough naltrexone concentrations on double-blind Days 1, 7, and 14 were below the detectable limit for the majority of subjects during Kadian NT treatment (77.6% to 86.6% of subjects (n= 65)). A total of 11 subjects had detectable trough naltrexone concentrations on double-blind Days 7 and 14 (range, 4.81 pg/ml to 25.5 pg/ml) during the Kadian NT treatment period. On Day 14 of Period 2, blood samples were collected over 12 hours. Naltrexone concentrations from serial blood sampling during this period were below the detection limit for the majority of subjects (80.6% to 83.6%). Nine subjects had detectable naltrexone concentrations after dosing with Kadian NT (ranged from 4.11 to 21 pg/ml). Only seven subjects out of 67 investigated had detectable naltrexone levels to compile a PK profile over the 12 hour period. The range of AUC₀₋₁₂ in these subjects was between 47.1 –183.4 pg.hr/ml.

5. SOURCES OF CLINICAL DATA AND REVIEW STRATEGY

Source of clinical data to support this NDA were primarily from the Applicant-sponsored studies, the efficacy database included one Phase 3 pivotal efficacy trial (placebo-controlled) and one phase 2 supportive trial (active-controlled) to assess the sequestered naltrexone can potentially compromise analgesic effects of morphine sulfate. And the safety database consists of nine of 12 trials by excluding three trials that evaluated different formulation of morphine than Kadian NT.

5.1 Tables of Clinical Studies

A total of 12 trials were submitted in NDA, as summarized below and listed in the following Table 5.1:

- one pivotal efficacy trial (ALO-KNT-301)
- one supportive efficacy/PK trial (ALO-KNT-202)
- one long-term open-label safety trial (ALO-KNT-302)
- three pharmacodynamic trials (abuse-deterrence)
- six PK trials

The safety database for ISS included nine of 12 trials by excluding three trials (ALO-KNT-201, ALO-01-07-106 and ALO-01-07-107) that evaluated different formulation of morphine and naltrexone than Kadian NT. However, these three trials were conducted to establish a proper ratio of morphine over naltrexone in terms of mitigation of positive subjective effects of morphine and are important to support the proposed formulation. The review of the three trials is primarily performed by the PK review team and the Controlled Substance Staff of OND. See Section 4.4 for details.

Table 5.1: Clinical studies submitted in NDA
(Extracted from the Applicant's ISS)

Study #	Phase	Design	Sites	Subject	Drug	Control	Outcome	Review location/section
ALO-KNT-301	3	R/DB/PC, 3-month	74/US	OA patients with moderate-to-severe pain	Kadian NT	Placebo	Efficacy	Section 6 Section 9.4.1
ALO-KNT-302	3	R/OL, 12-month	58/US	Chronic moderate-to-sever non-Ca pain	Kadian NT	NA	Safety	Section 7 Section 9.4.3
ALO-KNT-202	2	R/AC, 2-week	9/US	OA patients	Kadian NT	Kadian	PK, efficacy	Section 4.4.3 Section 9.4.2
ALO-KNT-201	1	R/DB/PC/CO, single-dose	1/CA	Healthy adult (18-55yo) opiate users (non-med)	MS+NT	Placebo	Abuse-deterrence	Section 4.4.2
ALO-01-07-205	1	R/DB/PC/AC/CO, single-dose	1/CA	Healthy adult (18-55yo) opiate users (non-med)	Kadian NT (crushed)	MS-IR solution & placebo	Abuse-deterrence	Section 4.4.2
ALO-01-07-106	1	R/DB/PC/CO, sing-dose	1/US	Healthy adults (18-50yo) recreational drug user	MS, NT (IV)	placebo	Abuse-deterrence	Section 4.4.2
ALO-01-07-107	1	OL, single-dose	1.US	Chronic moderate-to-severe non-Ca pain	Kadian & IV NT		PK (COWS)	Section 4.4.2
20-901-AU (pilot)	1	R/OP/CO, single-dose	1/US	Healthy adults	Kadian NT		PK (food)	
ALO-01-07-101	1	R/OP/CO, single-dose	1/US	Healthy adults (19-45yo)	Kadian NT	Kadian	PK (vs. Kadian)	Section 4.4.3
ALO-01-07-102	1	R/OP/CO, single-dose	1/US	Healthy adults (19-45yo)	Kadian NT (sprinkled on apple sauce)		PK (sprinkled)	Section 4.4.3
ALO-01-07-103	1	R/OP/CO, single-dose	1/US	Healthy adult (21-40yo) moderate alcohol users	Kadian NT (4%, 20%, 40% EtOH)		PK (EtOH)	Section 4.4.3
ALO-01-07-104	1	R/OP/CO, single-dose	1/US	Healthy adults (18-55yo)	Kadian NT (crushed)	NT solution	PK (crushed)	

R: Randomized; DB: double-blind; PC: placebo-controlled; AC: active-controlled; OL: open-label; CO: crossover

MS: morphine sulfate; NT: naltrexone; NA: not applicable; CA: Canada; non-Ca: non-cancer; non-med: non medical use (such as reaction use)

5.2 Review Strategy

The pivotal efficacy trial, *Study ALO-KNT-301*, was reviewed individually, and is summarized in the Section 6 (ISE). The individual study review is in the Appendix (Section 9.4.1).

The general safety review was based on the **Applicant's Summary of Clinical Safety and Integrated Summary of Safety**. The particular safety concerns of potential precipitation of opiate withdrawal syndrome associated with naltrexone released from Kadian NT were addressed by the Applicant in Studies ALO-KNT-302 (long-term open-label trial) and ALO-KNT-202 (active-controlled trial), which are reviewed individually (see the Appendix in Section 9.4.2 and 9.4.3) and summarized in the ISS (Section 7).

5.3 Discussion of Individual Studies

Study ALO-KNT-301: A pivotal Phase 3 efficacy trial in patients with moderate to severe pain due to osteoarthritis (knee or hip) under a SPA (Special Protocol Assessment) agreement. It was a randomized, double-blind, placebo-controlled, 12-week multiple-dose study with randomized withdrawal design. The results showed that Kadian NT was statistically, but marginally (both effect size and p-value), superior to placebo in the primary endpoint (the mean changes in *weekly average of pain intensity* from baseline to week 12). However, it is unknown if the analgesic outcome was compromised by **naltrexone release from Kadian NT capsule because there was no reference "effect size"** (Kadian vs. placebo) in the trial for comparison. See ISE in Section 6 and the individual review in Appendix 9.4.1 for details.

Study ALO-KNT-202: A Phase 2 PK (primary objective) and efficacy (secondary objective) trial in patients with moderate to severe pain due to osteoarthritis (knee or hip). It was a randomized, double-blind, multiple-dose, active-controlled, crossover design to compare the efficacy and PK profile of plasma morphine, naltrexone and its metabolite 6- β naltrexone between Kadian NT and Kadian. A total of 72 patients received Kadian NT or Kadian (20 mg to 160 mg bid) for two weeks after 2-way crossover (open-label Kadian treatment before, between and after crossover). Although the results showed the analgesic effects were comparable between Kadian NT and Kadian, the study was not primarily designed for efficacy assessment and the crossover treatment (between Kadian NT and Kadian) may have confounded the comparability (carry-over effect). Thus, the efficacy data are not integrated to the ISE of this review. See the individual review in Appendix 9.4.2 for details.

Study ALO-KNT-302: A 12-month open-label study in patients with chronic non-malignant pain to evaluate long-term safety of Kadian NT capsules. A total of 465 patients were enrolled and received at least one dose of Kadian NT during the 12-month treatment. Dose titration up or down was allowed throughout the study; no maximum allowable daily dose was set. The subjects returned to the study site monthly for safety assessment including opioid withdrawal syndrome (by Clinical Opiate Withdrawal Scale,

or COWS). A subset of patients (n=93) were selected from three daily dosing levels (20-60 mg, 80-120 mg and >120 mg) and age group (≥ 65 years) for plasma naltrexone, 6- β -naltrexol and morphine. Of 465 patients, 84 patients completed 6-month treatment and 124 patients were dosed for 12 months. The overall safety profile was consistent with other morphine products. There were apparently no cases of opiate withdrawal syndrome associated with naltrexone release during the study and no correlation between plasma naltrexone or 6- β -naltrexol and COWS scores. However, the study population (not opiate-dependent patients) and titration dosing regimen offered limited value for assessment of precipitating opiate withdrawal associated with naltrexone. See ISS in Section 7 and the individual review in Appendix 9.4.3 for details.

Three abuse liability trials: Studies ALO-KNT-201, Study ALO-01-07-205 and Study ALO-01-07-106 were conducted to establish and confirm the proper morphine-to-naltrexone ratio needed to provide clinically meaningful mitigation of drug liking and euphoria associated with opioid abuse. See Pharmacodynamic in Section 4.4.2 and the CSS's review for details.

6. INTEGRATED REVIEW OF EFFICACY

Summary of Efficacy Results and Conclusions

The Applicant submitted one pivotal Phase 3 efficacy trial (Study ALO-KNT-301) in this NDA to support the proposed indication “*The management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time*”. The trial was designed and conducted under the Division's SPA agreements. See the individual study review in Appendix 9.4.2 for details.

The trial was a randomized, double-blind, placebo-controlled study with a randomized withdrawal design. The study subjects were adult patients with moderate to severe pain due to osteoarthritis (knee or hip). After up to 6-week titration with open-label Kadian NT treatment to an optimal individual dose (effective and tolerable), the subjects were randomized to active treatment and placebo groups and treated with a fixed individual dose optimized from the titration for 12 weeks (the double-blind maintenance phase). The primary endpoint was the mean change in the *average daily pain* from baseline to the end of treatment (week 12) and primary efficacy analysis was based on ITT population with a BOCF/LOCF mixed imputation method for dropouts followed by three sensitivity analyses.

Approximately 43% patients in the placebo group and 36% patients in the Kadian NT group dropped out from the study during the 12-week maintenance phase. The major reasons for dropouts were lack of efficacy in the placebo group and adverse events in the Kadian NT group. The primary efficacy analysis showed that the Kadian NT treatment at a dose up to 80 mg BID was statistically superior to placebo in analgesic response. The primary imputation method for dropouts was supported by two of three sensitivity analyses; the one failed sensitivity analysis was most conservative (the baseline pain intensity values from the end of titration were used to impute all dropouts from both

placebo and Kadian NT groups). The result was consistent with secondary endpoints and secondary analyses, including cumulative responder analysis (defining dropouts as non-responders), WOMAC index, analgesic response across 12 weeks and profile of dropouts due to lack of efficacy, except use of rescue medication (with slight difference between two groups).

Overall, the study suggests that Kadian NT has analgesic superiority to placebo for treatment of chronic pain due to osteoarthritis. However, the study provided limited values to assess whether the analgesic effects were compromised by naltrexone released from Kadian NT because of no concurrent or historical reference (from naltrexone-free Kadian) for comparison.

6.1 Proposed Indication

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

6.2 Methods/Study Design

The trial (Study ALO-KNT-301) was a randomized, double-blind, placebo-controlled study in patients with moderate-to-severe pain due to osteoarthritis (OA) of knee. The trial was designed in a randomized withdrawal method (subjects directly entered the placebo-controlled/double-blind phase right after titration). The study conduction included the following periods:

Screening Period (2 weeks): The 14-screening period included 1- to 7-day Washout Period to discontinue all analgesics and prohibited medications to establish pain intensity ≥ 5 on 11-point BPI (Brief Pain Inventory) scale

Titration Phase (up to 6 weeks): Subjects with average 24-hour pain intensity ≥ 5 on 11-point BPI scale at the end of Washout were to enter the Titration Phase and received an open-label dose of Kadian NT with weekly visit to the study site (up to six weeks):

- starting dose at 20 mg at bedtime at the first 3 nights for opioid-naïve patients, otherwise 20 mg bid
- titrated up or down BID, the maximum allowed dose at 80 mg BID (160 mg/day)

Maintenance Phase (12 weeks): Subjects with “average pain in the last 24 hours ≤ 4 on BPI scale over the last 4-days and with **minimum 2-point decrease from baseline**” (defined as responders) during the Titration Phase were randomized into placebo and Kadian NT groups and received *the same effective dose* (fixed dose) achieved in the Titration Phase for 12 weeks. The mean daily dose was 43.5 mg/day (20-160 mg/day) at the end of the titration.

- Patients on placebo were force tapered gradually using double-dummy design
- Patients had visit every week for first two weeks and every two weeks up to 12 weeks.

Tapering Period: Subjects who completed the Maintenance Phase were to complete a 2-week Tapering Period and were to be scheduled for a Post-Treatment Follow-Up Visit at the end of the taper.

6.3 Demographics

Study subjects were patients with moderate to severe pain due to osteoarthritis (mostly at knee joints). The overall demographic profile of patients was similar between Titration and Maintenance Phases. The demographic characteristics of ITT population during the Maintenance Phase were well balanced between Kadian NT and placebo groups (Table 6.3), as summarized below (Kadian NT vs. Placebo):

- Age: 54.2±11.6 vs. 54.7±12.9
- Gender (M/F): 0.61 vs. 0.82
- Ethnicity: White (75% vs. 70%); Hispanic (21% vs. 23%)
- BMI (kg/m²): 32.5±6.9 vs. 31.8±6.3
- Opioid naïve: 74.9% vs. 75.4%
- OA history: 78% vs. 77% (knee) and 22% vs. 23% (hip)
- Baseline pain intensity (on 11-point BPI):
 - Titration Phase: 6.1±1.9 (*Screening Baseline*)
 - Maintenance Phase: 2.7±1.3 vs. 2.5±1.2 (*Randomization Baseline*)

**Table 6.3: Demographic characteristics in Maintenance Phase (ITT population)
(From the Applicant's Table 14 in the Study ALO-KNT-301 report)**

Category	Treatment Group n (%)		p-value ^a
	Placebo N = 173	ALO - 01 N = 171	
Gender			0.1910
Male	78 (45.1)	65 (38.0)	
Female	95 (54.9)	106 (62.0)	
Age (years)			0.7025
Mean (SD)	54.7 (12.92)	54.2 (11.62)	
Median	56.0	54.0	
Minimum, Maximum	21, 85	24, 81	
Hispanic Ethnicity	40 (23.1)	36 (21.1)	0.6973
Race			0.3358
White	121 (69.9)	128 (74.9)	
Black or African American	30 (17.3)	29 (17.0)	
American Indian or Alaska Native	4 (2.3)	2 (1.2)	
Asian	15 (8.7)	9 (5.3)	
Native Hawaiian or Other Pacific Islander	0	1 (0.6)	
Other	3 (1.7)	2 (1.2)	
BMI (kg/m²)	N = 167	N = 167	0.3099
Mean (SD)	31.78 (6.317)	32.52 (6.927)	
Median	31.00	31.90	
Minimum, Maximum	17.4, 44.9	17.1, 52.5	

a. P-value from Fisher's exact test for categorical variables and ANOVA for continuous variables.

P-values for race compared White vs non-White.

Reference: Section 14.1 Table 11.2.1

6.4 Patient Disposition

Of a total of 547 patients enrolled in the Titration Phase, 62.9% (n=344) completed the titration and were randomized into Kadian NT group (n=171) and placebo group (n=173) for the 12-week Maintenance Phase.

The dropout rate during the 12-week Maintenance Phase was 36% in the Kadian NT group and 43% in the placebo group. Major reasons for dropouts were (Kadian NT vs. placebo) adverse events (10.5% vs. 7.5%), lack of efficacy (3.5% vs. 18.5%) and subject withdrew from study (8.8% vs. 6.9%), as summarized in Table 6.4.

No dropouts were due to opiate withdrawal symptoms during the 12-week Maintenance Phase, as also confirmed with the sponsor by email during the review of this study. However, the Applicant reported three patients from placebo group who experienced moderate to severe opiate withdrawal symptoms had the Clinical Opiate Withdrawal Scale (COWS) score ≥ 23 , which resulted in two of them discontinuing from the Maintenance Phase. Both dropouts were counted as lack of efficacy or other reasons.

**Table 6: Patients disposition in the 12-week Maintenance Phase
(From the Applicant's Table 12 in the Study ALO-KNT-301 report)**

	Treatment Group n (%)		p-value ^a
	Placebo N = 173	ALO - 01 N = 171	
Subjects Enrolled in Maintenance Phase	173 (100.0)	171 (100.0)	
Subjects Completing Maintenance Phase	98 (56.6)	110 (64.3)	0.1531
Subjects Withdrawn from Maintenance Phase	75 (43.4)	61 (35.7)	
Reasons for Withdrawal			
Adverse Event	13 (7.5)	18 (10.5)	
Lack of Efficacy	32 (18.5)	6 (3.5)	
Non Compliance	6 (3.5)	9 (5.3)	
Investigator's Discretion	0	3 (1.8)	
Subject withdrew from study	12 (6.9)	15 (8.8)	
Lost to follow-up	2 (1.2)	3 (1.8)	
Did not meet inclusion/exclusion criteria	2 (1.2)	1 (0.6)	
Other reason	8 (4.6)	6 (3.5)	

a. P-value from Fisher's exact test to compare proportion of subjects between treatment groups.
Reference: Section 14.1 Table 10.1.2

6.5 Analysis of the Primary Endpoint(s)

Primary Endpoint: The mean change of weekly BPI diary average pain score from the randomization baseline to Week 12 (the end of maintenance treatment)

Primary Analysis: The primary analysis of the primary endpoint was based on ITT population with the following SPA-agreed BOCF/LOCF mixed imputation method for dropouts dependent on reason for dropout (Table 6.5).

Kadian NT was statistically superior to placebo in the mean change of *weekly diary BPI average score* from the randomization baseline to week 12 (Table 6.5):

- Kadian NT (n=170): -0.2 ± 1.94 (p=0.045 vs. placebo)
- Placebo (n=173): 0.3 ± 2.05

Table 6.5: Primary imputation method for dropouts: BOCF/LOCF mixed method

Reason for Dropout	Placebo	Kadian NT
COWS > Randomization Baseline & COWS \geq 13	BOCF: Randomization Baseline (<i>least pain</i>)	BOCF: Screening Baseline (<i>worst pain</i>)
AEs	BOCF: Screening Baseline for both groups	
<ul style="list-style-type: none"> • Lack of efficacy • Administrative Investigator • Patient withdrawal • Others 	LOCF: average of BPI diary average pain score from the last 7-day observations	

BOCF: Baseline Observation Carried Forward

LOCF: Last Observation Carried Forward)

COWS: Clinical Opiate Withdrawal Scale (11-item questionnaire)

Screening Baseline: The average pain in the last 24 hours (*In-Clinic BPI score*) at the first day of the Titration Phase (or at the end of Washout).

Randomization Baseline: As average of the *BPI diary average pain scores* from the last seven days of the Titration Phase (or right before randomization)

BPI: 11-point Brief Pain Inventory scale

Sensitivity Analyses: Three alternate imputation methods were used, as per SPA agreement, to assess sensitivity of the primary imputation method. One sensitivity analysis (Method #1: imputation of dropouts with Randomization Baseline) failed statistical superiority of Kadian NT over placebo (Table 10).

- Method #1: Randomization Baseline for all dropouts in both treatment groups
 - Kadian NT (n=170): -0.4 ± 1.34 (p=0.1223 vs. placebo)
 - Placebo (n=173): -0.2 ± 1.32
- Method #2: Screening Baseline for drop-outs due to AEs and Randomization Baseline for dropouts due to other reasons in both treatment groups
 - Kadian NT (n=170): 0.0 ± 1.91 (p=0.0051 vs. placebo)
 - Placebo (n=173): 0.7 ± 2.17
- Method #3: Screening Baseline (the end of washout right before titration, the worst pain) for all drop-outs in both treatment groups
 - Kadian NT (n=170): 0.6 ± 2.31 (p=0.0489 vs. placebo)
 - Placebo (n=173): 1.1 ± 2.37

**Table 6.5: Analysis results of primary efficacy endpoint in ITT population
(From the Applicant's Table 20 in Study ALO-KNT-301 report)**

Analysis	Primary Endpoint ^a Mean (SD)		P-value ^b
	Placebo N=173	Kadian NT N=170	
Primary Analysis^c			
BOCF or LOCF	0.3 (2.05)	-0.2 (1.94)	0.0445
Alternative Analysis^d			
LOCF (average of last 7 days)	0.2 (1.97)	-0.2 (1.92)	0.1041
LOCF (last day of diary entry)	0.3 (2.13)	-0.1 (1.97)	0.0347
Sensitivity Analyses (BOCF)^e			
Method 1: R-Baseline	-0.2 (1.32)	-0.4 (1.34)	0.1223
Method 2: S-Baseline	1.1 (2.37)	0.6 (2.31)	0.0489
Method 3: S-Baseline or R-Baseline	0.7 (2.17)	0.0 (1.91)	0.0051

- a. Primary endpoint: change in the weekly average of pain intensity score from the randomization baseline to the end of treatment (week 12).
- b. Means and standard deviations from an ANCOVA model with treatment as categorical factor and randomization baseline score as a covariate.
- c. Primary analysis: BOCF or LOCF imputation for dropouts, dependent on reasons for dropouts.
- d. Alternative analysis (not protocol-specified analysis): different last observation values were used for LOCF imputation.
 - LOCF (average of last 7 day): dropouts due to lack of efficacy or administrative reasons were imputed with the average of the last 7 days of available diary data (but not more than 2 days past drug discontinuation)
 - LOCF (last diary entry): dropouts due to lack of efficacy or administrative reasons were imputed with the last diary entry (but not more than 2 days past drug discontinuation).
- e. Sensitivity analyses (protocol-specified and SPA-agreed): different baseline values were used for BOCF imputation.
 - Method 1 (R-Baseline): **Randomization Baseline** (the end of titration, *the least pain*) for all drop-outs in both groups
 - Method 2 (S-Baseline): **Screening Baseline** (the end of washout right before titration, *the worst pain*) for all drop-outs in both groups
 - Method 3 (S-Baseline or R-Baseline): **Screening Baseline** for drop-outs due to AEs and **Randomization Baseline** for dropouts due to other reasons in both groups.

Continuous Responder Analysis: The analysis was based on pain intensity difference (in %) from baseline to Week 12 using the *In-Clinic BPI score* (average pain in the last 24 hours at visit) and the dropouts were defined as non-responders. The responder curves were separated between Kadian NT and placebo across all response levels (Figure 6.5). The difference in the *only* $\geq 30\%$ response was statistically significant between Kadian NT (73%) and placebo (58%).

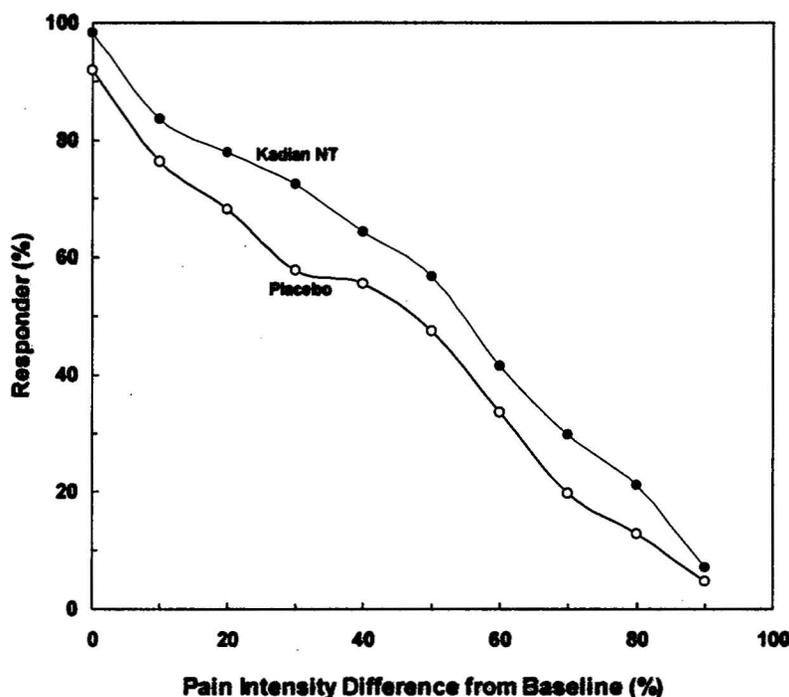


Figure 6.5: Continuous responder analysis of pain intensity difference from baseline to the end of treatment (week 12) in ITT population. The pain intensity difference from baseline at week 12, expressed as % response, was based on the in-clinic BPI score collected at the baseline and week 12 visits; the dropout was defined as non-responder. The difference in the only $\geq 30\%$ response was statistically significant between Kadian NT and placebo. (From the Applicant's Table 28 in Study ALO-KNT-301).

6.6 Secondary endpoint(s)

The following nine secondary endpoints were assessed during the 12-week Maintenance Phase. The analyses of the secondary endpoints were conducted in the ITT population with the same imputation method as in primary analysis for dropouts except where specified. The analyses for the multiple secondary endpoints were not adjusted for multiplicity.

1) *Diary BPI average pain averaged over the entire Maintenance Phase*

The mean changes from baseline in the *weekly BPI diary average pain score* to each visit was statistically significantly smaller in the Kadian NT group compared to the placebo group beginning at Week 2 (see Figure 6.10 in Section 6.10).

2) *In-clinic BPI (the last 24-hour pain intensity)*

The mean change from baseline to each visit was statistically significantly smaller in the Kadian NT group compared to the placebo group at all visits (Weeks 1 to 12) (see Figure 6.10 in Section 6.10).

- 3) ***Weekly diary BPI worst, least, and current pain (daily scores averaged over 7-day intervals to obtain weekly scores)***
The results on weekly BPI diary *worst, least and current* pain scores were consistent with those from analysis of *average* pain scores.
- 4) ***WOMAC Index (Pain, Stiffness and Physical Function) and Composite Index***
Kadian NT treatment was statistically superior to placebo in the mean change from baseline to each visit in composite score. The similar findings were seen in each of three WOMAC subscales.
- 5) ***Medical Outcome Study (MOS) Sleep Scale scores***
Overall, quality of sleep at the end of treatment (week 12) was worse than the baseline in both groups; Kadian NT treatment was slightly better than placebo in the mean change from baseline to Week 12 in the MOS scores but without statistical significance (some MOS subscales at week 4 or week 8 showed statistically differences between Kadian NT and placebo).
- 6) ***Beck Depression Inventory score***
The mean decrease from the screening baseline was numerically greater in the Kadian NT treatment group compared to the placebo group at each visit (but no statistically significance).
- 7) ***Amount of rescue medication (pill counts summed over 7-day intervals to obtain weekly counts)***
The average weekly number of tablets of rescue medication (acetaminophen) was slightly lower in the Kadian NT group than in the placebo group. However, higher percentage of patients in the Kadian NT **group used acetaminophen as “concomitant medications” than in the placebo group (18% vs. 11%)**, and also more patients in the Kadian NT group took other analgesics (21% vs. 16%; primarily contributed by acetaminophen) during the Maintenance Phase. The Applicant stated that no all acetaminophen uses were for the rescue medication purpose but did not provide justification how and in what degree the concomitant use of acetaminophen and other analgesics confounded the efficacy outcome.
- 8) ***Patient global impression of change (PGIC) (LOCF imputation for missing data)***
Numerically more patients in the Kadian NT treatment reported “*very much improved*” or “*much improved*” as compared to placebo treatment at all visits (44% vs. 38% at week 12).
- 9) ***Responders at Week 12 based on in-clinic BPI (dropouts were consider non-responders)*** See the Continuous Responder Analysis in Section 6.5.

6.7 Subpopulations

The primary endpoint was evaluated in subgroups of subjects defined by the baseline demographics, including age (<65 vs. ≥65 years), gender, race (white, black and others), initial opioid status (naïve or experienced). Overall, the subgroup analyses were directionally consistent with the primary analysis, except that patients from race background other than White or Black showed less analgesic effects with Kadian NT treatment than with placebo. The Applicant did not provide an explanation or discussion in the submission. However, the subset sample size is too small (multiple races included in the “Others”) to draw any conclusion.

**Table 6.8: Subgroup Analysis of Primary Endpoint
(From the Applicant’s Table 4 in the Summary of Clinical Efficacy)**

Subgroup	Placebo		Kadian NT	
	N	Mean (SD)*	N	Mean (SD)*
Age (year)				
<65	136	0.3 (2.0)	140	-0.1 (1.9)
≥65	37	0.1 (2.1)	30	-0.4 (2.3)
Gender				
Female	95	0.1 (2.1)	105	-0.1 (2.1)
Male	78	0.5 (2.0)	65	-0.3 (1.6)
Race				
White	121	0.4 (1.9)	127	-0.2 (1.8)
Black	30	0.8 (2.7)	29	0.2 (2.3)
Others†	22	-0.9 (1.6)	14	-0.5 (2.0)
Opiate status‡				
Naïve	129	0.1 (2.1)	125	-0.3 (1.8)
Experienced	42	0.7 (1.8)	41	0.1 (2.2)

* The mean change in weekly average of pain intensity from the randomization baseline to the end of treatment (week 12) in the ITT population with the primary imputation method (BOCF/LOCF) for dropouts.

† Other races included American Indian or Alaska native, Asian, Native Hawaiian or other Pacific Islanders.

‡ Opiate-naïve was defined as “not use opioids within the last 30 days”. The Applicant did not define “opiate-experienced” in both study protocols and reports, but “subjects with opiate-dependency” was excluded from all trials.

6.8 Analysis of Clinical Information Relevant to Dosing Recommendations

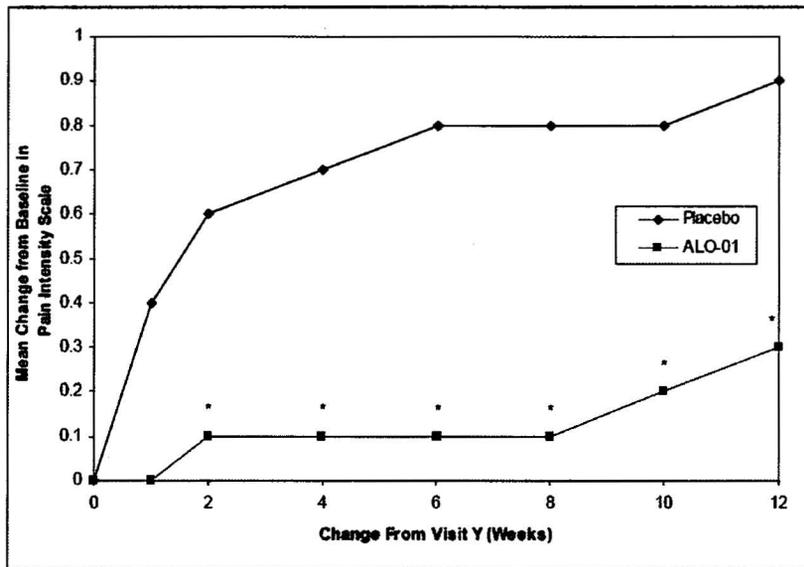
As is usual for opioid analgesics, no particular dosing recommendation was proposed in the labeled. Instead, dosing is to be based on the clinical conditions and opioid use history. The starting dose in the clinical trials was 20 mg Kadian NT qd or bid.

The clinical data from the pivotal Phase 3 placebo-controlled efficacy trial (ALO-KNT-301), the supportive Phase 2 active-controlled trail (ALO-KNT-202) and the 12-month

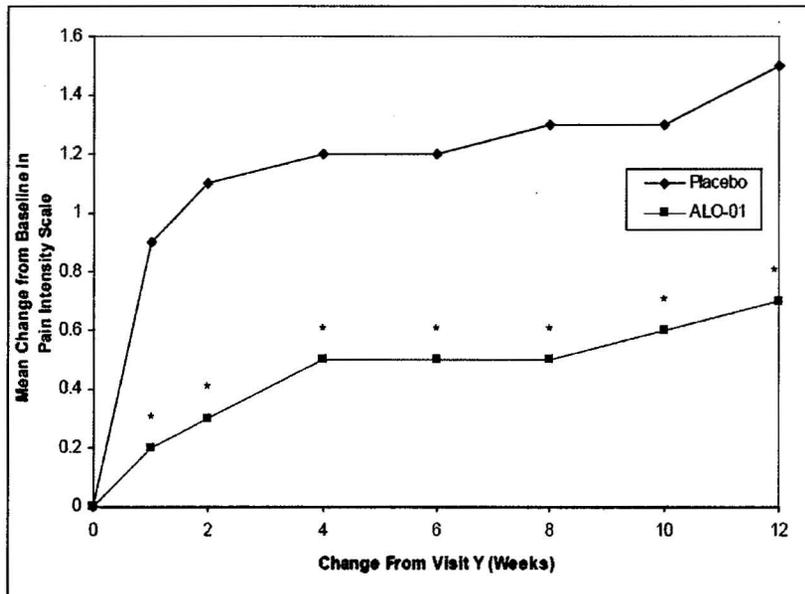
open-label safety trial (ALO-KNT-302) support that efficacy dose and regimen would be 20 mg up to 160 mg daily (qd or bid).

6.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

During the 12-week Maintenance phase (at fixed dose treatment), the mean changes in the *weekly diary average pain intensity score* or the *In-Clinic pain intensity score* from baseline to each visit (up to 12 weeks) were favorable to Kadian NT treatment as compared to placebo (Figure 6.10). Patients at the fixed dose regimens of 20-160 mg per day (qd or bid, which were individually titrated from the Titration Phase) showed good tolerance to the 3-month treatment. The tolerance effects were supported by the 12-month long-term safety trial (ALO-KNT-301), in which patients with chronic non-malignant pain received treatment with flexible dosing regimens (up to 222 mg/day).



Note: Actual values were derived weekly averages of daily average pain scores.
Reference: Section 14.2 Table 11.4.4.1



Note: Pain intensity scale: 0-10 (11-point scale, 0 = no pain and 10 = worst pain ["pain as bad as you can imagine"]).
* $p < 0.05$ for ALO-01 versus placebo using ANCOVA with treatment as a categorical factor and Visit Y as a covariate.
Reference: Section 14.2 Table 11.4.8

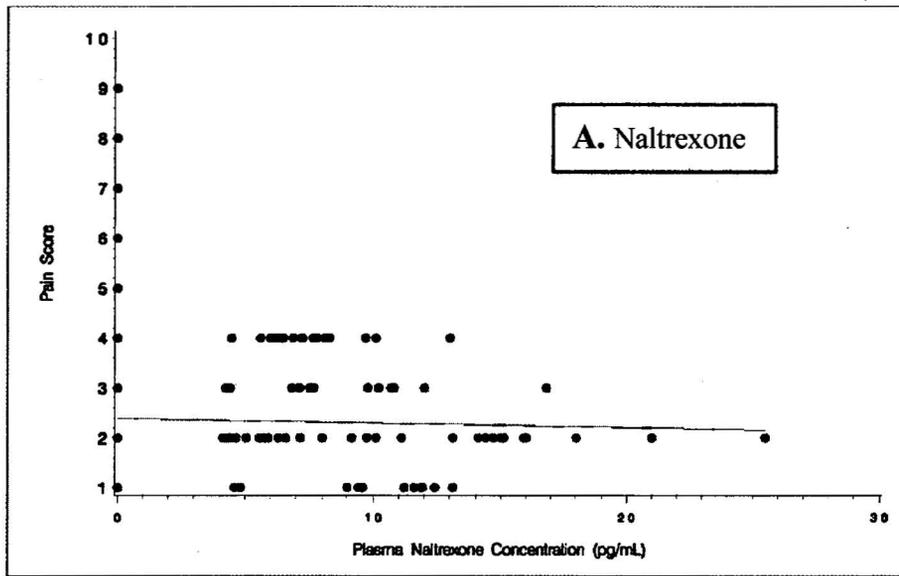
Figure 6.10: Time-course of the mean changes from baseline to each visit in the weekly BPI diary average pain intensity scores (Upper) and in the in-clinic BPI pain intensity scores (Lower). The analyses were based on the ITT population with LOCF imputation method (the average of the last seven days of BPI data) for dropouts and the mixed effect model. BPI: 11-point Brief Pain Inventory scale. (From Applicant's Figures 2 & 3 in the Study ALO-KNT-301 report).

6.10 Additional Efficacy Issues/Analyses

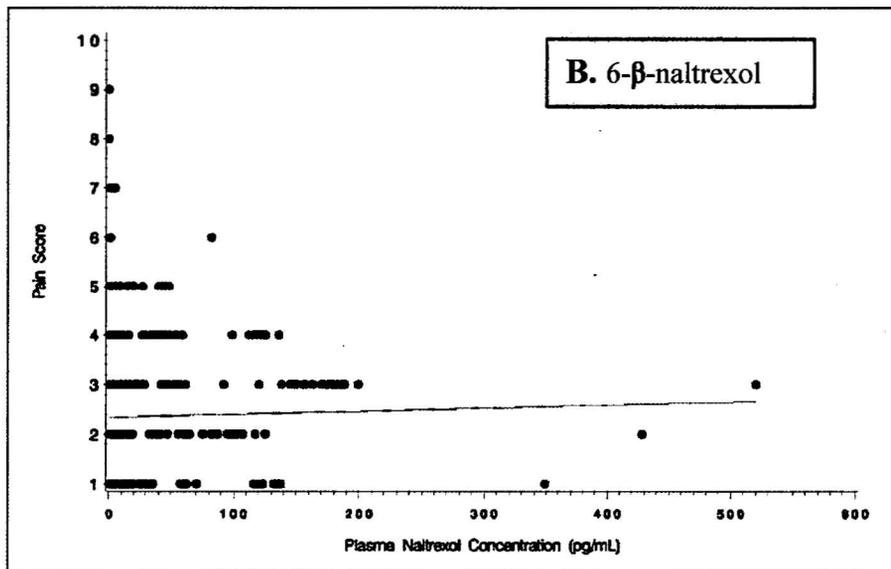
The major efficacy concern with this product is whether naltrexone sequestered in the core of morphine extended-release pellets (Kadian NT capsule) will release and compromise the analgesic effects of morphine sulfate. Although the 12-week placebo-controlled efficacy trial ALO-KNT-301 (pivotal phase 3) demonstrated that Kadian NT was statistically superior in analgesia to placebo, the superiority was marginal (small effect size with a p-values close to 0.05). Since no effect size from Kadian-controlled treatment can be referenced, it is unknown if the marginal analgesic superiority was compromised by naltrexone.

The correlation between the plasma profile of naltrexone/6- β -naltrexol and the analgesic effects of Kadian NT was assessed in the Phase 2 study ALO-KNT-202 (active-controlled PK and efficacy trial; with Kadian as a comparator). Plasma naltrexone or 6- β -naltrexol was detectable at multiple time-points in approximately 10% and 82% of patients, respectively. Comparisons of the detectable naltrexone and/or 6- β -naltrexol concentrations with the time-matched pain intensity score showed that there was no correlation of pain scores to naltrexone (Figure 6.11A) but slight correlation to 6- β -naltrexol (Figure 6.11B).

In the 12-month open-label trial (Study ALO-KNT-302), PK evaluation of naltrexone, 6- β -naltrexol and morphine were performed in a subset of study subjects (up to 20 subjects in each of three dosing range 40 mg to >120 mg/day, and up to 20 subjects over 65 years of age). Blood samples were collected at trough time (prior to dosing) of schedule visits (Visit 1-15 approximately 4 weeks apart for 52 weeks). Overall, 11% and 74% of the subjects had detectable naltrexone and 6- β -naltrexol, respectively, in their plasma across entire study. The incidence of detectable naltrexone concentrations tends to increase with longer duration of treatment; there were increasing trends in the detectable 6- β -naltrexol. The detectable levels of naltrexone or 6- β -naltrexol appear not to be correlated to the pain **intensity change from baseline at matching visits (the reviewer's analysis. The Applicant did not perform this correlation analysis)**. However, due to the high variations on data from both parameters (PK and analgesic response) and small subset sample size, the correlation analysis is inconclusive.



Source of data: Section 14.2.1, Ad Hoc Figure 2.



Source of data: Section 14.2.1, Ad Hoc Figure 1.

Figure 6.11: Correlation of naltrexone (A) or 6-β-naltrexol (B) concentration in plasma with the time-matched pain intensity score. (From the Applicant's Figure 11-4 and Figure 11-5 in Study ALO-KNT-202 report)

7. INTEGRATED REVIEW OF SAFETY

Summary of Safety Results and Conclusions

The safety database includes a total of 1251 subjects treated with at least one dose of Kadian NT capsule from nine clinical trials; 168 subjects were healthy adults (six Phase 1 trials), who received a single dose treatment, and 1083 adult subjects were from three chronic pain trials (two Phase 3: ALO-KNT-301 and ALO-KNT-302; and one Phase 2: ALO-KNT-202) who were exposed to multiple-dose of Kadian NT capsules. During the 12-month open-label trial (study ALO-KNT-302), 84 patients had 6-month exposure and 124 patients were treated for 12 months; and the mean daily dose was 85 mg and ranged from 45-222 mg. The overall extent of exposure to Kadian NT capsule meets the **Division's requirements for the size of the safety database** (during pre-IND and pre-NDA meetings).

In the chronic pain trials (phases 2 and 3), the majority of patients had chronic pain due to osteoarthritis (OA) of the knee or hip or from the lower back. Approximately 24-28% patients in the two short-term trials (up to 12 weeks) and 47% patients in the 12-month open-label trial were opiate-experienced. The overall dropout rate in the Kadian NT treatment groups was 36% during the 3-month double-blind maintenance phase of the placebo-controlled trial and 66% in the 12-month open-label trial. Approximately one third of dropout were due to AEs, which were mostly the severe common AEs of opiate type.

There were no deaths reported from all submitted clinical trials. No serious AEs (SAEs) were reported in Phase 1 trials (single-dose in healthy adult subjects) and Phase 2 trial (2-week Kadian NT dosing in OA patients). A total of 45 patients in the two phase 3 trials experienced one or more SAEs: n=12 in the 3-month placebo-controlled trial and n=33 (7%) in the 12-month open-label trial. The most common SAEs were related to gastrointestinal (GI) and cardiovascular systems, some of them such as colitis, abdominal pain, GI inflammation, hypotension, pancreatitis, cholelithiasis and vomiting may be possibly related to the study product due to opiate class effects; others were confounded by underlying medical conditions and concurrent medications and the causal relationship with Kadian NT treatment was uncertain.

The overall safety profile of Kadian NT capsule in both short-term and long-term trials was consistent with the class of opiate products by either the preferred terms or the organ system class (MedDRA). The common AEs were constipation, dry mouth, nausea, vomiting, dizziness and somnolence.

The opiate withdrawal syndrome associated with naltrexone release from Kadian NT capsule was evaluated in the placebo-controlled trial and the 12-month open-label trial with the Clinical Opiate Withdrawal Scale (COWS). Overall, the total COWS score at the end of treatment (week 12 in Study ALO-KNT-301) or at each monthly visit up to 12 months (Study ALO-KNT-302) tended to decrease from baseline by subgroup analyses

(dosing levels, age, opiate status, race, gender). There were one subject in Study ALO-KNT-301 and five subjects in Study ALO-KNT-302 who experienced moderate opiate withdrawal symptoms (COWS score ≥ 13); and all cases appeared to be due to non-compliance to the study drug (under-dosing of morphine), which theoretically may be also synergized by naltrexone release.

In the 12-month open-label study, plasma naltrexone and 6- β -naltrexol were monitored monthly in a subset (n=93) of patients and approximately 23% and 80% patients had detectable naltrexone and 6- β -naltrexol, respectively. The plasma levels appeared not increased (accumulate) over 12-month treatment of Kadian NT and there were also no correlation between plasma naltrexone or 6- β -naltrexol and COWS scores.

However, both trials were not adequately designed to assess precipitation of the opiate withdrawal symptoms associated with potential naltrexone release from Kadian NT.

- The titration regimen in both trials would have counter potential precipitation of opiate withdrawal symptoms associated with released naltrexone. In the placebo-controlled trial, opiate withdrawal was assessed after up to 6-week titration with open-label Kadian NT treatment, and in the long-term safety trial, all patients received a flexible dose (titration up and down).
- The study populations in both trials were not opioid dependent patients (susceptible population for precipitation of opiate withdrawal by opiate agonist). Approximately 25% of subjects enrolled in the placebo-controlled trial and 47% of subjects in the 12-month open-label trial were opiate-experienced. However, subjects with history of opiate dependence were excluded as indicated in the Exclusion Criteria in clinical trials:
Subject had a documented history of drug abuse/dependence/misuse or narcotic analgesic abuse/dependence/misuse within 5 years prior to the Baseline Visit.
- For appropriate assessment of precipitation of opiate withdrawal syndrome, subjects should have been titrated with **Kadian to a “dependent” optimal dosing regimen**, followed by randomization to Kadian and Kadian NT (at the same dosing regimen based on the titration); ideally, a placebo arm should be included.
- The timing (prior to dosing, or at least 12 hours after the last dosing) for monitoring of plasma naltrexone and 6- β -naltrexol levels was not appropriate at monthly visit in Study ALO-KNT-302. The mean elimination half-life for naltrexone and 6- β -naltrexol are 4 hours and 13 hours. The non-correlation of plasma naltrexone or 6- β -naltrexol with COWS may be due to missing optimal blood sampling.

7.1 Methods

7.1.1 Discussion of Clinical Studies Used to Evaluate Safety

The Applicant submitted 12 trials in the NDA, as listed in Table 5.1 (Section 5.1). Nine of the 12 trials were integrated into a safety database for Kadian NT by excluding three

trials (ALO-KNT-201, ALO-01-07-106 and ALO-01-07-107) that evaluated different formulation of morphine and naltrexone than Kadian NT capsules.

- ***PK studies in healthy subjects*** included five Phase 1 trials with a single dose of Kadian NT.
- ***PD studies in opioid experienced subjects*** included one Phase 1 trial in healthy subjects with opioid experience to assess mitigation of positive subjective effects of morphine with crushed Kadian NT capsule.
- ***Short-term studies in patients with chronic pain*** included one Phase 3 placebo-controlled 12-week trial and one Phase 2 active-controlled 2-week trial in patients with moderate-to-severe pain due to osteoarthritis.
- ***Long-term study in patient with chronic pain*** included one open-label 12-month Phase 3 trial in patient with chronic non-malignant pain.

7.1.2 Adequacy of Data

The Medical Dictionary for Regulatory Activities (MedDRA) was used for short-term and long-term studies to classify the treatment-emergent adverse events (TEAEs) by System Organ Class (SOC) and Preferred Term (PT). MedDRA 9.0 was used for the Phase 2 trial (ALO-KNT-202) and MedDRA 9.1 was used for both Phase 3 trials (ALO-KNT-301 and ALO-KNT-302). AEs from version 9.0 were converted to version 9.1 when data were pooled. The differences in the coding system for MedDRA 9.0 and 9.1 are minor and the conversion should not have impacted the data pooling.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

The Applicant presented the safety data in the following outline as per the Division's requests in the refuse-to-file letter of the first NDA submission:

- Safety data from phase 1 studies
- Titration and Double-blind portions of the short-term studies
- 12-month open-label study

The safety assessment was primarily based on three clinical trials in patients with chronic pain: two Phase 3 trials (ALO-KNT-301: placebo-controlled trial; and ALO-KNT-302: 12-month open-label trial) and one Phase 2 trial (ALO-KNT-202: Kadian-controlled, crossover trial). The safety data from the three trials were pooled based on duration of treatments in an attempt to compare Kadian NT with KADIAN:

Two treatments (Kadian NT vs. Kadian):

- Kadian NT database included:
 - All Kadian NT treatment periods (including Kadian crossovers) of Study ALO-KNT-202
 - Kadian NT Titration Phase and Maintenance Phase of Study ALO-KNT-301
 - All Kadian NT treatment of Study ALO-KNT-302
- Kadian database included all Kadian treatment periods (including Kadian NT crossovers) of Study ALO-KNT-202.

Short-term (up to 6 weeks Titration Phase) safety was assessed by comparing Kadian (the 4-week Kadian Titration Phase of Study ALO-KNT-202) to Kadian NT (the 6-week Kadian NT Titration Phase of Study ALO-KNT-301 and the first 4-week assessment of Study ALO-KNT-302).

Long-term (up to 16 weeks Maintenance Phase) safety was assessed by comparing Kadian (Periods 2-5 of Study ALO-KNT-202) to Kadian NT (Maintenance Period of Study ALO-KNT-301 and Maintenance Weeks 5-16 of Study ALO-KNT-302).

**Table 7.1.3: Pooling strategy of Phases 2 & 3 Studies
(From the Applicant's Table 2 in ISS)**

Study	Period	Pooled Analysis		Comments
		Titration	Maintenance	
ALO-KNT-202	1 – OL Titration	Kadian	Excluded	
	2 – Double-blind	Excluded	Kadian/ALO-01	As Treated
	3 – OL Washout	Excluded	Kadian	Excluded in CSR treatment comparisons
	4 – Double-blind	Excluded	Kadian/ALO-01	As Treated
	5 – OL Titration	Excluded	Kadian	Excluded in CSR treatment comparisons
ALO-KNT-301	Titration	ALO-01	Excluded	
	Double-blind	Excluded	Placebo/ALO-01	As Treated
ALO-KNT-302	Treatment	ALO-01 (Weeks 1-4)	ALO-01 (Weeks 5-16)	

7.2 Adequacy of Safety Assessments

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

Overall Exposure to Kadian NT capsules: A total of 1251 subjects received at least one dose of Kadian NT capsules from nine submitted clinical trials and deposited to the following two populations (Table 7.2.1a):

- N=1083 adult subjects with chronic pain on Kadian NT multiple-dose exposure
- N=173 adult subjects with chronic pain on placebo (but with up to 6-week open label Kadian NT treatment during the titration).
- N=168 healthy adult subjects (single-dose exposure)

Overall duration of exposure to Kadian NT capsules: The Applicant presented overall duration of exposure stratified by total cumulative dose of Kadian NT (Table 7.2.1b);

- N=124 subjects received 5-100g cumulative dose of Kadian NT for ≥ 12 months
- N=84 subjects received $> 1g$ cumulative dose of Kadian NT for ≥ 6 months

Mean daily dose: The Applicant did not present the mean daily dose of Kadian NT capsules in the summary of safety. The mean daily doses summarized in Table 7.2.1a are extracted from the individual study reports and/or their appendixes.

- Study ALO-KNT-301 (placebo-controlled trial): 43 mg (20-160 mg)/day
- Study ALO-KNT-302 (open-label trial): 85 mg (45-222 mg)/day
- Study ALO-KNT-202 (active-controlled trial): 120-180 mg/day

More detailed mean daily doses across all visits (up to 12 months) from the open-label trial (Study ALO-KNT-302) are summarized in Table 7.2.1c.

Table 7.2.1a: Overall extent of exposure to Kadian NT in the Clinical Development Program (Safety Population)

Protocol#	Study Type	Study Subject	Exposed to Kadian NT Capsules		
			No. of Subject	Mean Daily Dose	Mean Duration
ALO-KNT-301	Phase 3, Placebo-controlled	Chronic pain patients (OA of knee or hip)	547†	43 mg (20-160 mg)	11 week
ALO-KNT-302	Phase 3, Open-label, 12-month	Non-cancer chronic pain patients	465	85 mg (45-222 mg)	26 week
ALO-KNT-202	Phase 2, Active-controlled	Chronic pain patients (OA of knee or hip)	71‡	120-180 mg	2 week
Sub-total			(1083)		
ALO-01-07-205	Phase 1, single-dose, crossover, PK	Healthy adults (opiate-experienced, non-dependent)	32	60 mg	One dose
20-903-AU	Phase 1 pilot, single-dose, crossover, PK	Healthy adults	8	60 mg	One dose
ALO-01-07-101	Phase 1, single-dose, crossover, PK (vs. Kadian)	Healthy adults	36	100 mg	One dose
ALO-01-07-102	Phase 1, single-dose, crossover, PK	Healthy adults	36	100 mg	One dose
ALO-01-07-103	Phase 1, single-dose, crossover, 0-40% alcohol, PK	Health adults	32	60 mg	One dose
ALO-01-07-104	Phase 1, single-dose, crossover, crushed capsule, PK	Healthy adults	24	60 mg	One dose
Subtotal			(168)		
Total			1251		

† In Study ALO-KNT-301, 547 were entered to the Titration phase (open-label Kadian NT treatment up to 6 weeks); 344 of them were then randomized to double-blind, placebo-controlled Maintenance Phase (n=171 on Kadian NT for up to 12 weeks).

‡ in Study ALO-KNT-202, 71 patients completed 5-period crossover treatment, including 2-week Kadian NT and 2-week Kadian during the double-blind phase and 4-week open-label Kadian titration and 1-week Kadian between crossovers.

**Table 7.2.1b. Duration of exposure to Kadian NT by the total cumulative dose
(From the Applicant's Table 8 in the ISS)**

Dose Duration (days)	Total Drug Received (g)								Subtotal
	≤0.5	≥0.5-1.0	>1.0-5.0	>5.0-10	>10-20	>20-50	>50-100	>100	
1	172 ^a	1	0	0	0	0	0	0	173
2-10	138	7	3	0	0	0	0	0	148
11-30	33	75	114	2	1	0	0	0	225
31-90	2	12	144	27	9	0	0	0	194
91-180	2	0	75	119	70	8	1	0	275
181-360	0	0	1	4	31	39	6	3	84
≥361	0	0	0	3	36	63	19	3	124
SUBTOTAL	347	95	337	155	147	110	26	6	1223

Note: Subjects who were in a crossover study were counted for the first dosing period only.

a Eight subjects enrolled in Study 20-903-AU were not included but were to receive a single dose of 60 mg.

Reference: Appendix B.2, Table 4.3

Subjects without sufficient dosing information were excluded from the duration/dose analysis:
n=11 from study ALO-KNT-301, n=9 from Study ALO-KNT-302 and n=8 from Study 20-903.

**Table 7.2.1c: Average daily dose of Kadian NT capsules across all visits
(From the Applicant's Section 14.1/Table 11 in Study ALO-KNT-302 report)**

Visit Schedule	Average Daily Dose of Kadian NT						Overall N=465*	
	<80 mg N=299		80-120 mg N=79		>120 mg N=78			
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Visit 1 (Baseline)	293	40.91 (20.57)	75	61.25 (41.21)	75	157.93 (172.67)	443	64.16 (86.066)
Visit 2 (Week 1)	231	47.73 (21.55)	73	73.27 (34.77)	69	165.83 (163.17)	373	74.57 (85.891)
Visit 3 (Week 4)	172	50.34 (17.63)	62	81.80 (24.97)	58	168.82 (115.07)	292	80.55 (70.697)
Visit 4 (Month 2)	147	54.61 (20.98)	62	92.59 (18.15)	56	171.78 (91.94)	265	88.26 (64.770)
Visit 5 (Month 3)	133	54.51 (19.26)	59	107.15 (61.78)	55	192.79 (87.38)	247	97.87 (76.331)
Visit 6 (Month 4)	120	56.14 (18.58)	58	106.04 (30.05)	50	235.51 (203.36)	228	108.17 (119.72)
Visit 7 (Month 5)	112	56.16 (17.68)	50	100.13 (22.23)	47	370.47 (861.69)	209	137.36 (425.03)
Visit 8 (Month 6)	105	56.59 (19.29)	51	111.58 (24.76)	44	243.66 (245.06)	200	111.77 (137.03)
Visit 9 (Month 7)	94	57.45 (18.73)	50	111.54 (18.21)	40	223.72 (120.26)	184	108.30 (87.13)
Visit 10 (Month 8)	95	57.19 (21.83)	47	111.95 (15.80)	37	231.82 (134.22)	179	107.67 (92.35)
Visit 11 (Month 9)	91	57.90 (20.58)	45	108.78 (18.60)	35	237.81 (127.15)	171	108.11 (91.43)
Visit 12 (Month 10)	88	59.93 (21.21)	42	109.69 (17.94)	37	249.20 (135.13)	167	114.38 (99.51)
Visit 13 (Month 11)	86	57.55 (25.07)	39	114.46 (25.42)	36	262.84 (149.61)	161	117.24 (109.86)
Visit 14 (Month 12)	84	59.69 (21.72)	37	167.85 (328.90)	35	256.23 (160.37)	156	129.44 (194.00)
Visit 15 (Month 13)	1	30.00 (N/A)	1	101.70 (N/A)	0		2	65.85 (50.70)
Overall	299	45.39 (17.84)	79	97.34 (11.28)	78	221.79 (142.28)	456	84.56 (89.00)

* including nine subjects with missing dosing information.

Demographic characteristics:

Short-term (2-12 weeks) studies: Subjects who enrolled to the short-term trials (Study ALO-KNT-202 and Study ALO-KNT-301) and received Kadian NT capsule treatment were patients with moderate-to-severe pain due to osteoarthritis of knee or hip. The majority were females (61% and 69%) and White (76% and 88%) with mean age of 56 years (21-85 years) and mean BMI of 32.1 and 32.4 kg/m². Approximately 24-29% of subjects were opioid-experienced. See Table 7.2.1e for details.

Long-term (52 weeks) study: Subjects in the long-term open-label trial (Study ALO-KNT-302) were patients with chronic non-malignant pain. They were approximately 53% females and 88% White with the mean age of 52 years (19-74 years) and the mean BMI of 30.2 kg/m² (16.5 to 51.0 kg/m²). Of the 465 patients, 47% were opioid-experienced. See Table 7.2.1f for details. The majority of patients had chronic pain from sources of the lower back (57%), followed by knees or hips (22%) and posterior neck/middle back (8%).

**Table 7.2.1e: Demographic characteristic in short-term studies-Safety Population
(From the Applicant's Table 11 in the ISS)**

	Double-Blind ^a			Open-label	
	ALO-KNT-202	ALO-KNT-301		ALO-KNT-301	ALO-KNT-202
	Total Randomized N = 72	ALO - 01 N = 171	Placebo N = 173	ALO - 01 N = 547	KADIAN N = 111
Gender					
Male	22 (30.6)	65 (38.0)	78 (45.1)	215 (39.3)	35 (31.5)
Female	50 (69.4)	106 (62.0)	95 (54.9)	332 (60.7)	76 (68.5)
Age (years)					
Mean	55.6	54.2	54.7	55.7	56.8
Standard Deviation	10.50	11.62	12.92	12.27	11.12
Minimum/Maximum	28/83	24/81	21/85	21/85	28/83
Hispanic Ethnicity	6 (8.3)	36 (21.1)	40 (23.1)	100 (18.3)	7 (6.3)
Race					
White	66 (91.7)	128 (74.9)	121 (69.9)	413 (75.5)	98 (88.3)
Black or African American	6 (8.3)	29 (17.0)	30 (17.3)	89 (16.3)	9 (8.1)
American Indian or Alaska Native	0	2 (1.2)	4 (2.3)	8 (1.5)	2 (1.8)
Asian	0	9 (5.3)	15 (8.7)	26 (4.8)	2 (1.8)
Native Hawaiian or other Pacific Islander	0	1 (0.6)	0	1 (0.2)	0
Other	0	2 (1.2)	3 (1.7)	10 (1.8)	0
BMI (kg/m²)	(N = 72)	(N = 167)	(N = 167)	(N = 530)	(N = 111)
Mean	33.2	32.5	31.8	32.1	32.4
Standard Deviation	6.22	6.93	6.32	6.40	6.04
Minimum/Maximum	20.0/44.8	17.1/52.5	17.4/44.9	17.1/52.5	20.0/44.8
Opioid Experienced					
n (%)	20 (28.2)	42 (24.6)	42 (24.3)	133 (24.3)	32 (28.8)

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

Reference: Appendix B.2, Table 3.1 and Table 3.2; Module 5.3.5.1.1, Section 14.1 Table 2.1 and Listing 6; Module 5.3.5.1.2, Section 14.1 Table 11.2.2

**Table 7.2.1f: Demographic characteristic in long-term study (ALO-KNT-302)
(From the Applicant's Table 12 in the ISS)**

Category	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 (%)	
Gender				
Male	127 (42.5)	37 (46.8)	52 (66.7)	220 (47.3)
Female	172 (57.5)	42 (53.2)	26 (33.3)	245 (52.7)
Age (years)				
Mean (SD)	52.6 (10.68)	50.6 (10.47)	50.4 (9.32)	51.7 (10.56)
Median	53.0	50.0	51.5	53.0
Min, Max	19, 74	24, 68	28, 68	19, 74
Number (%) ≥65 years	39 (13.0)	5 (6.3)	4 (5.1)	48 (10.3)
Hispanic Ethnicity	30 (10.0)	4 (5.1)	2 (2.6)	36 (7.7)
Race				
White	263 (88.0)	70 (88.6)	69 (88.5)	410 (88.2)
Black or African American	27 (9.0)	5 (6.3)	8 (10.3)	41 (8.8)
American Indian or Alaska Native	3 (1.0)	0	0	3 (0.6)
Asian	3 (1.0)	1 (1.3)	0	4 (0.9)
Native Hawaiian or other Pacific Islander	0	0	0	0
Other	3 (1.0)	3 (3.8)	1 (1.3)	7 (1.5)
BMI (kg/m²)				
Mean (SD)	30.34 (5.744)	31.09 (6.835)	28.64 (6.125)	30.18 (3.026)
Median	29.90	29.80	27.60	29.60
Min, Max	17.9, 51.0	19.0, 44.6	16.5, 44.1	16.5, 51.0
Opioid Experienced				
n (%)	122 (40.8)	45 (57.0)	47 (60.3)	219 (47.1)

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

Reference: Appendix B.2, Table 3.1; Module 5.3.5.2.1, Section 14.1 Table.3.1 and Table 4.1

7.2.2 Explorations for Dose Response

Among the three clinical trials primarily contributed to the safety data, studies ALO-KNT-202 and ALO-KNT-301 were fixed-dose studies except the Titration Phase of ALO-KNT-301, and study ALO-KNT-302 was an open-label flexible-dose study. For the flexible-dose data, the Applicant, *post-hoc*, stratified the safety profile to three daily dose categories: <80 mg, 80-120mg and >120 mg. However, the decision to increase the dose was based on both analgesic response and tolerability (TEAEs) and patients with AEs were less likely to be up-titrated and more likely to remaining at dose levels < 120 mg. thus overall incidence of AEs among the three dosing categories were from low to high: <120 mg, 80-120 gm and < 80 mg.

The Applicant also presented the safety profile based on the planned duration of treatment short-term (2-12 weeks) and long-term (up to 52 weeks).

7.2.3 Special Animal and/or In Vitro Testing

No particular safety concerns with the proposed product were assessed with animal studies or in vitro testing.

7.2.4 Routine Clinical Testing

The routine clinical testing conducted during the clinical trials in both healthy subjects and chronic pain patients appears adequate in terms of safety monitoring types and frequency. The safety monitoring plan included: physical examination, vita signs, 12-lead ECG, clinical laboratory tests (hematology, chemistry and urinalysis) and treatment emerge adverse events.

7.2.5 Metabolic, Clearance, and Interaction Workup

The active ingredients, morphine sulfate and naltrexone HCl, have been individually formulated in many approved products, including Kadian (extended-release morphine) previously developed by the same Applicant. There were no particular safety concerns **with drug metabolism of the proposed “naltrexone-sequestered Kadian (Kadian NT) capsules”**. However, the **drug-drug interaction** between morphine and naltrexone on both PK and PD levels may cause a potential safety **consequence** – **naltrexone** precipitation of opiate withdrawal syndrome.

To address this safety issue, the Applicant included assessment of opiate withdrawal symptoms in studies ALO-KNT-301 and ALO-KNT-302. Plasma concentration of naltrexone and its active metabolite 6- β -naltrexol were monitored by collection of sparse blood sample (prior to daily dosing) across 12-months in subset patients of study ALO-KNT-302. More detailed PK profile of naltrexone and 6- β -naltrexol with multiple-doses of Kadian NT capsules were assessed in chronic pain patients in study ALO-KNT-202.

The results are summarized in the following Section 7.6.4 (Overdose, Drug Abuse Potential/ Withdrawal and Rebound).

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

The proposed product, Kadian NT capsule, is in the drug class of morphine and naltrexone. The safety profiles of both active ingredients have been well established. The routine safety monitoring, as the Applicant performed during the clinical development, appears adequately to address the class safety concerns (expected adverse reactions) of Kadian NT. However, potential precipitation of opiate withdrawal symptom by opiate antagonist, naltrexone, was not adequately addressed in the clinical development program (study design, study subjects and dosing regimen, etc.). Since PK studies of Kadian NT and sparse blood sampling in the long-term safety trial did not show a significant absorption of naltrexone, opiate withdrawal symptoms associated with Kadian NT may not be expected in the opioid-dependent patients who may switch from other opiates to Kadian NT.

7.3 Major Safety Results and Discussion

7.3.1 Deaths

There were no deaths reported in the clinical development program of Kadian NT capsules.

7.3.2 Nonfatal Serious Adverse Events

Phase 1 trials: No serious AEs were reported in the six single-dose studies in healthy subjects.

Phase 2 trial: No serious AEs associated with Kadian NT capsule were reported in Study ALO-KNT-202. One subjects (ID: 003-9309; 51-year-old white male with multiple medical history and medications) who received open-label Kadian developed chest pain and the symptoms were resolved after 2-day hospitalization. The subject withdrew from the study after discharge.

Phase 3 trials: a total 45 subjects reported one or more SAEs from two phase 3 studies: Study ALO-KNT-301; 3 subjects (0.5% of 547) during Titration Phase (Table 7.3.2a), 9 subjects (n=3 or 1.7% on placebo and n=6 or 3.5% on Kadian NT) during Maintenance Phase (Table 7.3.2b).

Study ALO-KNT-302: A total of 33 subjects (7.1% of 465 enrollee) reported one or more SAEs during the 12-month open-label Kadian NT treatment; 14 of them discontinued from the study due to a SAE. No individual SAE led to the discontinuation of more than one subject. Some SAEs such as colitis (n=2), GI inflammation (n=1), pancreatitis (n=1), vomiting (n=1) and cholelithiasis (n=1) may be possibly related to the study product due to opiate class effects; other SAEs, mostly cardiovascular events, were confounded by

underlying medical conditions and current medications and the causal relationship with **Kadian NT treatment** was uncertain. The Applicant's interpretation for the SAEs appears reasonable.

**Table 7.3.2a: Subjects with SAEs during Titration Phase of Study ALO-KNT-301
(From the Applicant's Table 19 in the ISS)**

Subject ID	Age/ Gender	Preferred Term	Study Day Start^a	Duration (days)	Intensity/ Relationship	Action Taken/ AE Outcome
122-0003	63/ Female	Hypotension	T 8	4	Severe/ Probable (Likely)	Discontinued Study Drug/ Resolved
142-0002	71/ Female	Atrial fibrillation	T 11	4	Severe/ Not Related	Discontinued Study Drug/ Resolved
150-0010	54/ Male	Concussion	T 19	2	Severe/ Unlikely	Medication ^b / Resolved with Sequelae

T = titration

a. Study Day was calculated as the days since first dose of study drug in the Titration Phase at AE onset.

b. Hydromorphone hydrochloride and acetylsalicylic acid

Reference: Module 5.3.5.1.2, Section 16.2.4 Listing 3, Section 16.2.5 Listing 10, and Section 16.2.7 Listing 7, Listing 14.1, and Listing 14.3

**Table 7.3.2b: Subjects with SAEs during Maintenance Phase of Study ALO-KNT-301
(From the Applicant's Table 20 in the ISS)**

Subject ID	Age/ Gender	Preferred Term	Study Day Start ^a	Duration (days)	Intensity/ Relationship	Action Taken/ AE Outcome
Placebo						
139-0007	56/ Female	Chest pain	M 56	3	Mild/ Not Related	None/ Resolved
142-0013	65/ Female	Abdominal pain ^b	M 55	8	Severe/ Possible	Discontinued Study Drug/ Resolved
182-0016	82/ Male	Transient ischaemic attack	M 76	3	Mild/ Not Related	None ^c / Resolved
ALO - 01						
109-0001	61/ Female	Pancreatitis	M 100	4	Severe/ Unlikely	None/ Resolved
		Renal cell carcinoma stage unspecified	M 100	ongoing	Severe/ Unlikely	None/ Ongoing
123-0005	63/ Male	Lung neoplasm malignant	M 16	ongoing	Severe/ Not Related	None/ Ongoing
126-0039	54/ Female	Cholelithiasis ^b	M 47	1	Severe/ Unlikely	None/ Resolved
146-0011	68/ Male	Intestinal blockage	M 39	3	Moderate/ Not Related	Medication ^d / Resolved
161-0005	60/ Female	Gastroenteritis viral	M 12	3	Moderate/ Not Related	None/ Resolved
168-0007	59/ Male	Basal cell carcinoma	M 54	40	Severe/ Not Related	Other ^e / Resolved

M = maintenance

- a. Study Day was calculated as the days since first dose of study drug in the Maintenance Phase at AE onset.
- b. Study drug was discontinued due to this adverse event.
- c. No action noted; however, clopidogrel sulfate and acetylsalicylic acid were administered.
- d. Antibiotic
- e. Radiation therapy

Reference: Module 5.3.5.1.2, Section 16.2.4 Listing 3, Section 16.2.5 Listing 10, and Section 16.2.7 Listing 7, Listing 14.1, and Listing 14.3

7.3.3 Dropouts and/or Discontinuations

The Applicant defined *discontinuation* as a subject who is not able to continue in the study for any reason and withdraws from the study. In this review, “dropout” will be interchangeably used with “discontinuation”. The overall dropout rates during Phases 2 and 3 studies were variable from Open-label/Titration to Double-blind/Maintenance treatments:

Dropouts in short-term studies (ALO-KNT-202 and ALO-KNT-301): the dropout profile is summarized in Table 7.3.3a.

- Open-label/titration phase:
 - Study ALO-KNT-301 (Kadian NT): 37% dropouts (n=203 of 547) and 61% of them due to AEs (n=124 of 203)

- Study ALO-KNT-202 (Kadian): 39% dropouts (n=44 of 113) and 66% of them due to AEs (n=29 of 44)
- Double-blind/Maintenance phase:
 - Study ALO-KNT-301: 43% on placebo (17% of them due to AEs) and 36% on Kadian NT (30% of them due to AEs)
 - Study ALO-KNT-202: 1.4% on Kadian NT (all, n=1, due to AEs) and 2.8% on Kadian (1.4% due to AEs)

**Table 7.3.3a: Subject dropout during the short-term studies
(Studies ALO-KNT-301 and ALO-KNT-202)
(From the Applicant's Table 9 in the ISS)**

	Double-Blind ^a				Open-label	
	ALO-KNT-202		ALO-KNT-301		ALO-KNT-301	ALO-KNT-202
	ALO - 01 N = 72	KADIAN N = 72	ALO - 01 N = 171	Placebo N = 173	ALO - 01 N = 547	KADIAN N = 113
Number of Subjects Enrolled	72 (100)	72 (100)	171 (100)	173 (100)	547 (100)	113 (100)
Number of Subjects in Safety Population	71 (98.6)	71 (98.6)	171 (100)	173 (100)	547 (100)	111 (98.2)
Number of Subjects 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
Subject Withdrew from Study	0	0	15 (8.8)	12 (6.9)	21 (3.8)	0
Subject Withdrew Consent	0	0	0	0	0	3 (2.7)
Termination of Study or Withdrawal of Subject 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.

Reference: Module 5.3.5.1.1, Section 14.1 Table 1; Module 5.3.5.1.2, Section 14.1 Table 10.1.1 and Table 10.1.2

Dropouts in long-term study (ALO-KNT-302): the overall dropout rate was 66% (n=307 of 467), as summarized in Table 7.3.3b.

- Reasons for dropouts:
 - Adverse events: 23.7% (n=110, or 36% of all dropouts)
 - Non-compliance: 13.7%
 - Subject withdrew from study: 11.1%
- Differences in dropout rates across dosing levels:
 - Daily dose <80 mg: 71.2% (mostly due to AE and subject withdrawal)
 - Daily dose >120 mg: 55.1%
 - Daily dose 80-120 mg: 50.6%

**Table 7.3.3b: Subject dropout during the long-term study (Study ALO-KNT-302)
(From the Applicant’s Table 9 in the ISS)**

	n (%)			
	Average Daily Dose of ALO-01			Overall
	< 80 mg	80-120 mg	>120 mg	
Subjects Enrolled	299 (100.0)	79 (100.0)	78 (100.0)	467 ^a
Subjects in Safety Population	299	79	78	465 ^b
Opioid naive	177 (59.2)	34 (43.0)	31 (39.7)	246 (52.7)
Opioid experienced	122 (40.8)	45 (57.0)	47 (60.3)	219 (46.9)
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)
Subject 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 subject was considered to be discontinued from the study if there was a negative response for “Did subject complete study?” on End of Study CRF.

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

a. There were 2 subjects who were not treated with study drug.

b. There were 9 subjects (Subjects 213-2001, 226-2006, 232-2005, 232-2018, 232-2020, 248-2004, 249-2002, 251-2011, and 252-2008) who did not have enough dosing information to categorize average daily dose. Therefore, the total number of subjects dosed (N = 465) exceeds the sum of the number of subjects presented by dose group (N = 456).

c. Listing 15.2 erroneously included Subject 260-2012 as an AE leading to study drug discontinuation; however, this subject actually completed study.

Reference: Module 5.3.5.2.1, Section 14.1 Table 1.1 and Table 1.2

As shown in Table 7.3.3b, higher dropout rate due to AEs at the lower dose group (31% in the daily dose <80 mg vs. 19-10% in >80 mg), which was consistent to AE profile by daily dosing group (Table 7.5.1, patients in the dose groups <80 mg and 80-120 mg reported more AEs than those in the >120 mg dose group). The Applicant explained, which appears reasonable that the dose groups were *post hoc* categorized but not pre-

specified, the higher incidence of AEs and higher dropouts due to AEs in the lower doses was likely due to dose up-titration, which based on both pain response and the occurrence of AEs. Therefore, subjects who had AEs were less likely to be up-titrated, and more likely to remain at dose levels <120 mg.

7.3.4 Significant Adverse Events

The AEs that lead to dropout from short-term and long-term studies were mostly due to severe common AEs or those AEs less likely related to treatments of the study drug.

Study ALO-KNT-202:

- Open-label Kadian titration period: A total of 27 subjects discontinued from study due to non-serious AEs, which mostly were common AEs associated with Kadian.
- Double-blind period: one patient who received Kadian NT dropped out due to non-serious AEs (crying, fatigue, vomiting and asthenia).

Study ALO-KNT-301:

- Titration Phase: 130 patients dropped out due to one or more TEAEs; five of them reported adverse events not previously reported with the use of morphine, including muscle cramps, proteinuria, cystitis, nephrolithiasis, and breast cancer.
- Maintenance Phase: 11% (n=18) on Kadian NT and 8% (n=13) on placebo prematurely discontinued from the study due to AEs. Adverse events that led to dropout in ≥ 2 subjects in either treatment group included nausea, vomiting, hyperhidrosis, diarrhea, constipation, and somnolence. All other TEAEs were reported by <2 dropout subjects each.

Study ALO-KNT-302: a total of 110 patients prematurely discontinued from the study due to at least one AE. The most common ($\geq 2\%$ of subjects) AEs that led to premature discontinuation were the typical opioid-related events of nausea (5.4%), constipation (3.4%), and vomiting (2.6%).

7.4 Supportive Safety Results and Discussion

7.4.1 Common Adverse Events

Overall, the adverse event (AE) profile in both short-term and long-term trials was consistent with other opioid products by either preferred terms or organ system class. Most of the frequently reported TEAEs are typical of opioid-related AEs: constipation, dry mouth, nausea, vomiting, dizziness, and somnolence.

Phase 1 trials (in healthy adult subjects):

- PK studies: TEAEs reported by $\geq 10.0\%$ of subjects in any regimen from the four PK studies included nausea, dizziness, headache, and vomiting. Other TEAEs reported by $\geq 10.0\%$ of subjects in any regimen in at least one of the healthy volunteer studies included pruritus generalized, somnolence, feeling hot, dysuria,

dry mouth, constipation, insomnia, back pain, diarrhoea, constipation, abdominal pain, multiple stools, lightheadedness, xerostomia, peristalsis, diaphoresis, and flushing.

- Abuse-deterrent Study (ALO-01-07-205): TEAEs reported by $\geq 10.0\%$ of subjects in any regimen included euphoric mood, somnolence, nausea, vomiting, dizziness, headache, and pruritus. These AEs are consistent with other opioid products.
- Alcohol interaction study (ALO-01-07-103): TEAEs reported by $\geq 10.0\%$ of subjects in any regimen included headache, nausea, vomiting, dizziness, and poisoning (described as intoxicated).

Phase 2/3 short-term trials (in chronic pain patients):

The TEAEs reported by $\geq 2.0\%$ of patients during the short-term trials is summarized in Table 7.4.1a, and severe TEAEs reported by $\geq 1\%$ patients included vomiting, constipation, nausea, and somnolence (Table 7.4.1b).

The treatment-related TEAEs (or Adverse Reactions) reported by $\geq 5.0\%$ patients during the double-blind phase of the short-term trials included constipation, nausea, and vomiting, which was a similar profile observed in patients who received double-blind Kadian in Study ALO-KNT-202 (Table 7.4.1c).

Table 7.4.1a: Treatment-Emergent Adverse Events (TEAEs) Reported by $\geq 2\%$ of Patients during Short-Term Trials (ALO-KNT-202 and ALO-KNT-301) in Safety Population (From the Applicant's Table 13 in ISS)

System Organ Class/ Preferred Term	n (%)					
	Double-Blind ^a				Open-label	
	ALO-KNT-202		ALO-KNT-301		ALO-KNT-301	ALO-KNT-202
	ALO - 01 N = 71	KADIAN N = 71	ALO - 01 N = 171	Placebo N = 173	ALO - 01 N = 547	KADIAN N = 111
Any Adverse Event	33 (46.5)	32 (45.1)	91 (53.2)	84 (48.6)	347 (63.4)	93 (83.8)
Eye disorders	1 (1.4)	1 (1.4)	2 (1.2)	9 (5.2)	10 (1.8)	3 (2.7)
Lacrimation increased	0	0	1 (0.6)	7 (4.0)	2 (0.4)	0
Vision blurred	0	1 (1.4)	0	1 (0.6)	5 (0.9)	3 (2.7)
Gastrointestinal disorders	21 (29.6)	22 (31.0)	52 (30.4)	38 (22.0)	272 (49.7)	84 (75.7)
Abdominal pain	1 (1.4)	1 (1.4)	2 (1.2)	4 (2.3)	4 (0.7)	2 (1.8)
Abdominal pain upper	0	3 (4.2)	7 (4.1)	4 (2.3)	7 (1.3)	5 (4.5)
Constipation	11 (15.5)	9 (12.7)	12 (7.0)	7 (4.0)	167 (30.5)	52 (46.8)
Diarrhoea	2 (2.8)	2 (2.8)	21 (12.3)	21 (12.1)	15 (2.7)	11 (9.9)
Dry mouth	0	1 (1.4)	3 (1.8)	2 (1.2)	31 (5.7)	17 (15.3)
Flatulence	1 (1.4)	0	1 (0.6)	0	3 (0.5)	5 (4.5)
Nausea	7 (9.9)	6 (8.5)	20 (11.7)	13 (7.5)	115 (21.0)	45 (40.5)
Stomach discomfort	1 (1.4)	1 (1.4)	1 (0.6)	1 (0.6)	4 (0.7)	5 (4.5)
Vomiting	6 (8.5)	3 (4.2)	12 (7.0)	4 (2.3)	50 (9.1)	27 (24.3)
General disorders and administration site conditions	3 (4.2)	6 (8.5)	18 (10.5)	15 (8.7)	51 (9.3)	21 (18.9)
Chills	0	2 (2.8)	4 (2.3)	6 (3.5)	4 (0.7)	2 (1.8)
Fatigue	2 (2.8)	0	2 (1.2)	2 (1.2)	19 (3.5)	10 (9.0)
Oedema peripheral	1 (1.4)	2 (2.8)	5 (2.9)	1 (0.6)	8 (1.5)	2 (1.8)
Pain	1 (1.4)	2 (2.8)	0	0	1 (0.2)	1 (0.9)
Pyrexia	0	2 (2.8)	2 (1.2)	1 (0.6)	4 (0.7)	2 (1.8)
Infections and infestations	3 (4.2)	4 (5.6)	20 (11.7)	17 (9.8)	31 (5.7)	10 (9.0)
Cellulitis	0	0	1 (0.6)	0	0	3 (2.7)
Nasopharyngitis	0	1 (1.4)	3 (1.8)	7 (4.0)	6 (1.1)	0
Sinusitis	0	0	5 (2.9)	1 (0.6)	4 (0.7)	3 (2.7)
Metabolism and nutrition disorders	1 (1.4)	2 (2.8)	6 (3.5)	3 (1.7)	18 (3.3)	4 (3.6)
Anorexia	1 (1.4)	2 (2.8)	4 (2.3)	1 (0.6)	7 (1.3)	4 (3.6)

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

Reference: Module 5.3.5.1.1, Section 14.3.1 Table 20.1; Module 5.3.5.1.2, Section 14.3.1 Table 12.2.3.1 and Table 12.2.3.4

Continued from Table 7.4.1a

System Organ Class/ Preferred Term	n (%)					
	Double-Blind ^a				Open-label	
	ALO-KNT-202		ALO-KNT-301		ALO-KNT-301	ALO-KNT-202
	ALO - 01 N = 71	KADIAN N = 71	ALO - 01 N = 171	Placebo N = 173	ALO - 01 N = 547	KADIAN N = 111
Musculoskeletal and connective tissue disorders	10 (14.1)	10 (14.1)	16 (9.4)	20 (11.6)	22 (4.0)	15 (13.5)
Arthralgia	1 (1.4)	2 (2.8)	2 (1.2)	6 (3.5)	1 (0.2)	5 (4.5)
Back pain	3 (4.2)	0	2 (1.2)	2 (1.2)	3 (0.5)	2 (1.8)
Joint stiffness	1 (1.4)	2 (2.8)	0	0	1 (0.2)	2 (1.8)
Muscle spasms	3 (4.2)	3 (4.2)	5 (2.9)	2 (1.2)	8 (1.5)	6 (5.4)
Myalgia	1 (1.4)	1 (1.4)	1 (0.6)	2 (1.2)	2 (0.4)	3 (2.7)
Pain in extremity	1 (1.4)	1 (1.4)	0	1 (0.6)	2 (0.4)	4 (3.6)
Nervous system disorders	10 (14.1)	14 (19.7)	22 (12.9)	17 (9.8)	149 (27.2)	57 (51.4)
Dizziness	1 (1.4)	5 (7.0)	3 (1.8)	3 (1.7)	47 (8.6)	23 (20.7)
Headache	3 (4.2)	6 (8.5)	12 (7.0)	6 (3.5)	33 (6.0)	18 (16.2)
Somnolence	7 (9.9)	6 (8.5)	2 (1.2)	5 (2.9)	78 (14.3)	32 (28.8)
Tremor	0	0	1 (0.6)	3 (1.7)	6 (1.1)	4 (3.6)
Psychiatric disorders	4 (5.6)	3 (4.2)	15 (8.8)	12 (6.9)	41 (7.5)	12 (10.8)
Anxiety	1 (1.4)	2 (2.8)	4 (2.3)	3 (1.7)	8 (1.5)	3 (2.7)
Insomnia	0	1 (1.4)	6 (3.5)	4 (2.3)	7 (1.3)	1 (0.9)
Restlessness	0	0	2 (1.2)	4 (2.3)	5 (0.9)	1 (0.9)
Respiratory, thoracic, and mediastinal disorders	0	3 (4.2)	10 (5.8)	15 (8.7)	26 (4.8)	6 (5.4)
Cough	0	0	2 (1.2)	4 (2.3)	4 (0.7)	1 (0.9)
Rhinorrhoea	0	0	4 (2.3)	12 (6.9)	2 (0.4)	0
Skin and subcutaneous tissue disorders	3 (4.2)	3 (4.2)	16 (9.4)	10 (5.8)	54 (9.9)	27 (24.3)
Hyperhidrosis	0	1 (1.4)	6 (3.5)	4 (2.3)	9 (1.6)	2 (1.8)
Pruritus	1 (1.4)	1 (1.4)	1 (0.6)	1 (0.6)	38 (6.9)	16 (14.4)
Pruritus generalized	0	2 (2.8)	0	0	0	7 (6.3)
Vascular disorders	2 (2.8)	0	6 (3.5)	3 (1.7)	9 (1.6)	4 (3.6)
Flushing	1 (1.4)	0	4 (2.3)	2 (1.2)	0	0
Hot flush	1 (1.4)	0	1 (0.6)	2 (1.2)	3 (0.5)	4 (3.6)

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

Reference: Module 5.3.5.1.1, Section 14.3.1 Table 20.1; Module 5.3.5.1.2, Section 14.3.1 Table 12.2.3.1 and Table 12.2.3.4

Table 7.4.1b: Severe TEAEs Reported by ≥1% of Patients during Short-Term Trials (ALO-KNT-202 and ALO-KNT-301) in Safety Population (From the Applicant's Table 15 in ISS)

System Organ Class/ Preferred Term	Double-Blind ^a				Open-label	
	ALO-KNT-202		ALO-KNT-301		ALO-KNT-301	ALO-KNT-202
	ALO - 01 N = 71	KADIAN N = 71	ALO - 01 N = 171	Placebo N = 173	ALO - 01 N = 547	KADIAN N = 111
Any Adverse Event	0	1 (1.4)	9 (5.3)	11 (6.4)	38 (6.9)	13 (11.7)
Gastrointestinal disorders	0	1 (1.4)	2 (1.2)	5 (2.9)	19 (3.5)	10 (9.0)
Constipation	0	1 (1.4)	0	0	10 (1.8)	4 (3.6)
Diarrhoea	0	0	1 (0.6)	2 (1.2)	0	0
Nausea	0	0	0	3 (1.7)	4 (0.7)	4 (3.6)
Vomiting	0	0	0	0	4 (0.7)	5 (4.5)
Musculoskeletal disorders	0	0	1 (0.6)	4 (2.3)	4 (0.7)	0
Arthralgia	0	0	0	3 (1.7)	1 (0.2)	0
Nervous system disorders	0	0	0	1 (0.6)	9 (1.6)	5 (4.5)
Dizziness	0	0	0	0	4 (0.7)	2 (1.8)
Headache	0	0	0	0	1 (0.2)	1 (0.9)
Somnolence	0	0	0	0	8 (1.5)	3 (2.7)
Psychiatric disorders	0	0	2 (1.2)	1 (0.6)	4 (0.7)	0
Insomnia	0	0	2 (1.2)	0	1 (0.2)	0

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

Reference: Module 5.3.5.1.1, Section 14.3.1 Table 21; Module 5.3.5.1.2, Section 14.3.1 Table 12.2.3.2 and Table 12.2.3.5

Table 7.4.1c: Treatment-related AEs (Adverse Reactions) Reported by ≥5% of Patients during Short-Term Trials (ALO-KNT-202 and ALO-KNT-301) in Safety Population (From the Applicant's Table 14 in ISS)

System Organ Class/ Preferred Term	n (%)					
	Double-Blind ^a				Open-label	
	ALO-KNT-202		ALO-KNT-301		ALO-KNT-301	ALO-KNT-202
	ALO - 01 N = 71	KADIAN N = 71	ALO - 01 N = 171	Placebo N = 173	ALO - 01 N = 547	KADIAN N = 111
Any Adverse Event	25 (35.2)	20 (28.2)	56 (32.7)	45 (26.0)	313 (57.2)	56 (50.5)
Gastrointestinal disorders	19 (26.8)	18 (25.4)	41 (24.0)	28 (16.2)	260 (47.5)	75 (67.6)
Constipation	11 (15.5)	9 (12.7)	12 (7.0)	7 (4.0)	165 (30.2)	52 (46.8)
Diarrhoea	1 (1.4)	0	12 (7.0)	12 (6.9)	6 (1.1)	9 (8.1)
Dry mouth	0	0	3 (1.8)	2 (1.2)	31 (5.7)	17 (15.3)
Nausea	7 (9.9)	5 (7.0)	19 (11.1)	11 (6.4)	106 (19.4)	42 (37.8)
Vomiting	6 (8.5)	3 (4.2)	7 (4.1)	2 (1.2)	46 (8.4)	26 (23.4)
General disorders and administration site conditions	2 (2.8)	2 (2.8)	9 (5.3)	10 (5.8)	39 (7.1)	17 (15.3)
Fatigue	2 (2.8)	0	1 (0.6)	2 (1.2)	16 (2.9)	10 (9.0)
Nervous system disorders	10 (14.1)	10 (14.1)	12 (7.0)	11 (6.4)	135 (24.7)	46 (41.4)
Dizziness	1 (1.4)	4 (5.6)	2 (1.2)	2 (1.2)	42 (7.7)	22 (19.8)
Headache	3 (4.2)	3 (4.2)	4 (2.3)	2 (1.2)	22 (4.0)	14 (12.6)
Somnolence	7 (9.9)	6 (8.5)	2 (1.2)	5 (2.9)	76 (13.9)	32 (28.8)
Skin and subcutaneous tissue disorders	3 (4.2)	3 (4.2)	7 (4.1)	7 (4.0)	46 (8.4)	25 (22.5)
Pruritus	1 (1.4)	1 (1.4)	0	1 (0.6)	34 (6.2)	15 (13.5)
Pruritus generalised	0	2 (2.8)	0	1 (0.6)	0	7 (6.3)

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

Reference: Module 5.3.5.1.1, Section 14.3.1 Table 23; Module 5.3.5.1.2, Section 14.3.1 Table 12.2.3.3 and Table 12.2.3.6

Phase 3 long-term trial (in chronic pain patients)

In the 2-month open-label trial (ALO-KNT-302), about 81% patients experienced at least one TEAE. The most common TEAEs (reported by $\geq 5.0\%$ of subjects) were the typical opioid-related events: constipation, nausea, headache, vomiting, somnolence, diarrhoea, fatigue, pruritus, and insomnia (Table 7.4.1d).

Table 7.4.1d: TEAEs Reported by $\geq 5\%$ of Patients during 12-month open-label trial (Study ALO-KNT-302) in Safety Population (From the Applicant's Table 16 in ISS)

System Organ Class Preferred Term	Overall N = 465 n (%)
Any Adverse Event	378 (81.3)
Gastrointestinal disorders	252 (54.2)
Constipation	148 (31.8)
Nausea	117 (25.2)
Vomiting	55 (11.8)
Diarrhoea	35 (7.5)
General disorders and administration site conditions	99 (21.3)
Fatigue	29 (6.2)
Nervous system disorders	133 (28.6)
Headache	56 (12.0)
Somnolence	36 (7.7)
Psychiatric disorders	74 (15.9)
Insomnia	27 (5.8)
Skin and subcutaneous tissue disorders	74 (15.9)
Pruritus	29 (6.2)

Reference: Module 5.3.5.2.1, Section 14.3.1 Table 18.2

The treatment-related AEs (Adverse Reactions) were typical of opioids (Table 7.4.1e), including constipation (31.2%), nausea (22.2%), vomiting (8.0%), somnolence (7.3%), headache (6.9%), and pruritus (5.6%).

The adverse reactions were more common in the <80 mg dose group and 80-120 mg dose group than in the >120 mg dose group. The Applicant interpreted that flexible dosing regimen (up-/down titration) during the study was based on analgesia and the occurrence of TEAEs and **patients** who had TEAEs were less likely to be up-titrated, and more likely to remain at dose levels <120 mg. This might be true because the dosing level was post-hoc categorized but pre-specified.

Table 7.4.1e: Treatment-related AEs (Adverse Reactions) Reported by $\geq 5\%$ of Patients during 12-month open-label trial (Study ALO-KNT-302) in Safety Population (From the Applicant's Table 17 in ISS)

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	203 (67.9)	48 (60.8)	36 (46.2)	288 (61.9)
Constipation	108 (36.1)	23 (29.1)	14 (17.9)	145 (31.2)
Nausea	73 (24.4)	21 (26.6)	9 (11.5)	103 (22.2)
Vomiting	30 (10.0)	5 (6.3)	2 (2.6)	37 (8.0)
Headache	22 (7.4)	7 (8.9)	3 (3.8)	32 (6.9)
Somnolence	26 (8.7)	4 (5.1)	4 (5.1)	34 (7.3)
Pruritus	20 (6.7)	4 (5.1)	1 (1.3)	26 (5.6)

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

Note: Related = sum of all possibly, probably, and definitely related TEAEs

Reference: Module 5.3.5.2.1, Section 14.3.1 Table 18.5

Approximately 17% of patients experienced severe TEAEs during the 12-month treatment, including constipation, nausea and headache (Table 7.4.1f).

Table 7.4.1f: Severe TEAEs Reported by $\geq 1\%$ of Patients during long-term Trial (ALO-KNT-302 in Safety Population (From the Applicant's Table 18 in ISS)

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

Reference: Module 5.3.5.2.1, Section 14.3.1 Table 18.4

7.4.2 Less Common Adverse Events

The Applicant did not analyze the less common AEs reported by <1% of subjects in the integrated summary of safety, nor in the individual study reports (ALO-KNT-202, ALO-KNT-301 and ALO-KNT-302). Those AEs were listed in tables of appendices of ISS and individual study reports by System Organ Class (SOC) and Preferred Terms (MedDRA).

The less common AEs were sporadic across all SOCs and there were no clinically meaningful clusters.

7.4.3 Laboratory Findings

Trials in healthy subjects: There were no clinically significant laboratory abnormalities associated with Kadian NT treatment during PK and PD studies in healthy subjects.

Short-term trials (Study ALO-KNT-301 and Study ALO-KNT-202):

- Hematology: No normal to low or normal to high shift was reported by >5% of subjects in any groups during both studies. Some notable differences between Kadian NT and placebo with shifts from normal to high or normal to low were observed for basophils (normal to high) and neutrophils (normal to low) in study ALO-KNT-301 (Table 7.4.3a).
- Blood chemistry: no abnormalities were reported in Study ALO-KNT-202, except one subject who had low potassium and later back to normal during the study. **The abnormality was likely due to the patient's multiple medications. During Study ALO-KNT-301, the most common shifts in each treatment group were normal to high shifts in total cholesterol and random serum glucose and normal to low shifts in potassium. In addition, shifts from normal to low blood urea nitrogen (BUN) were common in the Kadian NT treatment group. Notable differences between the treatment groups in the percentage of subjects with shifts from normal were observed for total cholesterol (normal to high) (Table 7.4.3b).**
- Urinalysis: a few subjects had abnormal values but there were no clinically notable patterns in the changes of the laboratory values.

Table 7.4.3a: Laboratory abnormality in hematology during maintenance phase of Study ALO-KNT-301 (From the Applicant's Table 30 in ISS)

Hematology Parameter	Shift	n (%)	
		Placebo N = 173	ALO - 01 N = 171
Basophils	Normal to Low	0 (0.0)	0 (0.0)
	Normal to High	5 (2.9)	0 (0.0)
Eosinophils	Normal to Low	0 (0.0)	0 (0.0)
	Normal to High	0 (0.0)	1 (0.6)
Hematocrit	Normal to Low	3 (1.7)	3 (1.8)
	Normal to High	4 (2.3)	2 (1.2)
Hemoglobin	Normal to Low	3 (1.7)	6 (3.5)
	Normal to High	2 (1.2)	3 (1.8)
Lymphocytes	Normal to Low	5 (2.9)	5 (2.9)
	Normal to High	3 (1.7)	3 (1.8)
Monocytes	Normal to Low	6 (3.5)	6 (3.5)
	Normal to High	5 (2.9)	4 (2.3)
Neutrophils	Normal to Low	1 (0.6)	5 (2.9)
	Normal to High	6 (3.5)	8 (4.7)
Platelets	Normal to Low	3 (1.7)	3 (1.8)
	Normal to High	1 (0.6)	3 (1.8)
White Blood Cell Count	Normal to Low	1 (0.6)	1 (0.6)
	Normal to High	5 (2.9)	3 (1.8)

Reference: Module 5.3.5.1.2, Section 14.3.4 Table 12.4.2.1.2

**Table 7.4.3b: Laboratory abnormality in blood chemistry during maintenance phase of Study ALO-KNT-301
(From the Applicant's Table 32 in ISS)**

Chemistry Parameter	Shift	n (%)	
		Placebo N = 173	ALO-01 N = 171
Albumin	Normal to Low	2 (1.2)	3 (1.8)
	Normal to High	0 (0.0)	1 (0.6)
Alkaline Phosphatase	Normal to Low	0 (0.0)	2 (1.2)
	Normal to High	1 (0.6)	1 (0.6)
ALT	Normal to High	3 (1.7)	0 (0.0)
AST	Normal to High	4 (2.3)	2 (1.2)
Bicarbonate	Normal to Low	2 (1.2)	1 (0.6)
Calcium	Normal to High	5 (2.9)	3 (1.8)
Total Cholesterol	Normal to High	6 (3.5)	12 (7.0)
Creatinine	Normal to High	3 (1.7)	4 (2.3)
Serum Glucose, Random	Normal to Low	1 (0.6)	4 (2.3)
	Normal to High	7 (4.0)	9 (5.3)
LDH	Normal to High	2 (1.2)	0 (0.0)
Potassium	Normal to Low	7 (4.0)	8 (4.7)
	Normal to High	0 (0.0)	1 (0.6)
Sodium	Normal to Low	0 (0.0)	1 (0.6)
	Normal to High	0 (0.0)	1 (0.6)
Total Bilirubin	Normal to High	2 (1.2)	1 (0.6)
Total Protein	Normal to Low	1 (0.6)	1 (0.6)
	Normal to High	3 (1.7)	3 (1.8)
BUN	Normal to Low	5 (2.9)	8 (4.7)
	Normal to High	4 (2.3)	2 (1.2)

Reference: Module 5.3.5.1.2, Section 14.3.4 Table 12.4.2.1.5

Long-term trial (Study ALO-KNT-302):

- Hematology: The most common changes from Baseline were normal to high shifts for neutrophils (8.4%), and normal to low shifts in lymphocytes (11.2%), RBC count (8.8%), hemoglobin (8.2%), and hematocrit (7.1%).
- Blood chemistry: The most common shifts were normal to high shifts in ALT and AST. Based on the highest value reported in the study, there were 37 subjects (8.0%) with normal to high shifts for ALT and 41 subjects (8.8%) with normal to high shifts in AST. At the end of the study, there were 21 (4.5%) subjects with normal to high shifts in ALT and 21 subjects (4.5%) with normal to high shifts in AST (Table 7.4.3c). **None of subjects met Hy's Law criteria.**
- Urinalysis: There were no clinically notable patterns in the number of subjects with normal to abnormal shifts in urinalysis values.

Table 7.4.3c: Laboratory abnormality in blood chemistry during long-term safety study ALO-KNT-301 (From the Applicant's Tables 35 and 36 in ISS)

Chemistry Parameter	Criterion	n (%)	
		Titration ^a	Maintenance ^b
		ALO - 01 N = 465	ALO - 01 N = 322
ALT	≥ 165 U/L - High	1 (0.2)	0 (0.0)
AST	≥ 165 U/L - High	1 (0.2)	1 (0.3)
BUN	≥ 30 mg/dL - High	1 (0.2)	4 (1.2)
Chloride	≤ 90 mEq/L - Low	0 (0.0)	4 (1.2)
Creatinine	≥ 2 mg/dL - High	0 (0.0)	1 (0.3)
Glucose, Random Serum	≥ 175 mg/dL - High	6 (1.3)	15 (4.7)
Potassium	≤ 3 mEq/L - Low	0 (0.0)	2 (0.6)
	≥ 6 mEq/L - High	0 (0.0)	3 (0.9)
Sodium	≤ 126 mEq/L - Low	0 (0.0)	1 (0.3)

a. Includes only the data from the first 4 weeks of ALO - 01 treatment.

b. Includes only the data from the Weeks 5 through 16 of ALO - 01 treatment.

Reference: Appendix B.2, Table 11.1 and Table 11.2

Chemistry Parameter	Shift	Minimum N = 465 n (%)	Maximum N = 465 n (%)	End of Study N = 465 n (%)
ALT (U/L)	Normal to High	0 (0.0)	37 (8.0)	21 (4.5)
Alkaline Phosphatase (U/L)	Normal to High	0 (0.0)	15 (3.2)	8 (1.7)
AST (U/L)	Normal to High	0 (0.0)	41 (8.8)	21 (4.5)
BUN (mmol/L)	Normal to High	0 (0.0)	13 (2.8)	5 (1.1)
Creatinine (µmol/L)	Normal to High	0 (0.0)	16 (3.4)	6 (1.3)
Total Protein (g/L)	Normal to Low	12 (2.6)	0 (0.0)	7 (1.5)
	Normal to High	0 (0.0)	8 (1.7)	5 (1.1)

Reference: Module 5.3.5.2.1, Section 14.3.5 Table 23.3

7.4.4 Vital Signs

Vital signs (including heart rate, respiratory rate, blood pressure (after sitting for three minutes) and oral temperature) were measured at all visits (screening, baseline, in-treatment), discharge or early termination and post-treatment follow-up (where applied) across the clinical program. Abnormal vital signs were recorded as adverse events using MedDRA 9.0 or 9.1 coding system.

Overall, there were no clinically significant changes in vital signs associated with the Kadian NT treatment during trials in either healthy adult subjects or chronic pain patients.

7.4.5 Electrocardiograms (ECGs)

A thorough QT (ECG) study was not conducted, nor required, because of the well-known safety profile of both active ingredients in Kadian NT. Routine ECG recording was performed at screening visit for patient selection in the clinical development program and it was also performed at months 6 and 12 or early termination of Study ALO-KNT-302.

The Applicant briefly summarized the ECG data only from Study ALO-KNT-302 in their ISS. The following ECG data were summarized from both the Applicant's ISS and the study report of Study ALO-KNT-302.

- ECG abnormalities experienced by seven subjects during the 12-month open-label treatment were reported as TEAE and considered not related to study drug by the Applicant (Table 7.4.5).
- At Month 6 (visit 8), about 31% (n=62) patients had ECG changes from baseline; no changes were reported as clinically significant abnormalities.
- At Month 12 (visit 15, the final treatment visit), about 21% (n=79) patients had ECG changes from Baseline. One of the subjects (Subject 224-2003) was reported as clinically significant abnormality; was diagnosed with an incomplete right bundle branch.

Table 7.4.5: ECG abnormalities reported as TEAE during the 12-month open-label trial (From the Applicant's Table 30 in the Study ALO-KNT-302 report)

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 (%)	
Acute myocardial infarction	1 (0.3)	0	0	1 (0.2)
Angina pectoris	1 (0.3)	0	0	1 (0.2)
Bradycardia	2 (0.7)	0	1 (1.3)	3 (0.6)
Bundle branch block right	0	1 (1.3)	0	1 (0.2)
Cardiac failure congestive	0	1 (1.3)	0	1 (0.2)

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

Reference: Section 14.3.1, Table 18.2

7.4.6 Special Safety Studies

There were no special safety studies other than abuse liability studies to establish and confirm the ratio of morphine and naltrexone in the Kadian NT formulation (see summary in PD Section of this review for detail).

7.4.7 Immunogenicity

No particular immunotoxicity concerns associated with the proposed formulation were raised during the clinical development.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Findings

No dose-response analysis was designed in all clinical trials. The dosing regimen was individually titrated in three multiple-dose trials. The Applicant performed dose-response analysis of AE data in the 12-month open-label trial (Study ALO-KNT-302) by stratifying the AEs to three dosing levels of Kadian NT: <80 mg, 80-120 mg and >120 mg. As shown in Table 7.5.1, patients in the dose groups <80 mg and 80-120 mg reported more AEs than those in the >120 mg dose group. Since the dose groups were *post hoc* categorized but not pre-specified, the higher incidence of AEs in the lower doses (<120 mg) was likely due to dose up-titration, which based on both pain response and the occurrence of AEs. Therefore, subjects who had AEs were less likely to be up-titrated, and more likely to remain at dose levels <120 mg.

Table 7.5.1: The Common AEs (reported by ≥5% patients) categorized by dose group in the 12-month open-label trial (Study ALO-KNT-302) (From Applicant's Table 37 in the ISS)

System Organ Class 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 TEAE	246 (82.3)	72 (91.1)	59 (75.6)	378 (81.3)
Gastrointestinal disorders	173 (57.9)	44 (55.7)	35 (44.9)	252 (54.2)
Constipation	109 (36.5)	24 (30.4)	15 (19.2)	148 (31.8)
Nausea	82 (27.4)	23 (29.1)	12 (15.4)	117 (25.2)
Vomiting	42 (14.0)	10 (12.7)	3 (3.8)	55 (11.8)
Diarrhoea	21 (7.0)	9 (11.4)	5 (6.4)	35 (7.5)
General disorders and administration site conditions	61 (20.4)	21 (26.6)	17 (21.8)	99 (21.3)
Fatigue	19 (6.4)	7 (8.9)	3 (3.8)	29 (6.2)
Nervous system disorders	85 (28.4)	31 (39.2)	17 (21.8)	133 (28.6)
Headache	34 (11.4)	16 (20.3)	6 (7.7)	56 (12.0)
Somnolence	27 (9.0)	5 (6.3)	4 (5.1)	36 (7.7)
Psychiatric disorders	47 (15.7)	16 (20.3)	11 (14.1)	74 (15.9)
Insomnia	17 (5.7)	4 (5.1)	6 (7.7)	27 (5.8)
Skin and subcutaneous tissue disorders	50 (16.7)	17 (21.5)	6 (7.7)	74 (15.9)
Pruritus	22 (7.4)	5 (6.3)	1 (1.3)	29 (6.2)

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

Reference: Module 5.3.5.2.1, Section 14.3.1 Table 18.2

7.5.2 Time Dependency for Adverse Findings

The overall incidence and prevalence of AEs stratified by a 30-day interval in the 12-month open-label trial (Study ALO-KNT-302) appeared constant from days 31-390, with the incidence of 17-26% and prevalence of 46-65% (Table 7.5.2). The incidence at the first 30 days was 66%, higher than at any other time intervals. The decrease in incidence after 30 days was mostly due to AE-related dropouts because approximately 30% of subjects dropped out from the study at the first 30 day and the most common reason for dropout was AEs. Patients remained in the study would be more tolerable to the treatment (less AEs).

Table 7.5.2: overall incidence and prevalence of AEs by a 30-day interval in the 12-month open-label trial (Study ALO-KNT-302) (From the Applicant's Table 61 in the ISS)

Interval	Subjects at Risk	Incidence (%) ^a	Prevalence (%) ^b
0-30	465	66.2	66.2
31-60	454	22.5	46.0
61-90	328	25.6	53.4
91-120	284	23.6	54.9
121-150	257	26.1	59.5
151-180	241	21.2	56.8
181-210	217	24.0	61.3
211-240	208	21.6	58.7
241-270	192	19.8	62.0
271-300	184	17.4	63.0
301-330	180	20.0	62.8
331-360	172	19.8	64.5
361-390	164	17.1	50.6

Note: As AEs were counted up to 30 days after last dose, subjects were at risk through that period.

- a. Incidence rate for interval = (number of subjects with an adverse event beginning in that interval)/(number of subjects receiving ALO-01 in that interval).
- b. Prevalence rate for interval = (number of subjects with an adverse event beginning in that interval or continuing from previous interval)/(number of subjects receiving study drug in that interval)

Reference: Module 5.3.5.2.1, Section 14.3.1 Table 21.1

7.5.3 Drug-Demographic Interactions (gender, race)

The Applicant stratified AEs, clinical laboratory values and Clinical Opiate Withdrawal Scale (COWS) score by gender, age (<65 years and ≥65 years), race, alcohol use, opioid status (naïve or experienced) and food effect. Apparently, there were no clinically important effects with the subgroup analyses.

7.5.4 Drug Disease Interactions

The Applicant did not perform analysis of drug-disease interaction in their ISS.

7.5.5 Drug-Drug Interactions

No drug-drug interactions (DDI), including any potential interactions between morphine sulfate and naltrexone HCl, were studied during the clinical development program of Kadian NT capsules. The overall safety profile of Kadian NT was similar to Kadian in both short-term and long-term trials, suggesting that the DDIs between them may be less likely.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No data and analysis on human carcinogenicity were provided in the submission. Sporadic tumors were reported during the clinical development, primary from the 12-month open-label trial (ALO-KNT-32), which is insufficient for systemic assessment.

7.6.2 Human Reproduction and Pregnancy Data

No data were submitted. The pregnancy information in the proposed labeling was cross-referenced to previously approved drugs containing morphine sulfate and naltrexone through 505(b)(2) regulation.

In the 120-day safety update, the Applicant reported one subject who became pregnant during the 12-month open-label treatment (study ALO-KNT-302). This was a 27-year-old white female (Subject 220-2007) had positive urine pregnancy test about one month after 1-year Kadian NT treatment (from 20 mg qd at initial dose on Jan 30, 2007 to 40 mg qd by the end of study on Jan 30, 2008). The subject delivered a full term healthy male boy on September 21, 2008. The Applicant did not provide further information was provided.

7.6.3 Pediatrics and Assessment and/or Effects on Growth

All subjects enrolled in the entire clinical program of Kadian NT were adults aged 18 years and above (b) (4)

[REDACTED]
[REDACTED]
[REDACTED]
A brief plan, including two PK studies (single-dose and multiple-dose) and timeline, was submitted in the NDA.

A revised pediatric plan was requested by the Division following a meeting with the Pediatric Review Committee (PeRC) in CDER: pediatric studies are required for age 2-17. The studies should include assessments of efficacy, safety and single-/multiple-dose PK. An age-appropriate formulation for children aged 2-5 years may need to be developed.

7.6.4 Overdose, Drug Abuse Potential/ Withdrawal and Rebound

One of the major safety concerns with Kadian NT capsules that was raised by the Division during the clinical development was that naltrexone released from the sequestered formulation may precipitate opiate withdrawal symptoms, particularly in

opiate-dependent patients. To address this concern, the Applicant incorporated monitoring of opiate withdrawal symptoms in the two Phase 3 trials: ALO-KNT-301 (placebo-controlled, short-term trial) and ALO-KNT-302 (12-month open-label trial). Sparse blood samples (at trough) in a subset of patients were also collected in the 12-month study to detect plasma level of morphine, naltrexone and 6- β -naltrexol.

Opiate withdrawal assessment:

Method: The opiate withdrawal symptoms were primarily assessed with the Clinical Opiate Withdrawal Scale (COWS). COWS includes 11 common opiate withdrawal signs and symptoms; each item is scored from 0-4 or 0-5 (various among different items) and **total COWS score (sum of all item) is used to assess a patient's level of opiate withdrawal; and to make inferences about the patient's level of physical dependence on opioids.** The severity of opiate withdrawal based on the total COWS score is categorized to: mild (COWS=5-12), moderate (COWS=13-24), moderately severe (COWS=25-36) and severe withdrawal (COWS >36).

The COWS was administered to patients at weeks 1 and 2, and monthly up to 12 months or early termination in the 12-month open-label trial (ALO-KNT-302), and at weeks 0 (baseline, at randomization), 1, 2, and 12, or early termination of the Maintenance Phase in the 3-month placebo-controlled trial (ALO-KNT-301).

The Applicant presented the mean changes in total COWS score from baseline to the end of the treatment for both study reports and ISS. The data was stratified by dosing levels, opiate status (naïve vs. experienced), age (<65 years vs. \geq 65 years), gender and race. The mean changes in COWS score from baseline to each visit (up to 12 months) were presented by three different daily dosing levels in the individual study report of ALO-KNT-302. Based on the datasets submitted with NDA, this reviewer performed additional analyses to explore potential correlation of plasma naltrexone and 6- β -naltrexol with COWS scores (See below "Correlation of COWS with Naltrexone PK" for details).

COWS Results: Overall, the mean COWS score tended to decrease after baseline. The mean changes in total COWS scores from baseline at each visit up to 12 months in Study ALO-KNT-302 showed negative values (decreased from baseline) at all three daily dosing levels, as summarized in Table 7.6.4a. The subgroup analyses of the mean COWS changes from baseline to the end of treatment did not reveal clinically important opiate withdrawal symptoms associated with Kadian NT treatment by age, gender, race or opioid status in both short-term and long-term studies (Tables 7.6.4b-e).

In Study ALO-KNT-302, five subjects experienced moderate opiate withdrawal symptoms (total COWS score \geq 13) during the 12-month study. The withdrawal symptoms appeared due to non-compliance to the study medication (under-dosing of morphine). However, it may also be synergized by naltrexone release.

Subject 302-206-2001: A 50-years-old Caucasian male, opiate-experienced, chronic lower back pain had COWS score of 23 at early termination (5.5 months), 19 at visit 7

(month 5), 10 at visit 4 (month 2, 6 at visit 3 (month 1), 7 at visit 5 (month 3) and 5 at visit 2 (week 1). The patient was non-compliant, adjusted own dosage, and lost 2 bottles of study drug and was positive for hydrocodone in urine drug screen (UDS). The Applicant suspected that the patient had not taken study medication as indicated.

Subject 206-2005: A 50-years-old Caucasian male, chronic lower back pain, opiate-experienced had COWS of 17 (week 1) and 13 at the early termination. The subject was non-compliant and only took study drug for 7 days with positive UDS for oxycodone.

Subject 228-2002: A 56-years-old Caucasian female, chronic lower back pain, opiate-naïve had COWS of 14 at the early termination visit (due to discrepancies with study medication -- site was using improper dosing). **The patient's UDS were positive for study medication.**

Subject 248-2007: 38-years-old Caucasian female, chronic lower back pain, opiate-naïve had COWS of 18 at the early termination. This subject informed the site that she lost one bottle of study medication and ran out of study medication prior to her next visit. This subject was positive for prohibited medication, did not take study medication as prescribed.

Subject 256-2008: A 54-years-old Caucasian male, chronic lower back pain, opiate-naïve had a COWS of 13 at the early termination visit (due to an AE of lethargy). The subject returned 30 capsules in 1 bottle and 1 bottle was never returned. It was suspected that the subject was not taking study medication as prescribed due to the AE.

In Study ALO-KNT-301, there was one subject in the Kadian NT group reported moderate opiate withdrawal symptoms with total COWS scores increasing from 1 at the Baseline, 0 at weeks 1 and 2, to 28 at day 52. The patient, Subject 126-0026, was a 51-years-old Caucasian opiate-naïve female with osteoarthritis of the knee. She stopped taking the study drug on Maintenance Day 50 without tapering, experienced opiate withdrawal symptoms and discontinued from the study on Day 52. Apparently, the opiate withdrawal symptoms were precipitated by suddenly stopping morphine administration.

**Table 7.6.4a. Clinical Opioid Withdrawal Scale (COWS) changes from baseline to each visit up to 12 month in Study ALO-KNT-302
(From the Applicant's Table 13 in the Study ALO-KNT-302 report)**

Visit	Mean Daily Dose of Kadian NT			Overall N=465
	<80 mg N=299	80-120 mg N=79	>120 mg N=78	
Baseline COWS Mean (SD)	n=237	n=72	n=74	n=383
	1.2 (2.06)	1.0 (1.70)	1.5 (2.26)	1.2 (2.04)
Change from Baseline: n, mean (SD)				
Visit 3/Week 4	n=43	n=13	n=29	n=85
	-0.9 (2.52)	-0.1 (1.19)	-0.9 (1.73)	-0.7 (2.11)
Visit 4/Month 2	n=165	n=66	n=59	n=290
	-0.2 (1.61)	-0.1 (1.64)	-0.6 (1.94)	-0.3 (1.69)
Visit 5/Month 3	n=142	n=62	n=58	n=262
	-0.3 (1.76)	-0.2 (1.78)	-0.3 (1.75)	-0.3 (1.75)
Visit 6/Month 4	n=129	n=61	n=51	n=241
	-0.3 (1.79)	-0.0 (2.01)	-0.5 (1.71)	-0.3 (1.83)
Visit 7/Month 5	n=118	n=56	n=50	n=224
	-0.4 (1.66)	0.0 (2.32)	-0.5 (1.96)	-0.3 (1.91)
Visit 8/Month 6	n=113	n=53	n=44	n=210
	-0.4 (1.42)	0.1 (1.48)	-0.4 (1.48)	-0.3 (1.45)
Visit 9/Month 7	n=104	n=51	n=42	n=197
	-0.4 (1.76)	-0.2 (1.71)	-0.3 (1.96)	-0.3 (1.79)
Visit 10/Month 8	n=100	n=49	n=38	n=187
	-0.3 (1.83)	-0.3 (1.09)	-0.2 (2.00)	-0.3 (1.70)
Visit 11/Month 9	n=95	n=46	n=38	n=179
	-0.4 (1.91)	-0.3 (1.20)	-0.2 (2.26)	-0.3 (1.83)
Visit 12/Month 10	n=94	n=45	n=38	n=177
	-0.1 (2.34)	-0.2 (1.08)	-0.6 (1.70)	-0.2 (1.96)
Visit 13/Month 11	n=93	n=42	n=36	n=171
	-0.6 (1.72)	-0.3 (1.32)	-0.5 (1.76)	-0.5 (1.63)

**Table 7.6.4b: Age comparisons of opiate withdrawal symptoms
(From the Applicant's Tables 43 and 44 in ISS)**

Study ALO-KNT-301

		ALO - 01 Dose at Randomization ≤80 mg											
		Placebo					ALO - 01						
Clinical Opioid	Withdrawal Scale	<65 years N = 95			≥65 years N = 24			<65 years N = 99			≥65 years N = 24		
		N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)
	Visit Y	95	0.8	(1.4)	24	0.4	(0.8)	99	0.6	(1.3)	24	0.2	(0.4)
	Δ from Visit Y to Visit Y + 12 Weeks	57	-0.2	(1.2)	10	-0.5	(0.7)	61	-0.1	(0.9)	12	-0.2	(0.6)
		ALO - 01 Dose at Randomization >80 mg											
		Placebo					ALO - 01						
Clinical Opioid	Withdrawal Scale	<65 years N = 35			≥65 years N = 11			<65 years N = 41			≥65 years N = 5		
		N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)
	Visit Y	35	0.6	(1.2)	11	0.6	(1.1)	41	0.4	(0.8)	5	0.4	(0.5)
	Δ from Visit Y to Visit Y + 12 Weeks	18	-0.1	(1.0)	5	-0.2	(1.1)	22	0.1	(0.6)	3	0.3	(0.6)

Reference: Appendix C.1, Table 3.1

Study ALO-KNT-302

Clinical Opioid	<65 years N = 417			≥65 years N = 48		
	N	Mean	(SD)	N	Mean	(SD)
Baseline	343	1.2	(2.1)	40	0.8	(1.3)
Mean Δ at Last Assessment During Treatment	326	-0.1	(2.6)	39	0.3	(1.5)

Reference: Appendix C.2, Table 2.1

ALO-01: Kadian NT; Visit Y: baseline visit (at randomization);
Visit Y+12: the end of 12-week treatment

**Table 7.6.4c: Gender comparisons of opiate withdrawal symptoms
(From the Applicant's Tables 48 and 49 in ISS)**

Study ALO-KNT-301

		ALO - 01 Dose at Randomization ≤80 mg											
		Placebo						ALO - 01					
Clinical Opioid	Withdrawal Scale	Females N = 72			Males N = 47			Females N = 80			Males N = 43		
		N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)
	Visit Y	72	0.8	(1.4)	47	0.6	(1.2)	80	0.6	(1.3)	43	0.3	(0.8)
	Δ from Visit Y to Visit Y + 12 Weeks	45	-0.2	(1.2)	22	-0.3	(1.1)	45	-0.2	(0.8)	28	0.2	(0.9)
		ALO - 01 Dose at Randomization >80 mg											
		Placebo						ALO - 01					
Clinical Opioid	Withdrawal Scale	Females N = 22			Males N = 24			Females N = 24			Males N = 22		
		N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)
	Visit Y	22	0.5	(1.1)	24	0.8	(1.2)	24	0.6	(1.0)	22	0.2	(0.4)
	Δ from Visit Y to Visit Y + 12 Weeks	14	0.2	(0.8)	9	-0.6	(1.1)	12	0.3	(0.8)	13	0.1	(0.5)

Reference: Appendix C.1, Table 3.2

Study ALO-KNT-302

Clinical Opioid	Withdrawal Scale	Females N = 245			Males N = 220		
		N	Mean	(SD)	N	Mean	(SD)
	Baseline	206	1.2	(1.8)	177	1.2	(2.3)
	Mean Δ at Last Assessment During Treatment	200	-0.1	(2.5)	165	0.1	(2.6)

Reference: Appendix C.2, Table 2.2

**Table 7.6.4d: Race comparisons of opiate withdrawal symptoms
(From the Applicant's Tables 48 and 49 in ISS)**

Study ALO-KNT-301

		ALO - 01 Dose at Randomization ≤80 mg																	
		Placebo									ALO - 01								
Clinical Opioid	Withdrawal Scale	White N = 85			Black N = 15			Other N = 19			White N = 92			Black N = 17			Other N = 14		
		N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)
Visit Y		85	0.7	(1.4)	15	0.8	(1.3)	19	0.7	(1.1)	92	0.5	(1.2)	17	0.5	(1.3)	14	0.4	(1.1)
Δ from Visit Y to Visit Y + 12 Weeks		46	-0.1	(0.9)	8	-1.0	(1.8)	13	-0.3	(1.5)	53	-0.2	(0.7)	8	0.4	(1.1)	12	0.1	(1.4)

		ALO - 01 Dose at Randomization >80 mg																	
		Placebo									ALO - 01								
Clinical Opioid	Withdrawal Scale	White N = 31			Black N = 13			Other N = 2			White N = 34			Black N = 12			Other N = 0		
		N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)
Visit Y		31	0.4	(0.8)	13	1.2	(1.7)	2	0.0	(0.0)	34	0.4	(0.9)	12	0.4	(0.5)	n/a	n/a	n/a
Δ from Visit Y to Visit Y + 12 Weeks		16	0.1	(1.1)	5	-0.6	(0.9)	2	0.0	(0.0)	18	0.2	(0.6)	7	0.0	(0.6)	n/a	n/a	n/a

n/a = not applicable

Reference: Appendix C.1, Table 3.3

Study ALO-KNT-302

Clinical Opioid	Withdrawal Scale	White N = 410			Black N = 31			Other N = 10		
		N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)
Baseline		342	1.1	(2.0)	31	1.7	(2.4)	10	1.7	(2.2)
Mean Δ at Last Assessment During Treatment		327	0.0	(2.5)	28	-0.2	(2.4)	10	-0.9	(2.1)

Reference: Appendix C.2, Table 2.3

**Table 7.6.4e: Opiate status comparisons of opiate withdrawal symptoms
(From the Applicant's Tables 59 in ISS)**

Study ALO-KNT-301 (Extracted from Applicant's Table 3.4 in Appendix)

Opiate Status	Kadian NT >80 mg/day		Kadian NT ≤80 mg/day	
	Placebo	Kadian NT	Placebo	Kadian NT
Experienced	N=9	N=10	N=12	N=13
	-0.1±0.9	0.2±0.6	0.3±1.1	0.2±0.9
Naive	N=14	N=15	N=54	N=58
	-0.1±1.1	0.1±0.6	-0.4±1.2	-0.1±0.7

Study ALO-KNT-301 (From the Applicant's Table 59 in ISS)

Clinical Opioid Withdrawal Scale	Opioid Naïve N = 208			Opioid Experienced N = 257		
	N	Mean	(SD)	N	Mean	(SD)
Baseline	199	1.1	(1.9)	184	1.3	(2.2)
Mean Δ at Last Assessment During Treatment	192	-0.0	(2.4)	173	-0.0	(2.6)

Reference: Appendix C.2, Table 2.4

Correlation of COWS with Naltrexone PK

In Study ALO-KNT-301, 93 patients from 34 study sites participated in the sparse blood sampling at monthly visits (up to 12 months) for plasma naltrexone, 6-β-naltrexol and morphine. Up to 20 patients per group were planned for the PK sub-study from each of the following four groups: 20-60 mg, 80-120 mg >120 mg (based on the initial starting dose) and age ≥65 years (The actual disposition of patients in the four groups was not provided in the study report). The blood samples were taken prior to dosing (trough) at each visit.

Plasma naltrexone: Approximately 23% of subjects (n=21 of 93) had detectable naltrexone levels (>4.0 pg/ml) at some time during the study, ranged from 4.03 to 145 pg/ml. The overall detectable frequency based on the number of evaluable blood samples was 11% (n=44 of 444 evaluable blood samples).

The detectable frequency slightly increased monthly at the first 6 months. The plasma naltrexone concentration did not increase over 12 months but tended to slightly increase with increasing doses of Kadian NT.

The profile of plasma naltrexone was not correlated to age and appeared similar between males and female.

Time-matched correlation analysis showed that the detectable naltrexone levels were not correlated to the total COWS scores of either opiate-naïve or opiate-experienced patients at the same visit time windows (Figure 7.6.4a).

Four subjects (Subjects 222-2002, 212-2005, 234-2005 and 214-2006) had at least one outlying plasma naltrexone concentrations during the study (the outlier was defined as “**outside of one standard deviation of the arithmetic mean, or > 49.4 pg/ml**”). The total COWS scores of these subjects were from 0 to 4, which were not correlated to the levels of plasma naltrexone.

Seven opiate-naïve patients and eight opiate-experienced patients at some visits during the 12-month study (ALO-KNT-302) developed mild opiate withdrawal symptoms (with a total COWS score 5-11. The time-matched plasma levels of naltrexone or 6-β-naltrexol were either undetectable or low and had no trends to be correlated to the COWS scores.

Table 7.6.4e: Frequency of detectable plasma naltrexone and 6-β-naltrexol across 12-month visits (% of evaluable blood samples)
(From the Applicant’s Table 2 in the Appendix of Study ALO-KNT-302)

Study Week	Number of Detectable Naltrexone Concentrations / Total Evaluable Data (%)	Number of Detectable 6-β-Naltrexol Concentrations / Total Evaluable Data (%)
1	4/75 (5.33)	50/73 (68.5)
4	5/48 (10.4)	36/49 (73.5)
8	4/42 (9.52)	33/45 (73.3)
12	3/38 (7.89)	30/39 (76.9)
16	6/29 (20.7)	23/31 (74.2)
20	3/26 (11.5)	25/29 (86.2)
24	5/29 (17.2)	27/29 (93.1)
28	5/24 (20.8)	16/23 (69.6)
32	4/24 (16.7)	17/23 (73.9)
36	6/29 (20.7)	18/31 (58.1)
40	0/21 (0.00)	17/22 (77.3)
44	0/20 (0.00)	15/21 (71.4)
48	2/18 (11.1)	14/20 (70.0)
52	2/21 (9.52)	17/22 (77.3)
All Weeks	49/444 (11.0)	338/457 (74.0)

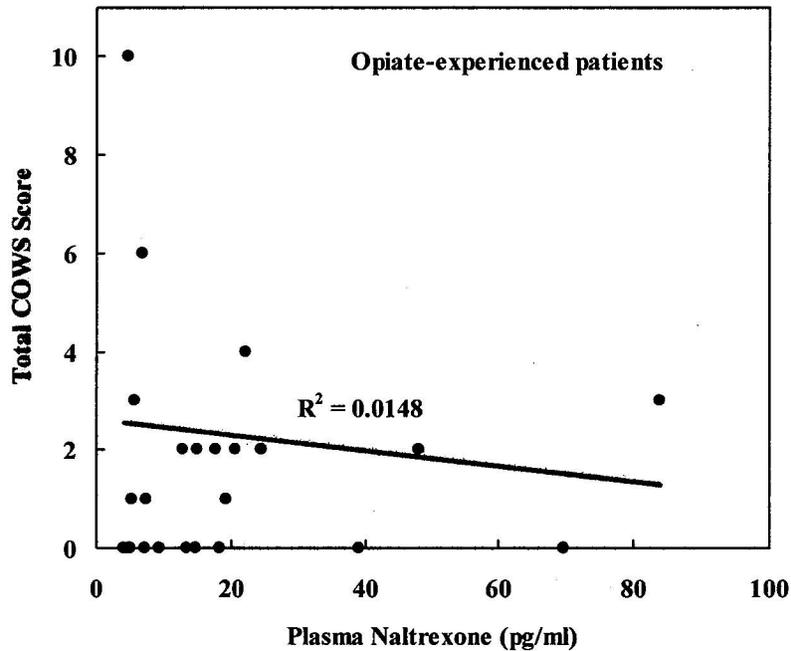
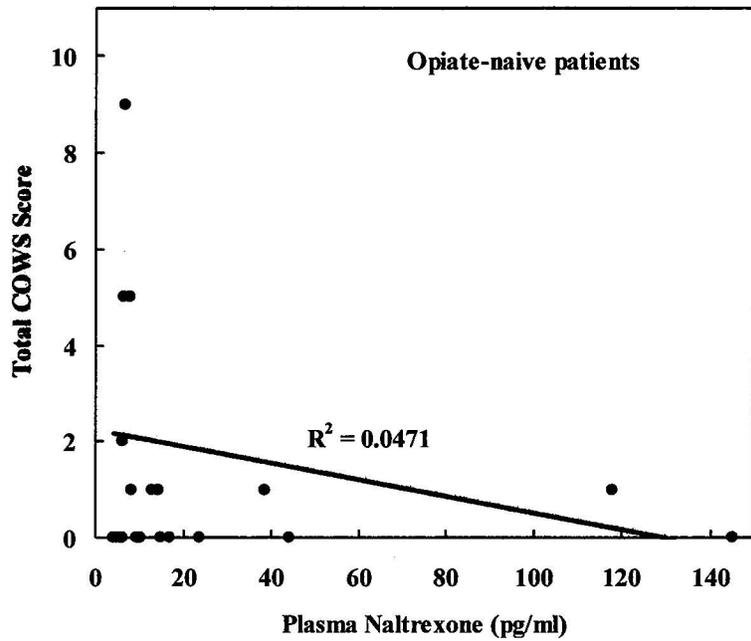


Figure 7.6.4a: Time-matched correlation of plasma naltrexone levels and COWS scores in patients with chronic non-malignant pain treated with flexible dose of Kadian NT for up to 12 months (based on the COWS and PK datasets of Study ALO-KNT-302). PK blood samples were collected prior to dosing (trough time) at each monthly visit. The COWS score recording was time-matched (visit days) to the PK blood sampling; only subjects with detectable plasma naltrexone are presented.

Plasma 6- β -naltrexol: Approximately 80% of subjects (n=74 of 93) had detectable 6- β -naltrexol level throughout the study, ranged from 0.471 to 3720 pg/ml. The overall detectable frequency based on evaluable blood samples was 74% (n=338 of 457 evaluable blood samples).

The plasma 6- β -naltrexol concentration did not increased during the course of the study in either individual subject or group.

There was a small trend that plasma 6- β -naltrexol increased with increasing doses of Kadian NT.

The profile of plasma 6- β -naltrexol was not correlated to age and appeared similar between males and female.

Time-matched correlation analysis showed that the detectable 6- β -naltrexol levels were not correlated to the total COWS scores of either opiate-naïve or opiate-experienced patients at the same visit time windows (Figure 7.6.4b).

Three subjects had 16 outlying plasma 6- β -naltrexol concentrations (the outlier was defined as outside of one standard deviation of the arithmetic mean, or >446 pg/ml). They were the same three subjects identified as “naltrexone outliers” (Subjects 222-2002, 212-2005 and 234-2005); their plasma 6- β -naltrexol levels were not correlated to total COWS scores.

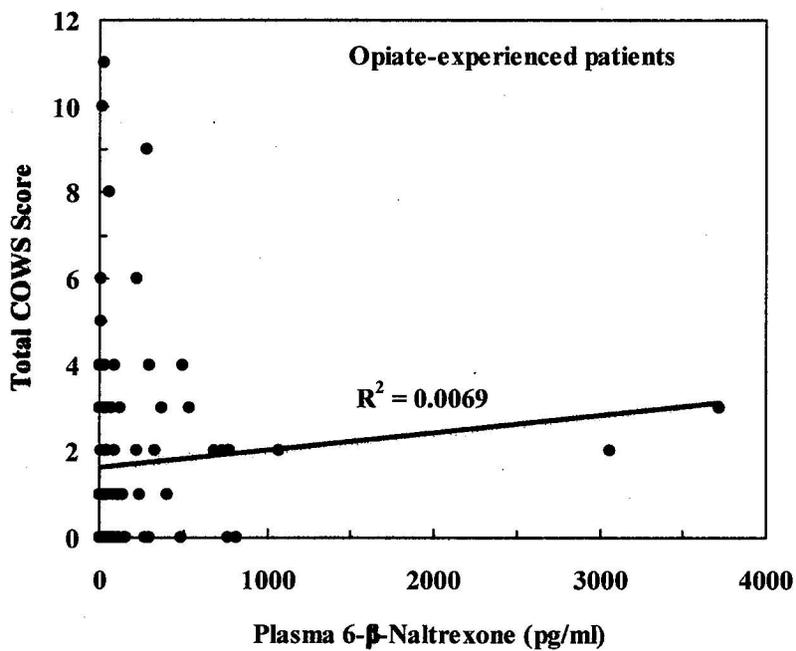
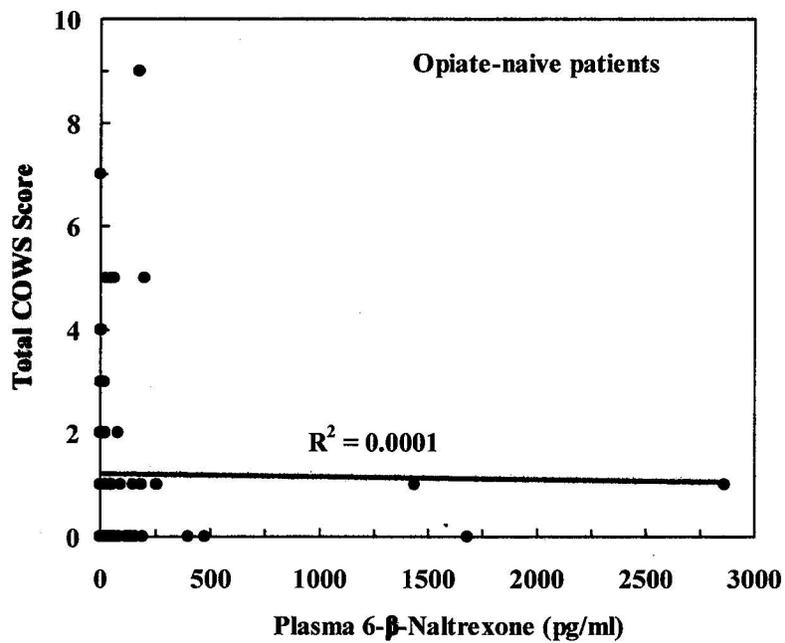


Figure 7.6.4b: Time-matched correlation of plasma 6-β-naltrexol levels and COWS scores in patients with chronic non-malignant pain treated a flexible dose of Kadian NT for up to 12 months (based on COWS and PK datasets of Study ALO-KNT-302). PK blood samples were collected prior to dosing (trough time) at each monthly visit. The COWS score recording was time-matched (visit days) to the PK blood sampling; only subjects with detectable plasma 6-β-naltrexol are presented.

Plasma Morphine: Approximately 84% of subjects (n=84 of 93) had detectable plasma morphine during the study, ranged from 0.214 to 204 ng/ml. Mean plasma morphine concentrations were driven by dose titration and increased in a dose-related manner. The COWS score slightly decreased with increasing plasma concentration of morphine but with high in-subject variations.

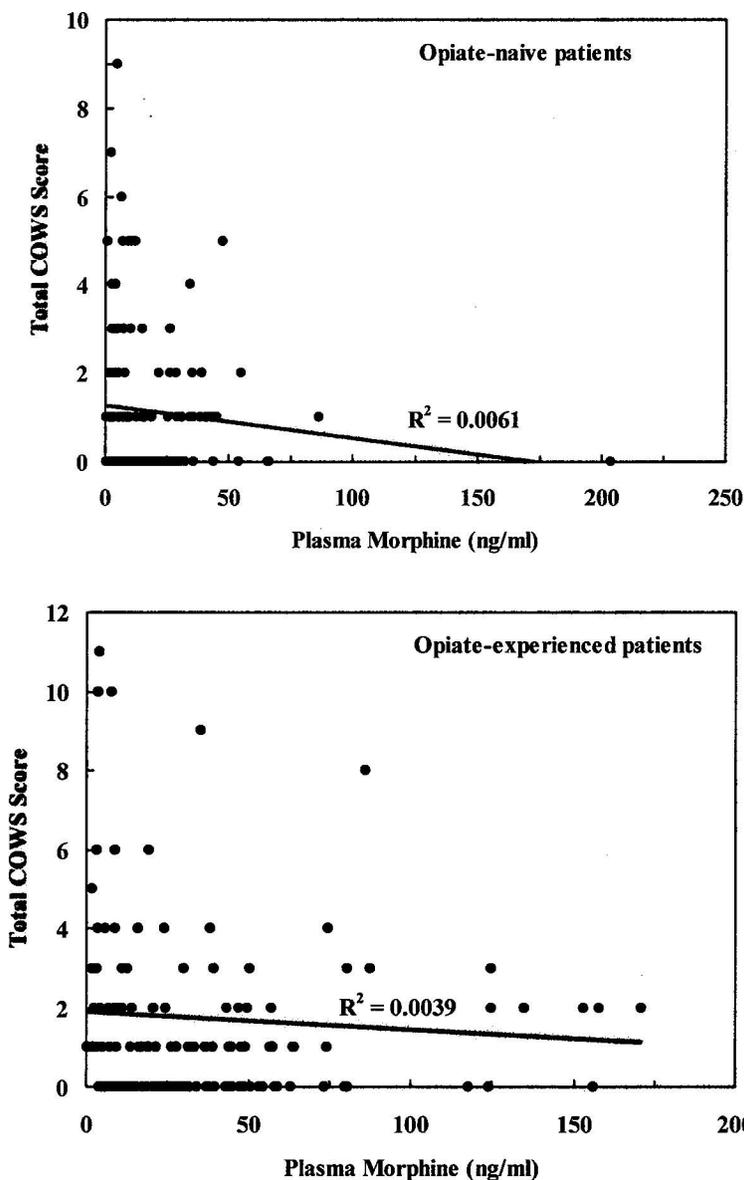


Figure 7.6.4c: Time-matched correlation of plasma morphine levels and COWS scores in patients with chronic non-malignant pain treated a flexible dose of Kadian NT for up to 12 months (based on COWS and PK datasets of Study ALO-KNT-302). PK blood samples were collected prior to dosing (trough time) at each monthly visit. The COWS score recording was time-matched (visit days) to the PK blood sampling; only subjects with detectable plasma morphine are presented.

Naltrexone-related AEs including opioid withdrawal:

In the 120-day safety update, the Applicant compiled all potential naltrexone-related AEs from three Phases 2 & 3 trials in chronic pain patients (ALO-KNT-202, ALO-KNT-301 and ALO-KNT-302). The AE data included opioid withdrawal symptoms and hepatic enzyme elevations.

AE and opiate withdrawal: the data did not reveal a pattern of opioid withdrawal syndrome but rather sporadic withdrawal symptoms which may be associated with naltrexone, such as nausea, vomiting, insomnia, anxiety/irritability, lacrimation increased, abdominal pain, piloerection and rhinorrhea (Table 7.6.4f). Overall, the AE profile was comparable between Kadian NT and Kadian during open-label titration and double-blind maintenance periods.

Table 7.6.4f: all potential naltrexone-associated AEs in chronic pain trials (Phase 2 and 3)
(From the Applicant Table 1 in the 120-day safety update dated on Oct 31, 2008)

AE Term	Maintenance				Titration			
	202 ¹		301 ¹		302 ²	301 ³	302 ⁴	202 ²
	ALO-01 (N=71)	KADIAN (N=71)	ALO-01 (N=171)	Placebo (N=173)	ALO-01 (N=322)	ALO-01 (N=547)	ALO-01 (N=465)	KADIAN (N=111)
ANY SELECT AE	19 (26.8)	21 (29.6)	57 (33.3)	49 (28.3)	77 (23.9)	193 (35.3)	148 (31.8)	63 (56.8)
Abdominal Pain	2 (2.8)	5 (7.0)	9 (5.3)	8 (4.6)	8 (2.5)	11 (2.0)	15 (3.2)	4 (3.6)
Anxiety/Irritability	1 (1.4)	1 (1.4)	7 (4.1)	7 (4.0)	9 (2.8)	21 (3.8)	15 (3.2)	6 (5.4)
Chills		2 (2.8)	4 (2.3)	6 (3.5)	3 (0.9)	4 (0.7)	7 (1.5)	1 (0.9)
Dianthoea	2 (2.8)	2 (2.8)	21 (12.3)	21 (12.1)	14 (4.3)	15 (2.7)	12 (2.6)	5 (4.5)
Headache	3 (4.2)	6 (8.5)	12 (7.0)	6 (3.5)	11 (3.4)	33 (6.0)	37 (8.0)	14 (12.6)
Hypertension			1 (0.6)		4 (1.2)	3 (0.5)	1 (0.2)	
Increased Sweating	1 (1.4)	1 (1.4)	7 (4.1)	6 (3.5)	6 (1.9)	12 (2.2)	11 (2.4)	3 (2.7)
Insomnia		1 (1.4)	6 (3.5)	4 (2.3)	9 (2.8)	7 (1.3)	10 (2.2)	1 (0.9)
Joint Pain/Stiffness	1 (1.4)	3 (4.2)	2 (1.2)	6 (3.5)	4 (1.2)	2 (0.4)	5 (1.1)	3 (2.7)
Lacrimation Increased			1 (0.6)	7 (4.0)	3 (0.9)	2 (0.4)		
Muscle Pain/Stiffness	4 (5.6)	5 (7.0)	8 (4.7)	7 (4.0)	6 (1.9)	12 (2.2)	6 (1.3)	7 (6.3)
Nausea	7 (9.9)	6 (8.5)	20 (11.7)	13 (7.5)	30 (9.3)	115 (21.0)	81 (17.4)	43 (38.7)
Nightmare			2 (1.2)	1 (0.6)	1 (0.3)	3 (0.5)	3 (0.6)	
Piloerection			1 (0.6)	1 (0.6)		1 (0.2)		
Pyrexia		2 (2.8)	2 (1.2)	1 (0.6)	4 (1.2)	4 (0.7)	4 (0.9)	
Rhinorrhoea/Nasal Congestion			6 (3.5)	13 (7.5)	4 (1.2)	5 (0.9)	2 (0.4)	1 (0.9)
Vomiting	6 (8.5)	3 (4.2)	12 (7.0)	4 (2.3)	13 (4.0)	50 (9.1)	33 (7.1)	25 (22.5)

¹ Includes only the double blind maintenance data.

² Includes AEs collected during the first 4 weeks of the study.

³ Includes only the open label titration data.

⁴ Includes AEs collected between weeks 5 and 16 of the study.

Note: 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.

Study References: ALO-KNT-202 (202), ALO-KNT-301 (301), ALO-KNT-302 (302)

Source data: ntx_ae.pdf

Hepatotoxicity: As warned (boxed warning) in the labeling of naltrexone tablets, naltrexone may induced hepatotoxicity at high dose (5 times recommended dose 50 mg/day). In the short-term trials (ALO-KNT-202 and ALO-KNT-301), no patients had

ALT or AST greater than 3x ULN. There were about 8-9% of patients with normal to high shifts in ALT or AST) during the 12-month open-label trial (see above Section 7.4.3); four patients had ALT or AST elevation greater than 3xULN (from the 120-day safety update). The transaminase elevations were either transient or attributable to concomitant medical condition or medication. In addition, six patients with ALT 2xULN at the entry of the study had the ALT returned to the normal range during the study. Apparently, the low naltrexone exposure from chronic administration of Kadian NT capsules, as compared to oral naltrexone tablets, may not pose significant hepatic risk.

7.7 Additional Submissions

The Applicant submitted an amended integrated summary of safety (ISS) on Oct 1, 2008 with editorial changes on errors, as compared with the original version (June 30, 2008). This review is based on the amended version of the Applicant ISS.

There were no additional safety data except the 120-day safety update submitted on October 31, 2008 by the Applicant since the original NDA was received on June 30, 2008. The 120-day safety update included no new safety data, but revised presentation of naltrexone-related AEs, including opioid withdrawal and hepatic enzyme elevation associated with Kadian NT capsules and one female subject who was pregnant during the 12-month open-label trial (Study ALO-KNT-302). The information from the 120-day update had been incorporated to appropriate sections of this review.

8. POSTMARKETING EXPERIENCE

There is no post-marketing experience with this product world-wide since the proposed product has not been marketed in any country.

9. APPENDICES

9.1 Literature Review and other Important Relevant Materials/References

No information in this review is from literature. Since the proposed product is under 505(b)(2) regulation, the current labeling of Kadian (NDA 20-616) and Revia (18-932) are referenced for labeling review of Kadian NT.

9.2 Labeling Recommendations

The trade name for this product, "EMBEDA", was reviewed by the Division of Medication Error and Technical Support (DMETS) through consultation. There are no outstanding issues with the proposed trade name as per the DMETS preliminary results.

The product meets the requirements of the Risk Evaluation and Mitigation Strategy (REMS). The Applicant has submitted a REMS proposal, which is under review by the Office of Surveillance and Epidemiology (OSE).

9.3 Advisory Committee Meeting

A joint advisory committee meeting of the *Anesthetic and Life Support Drugs Advisory Committee* and Drug Safety & Risk Management Advisory Committee was held on November 14, 2008 at Gaithersburg, Maryland. The following questions (without voting) were discussed by the committees:

1. a. Discuss the adequacy of the tools we have to assess the impact of a novel opioid formulation on abuse, misuse and diversion of the product in the community.
b. Discuss whether or not the available data suggest that this formulation will be less susceptible to abuse and misuse.
2. Many of the cases of addiction, overdose and death are associated with abuse of intact controlled-release opioid products. EMBEDA is formulated to release naltrexone only following physical manipulation.
 - a. Discuss whether inclusion of data on the release characteristics of the naltrexone in this new formulation into the product labeling could potentially mislead prescribers or patients into thinking that this new formulation, when taken as directed, is less likely to be addictive, or unlikely to be abused or result in addiction or overdose.
 - b. If you believe that patients or prescribers could be misled, discuss whether this risk is acceptable, considering the potential benefits of the changes to the formulation.
3. a. If, from Question 1, you believe that the data suggest that this formulation of controlled-release morphine is likely to reduce its abuse and misuse, discuss whether or not any of the data should be included in the product labeling.
b. If so, which specific data do you think should be incorporated into the labeling?

Overall, the committees agreed that the proposed formulation did show some abuse deterrent potential and may incrementally mitigate misuse/abuse, which must be assessed post marketing. However, they also had following concerns:

(b) (4)

- The variation of drug liking study on the intact and crushed Kadian NT pellets was too high to be clinical meaningful.
- The product may be misleading prescribers, which may not be sufficiently prevented by REMS pathway.

9.4 Individual Study Reviews

9.4.1 Study ALO-KNT-301

A multicenter, randomized, double-blind, placebo-controlled, Phase 3 efficacy study of Kadian NT (Morphine sulfate plus naltrexone hydrochloride extended-release) capsules, in subjects with moderate-to-severe chronic pain due to osteoarthritis of the hip or knee

Study location: 74 study sites in US

Study duration: December 22, 2006 (the first subject consented) to

November 8, 2007 (the last visit for the last enrolled subject)

Contract research organization (CRO): (b) (4)

OBJECTIVES

- **Primary:** to evaluate the efficacy of Kadian NT (BID) compared with placebo for the treatment of chronic moderate-to-severe pain due to osteoarthritis (OA) of the hip or knee
- **Secondary:**
 - To evaluate other efficacy outcomes, including WOMAC index, Sleep Scale, Beck Depression Inventory, and the Patient Global Impression of Change
 - To evaluate the safety and tolerability including opioid withdrawal.

STUDY DESIGN

The study was conducted using a randomized withdrawal design, which was a randomized, double blind, placebo-controlled trial (immediately following an open-label titration treatment).

Study subject

Approximately 728 patients with moderate-to-severe chronic pain due to OA of the hip or knee were to be recruited for the open-label Titration Phase followed by randomization and double-blind treatment. The sample size, n=200/arm (maintenance phase), was estimated based on an effect size of 0.33 (primary efficacy analysis) and a Type I error of 0.05 for a 2-tailed test with at least 90% power.

Subjects who met the following criteria were enrolled:

Key inclusion criteria:

- 1) 21 years of age or older, males and females
- 2) Primary diagnosis of Functional Class I-II osteoarthritis (OA) of the knee or hips based on ACR criteria.
- 3) An average 24-hour pain intensity of ≥ 5 on the 11-point BPI (*Brief Pain Inventory*) scale at the Baseline Visit

- 4) Required treatment of target joint pain within the last 90 days and met at least one of the following criteria:
 - a. unable to consistently control target joint pain with non-opioid analgesics (e.g., NSAIDs) or tramadol; OR
 - b. required opioid treatment (single or combination product) with the equivalent of ≤ 40 mg/day of oral morphine sulfate.
- 5) Generally good health at screening based on medical history, physical examination, 12-lead ECG and clinical laboratory tests

Key exclusion criteria:

- 1) History of drug abuse/dependence/misuse or narcotic analgesic abuse/dependence/misuse within 5 years prior to screening.
- 2) A positive result for non-prescription drugs of abuse at screening (e.g., cocaine, heroin, marijuana).
- 3) Any chronic pain syndrome (i.e., fibromyalgia) that would have interfered with the assessment of pain and/or other symptoms of OA.
- 4) Epidural or local corticosteroid injections in target joint within 2 months of screening, or target joint viscosupplementation within the past 3 months
- 5) Oral or intramuscular corticosteroids within the past 90 days. Topical, nasal, and inhaled corticosteroids were permitted.
- 6) Effective dose of Kadian NT resulting from the Titration Phase of the study was < 20 mg BID or > 80 mg BID.
- 7) Historically non-responsive to morphine.

STUDY CONDUCT

Study schedule (Table 1)

- Screening Period (14 days): including 1- to 7-day Washout Period to discontinue all pain and prohibited medications to establish pain intensity ≥ 5 on 11-point BPI scale
- Baseline Visit: at the end of the Washout patients with average 24-hour pain intensity ≥ 5 on 11-point BPI scale were to enter the Titration Phase.
- Titration Phase: up to 6 weeks
 - open-label Kadian NT treatment (flexible dose) with weekly visit
 - starting dose at 20 mg at bedtime at the first 3 nights for opioid-naïve patients, otherwise 20 mg bid
 - titrated up or down in BID, the maximum allowed dose at 80 mg BID
 - **responder was defined as “pain on average in the last 24 hours” ≤ 4 BPI score over the last 4-days and with minimum 2-point decrease from baseline**
- Maintenance Phase: 12 weeks
 - All responders from the titration were randomized and received *the same effective dose* (fixed dose) achieved in the Titration Phase for 12 weeks.
 - Patients on placebo were force tapered up to 2 weeks.
 - Weekly visit for first two weeks and every two weeks up to 12 weeks.
- Tapering Period after the end of Maintenance: 2 weeks
- Follow-Up Visit: at the end of the taper

Table 1. Study schedule and assessment (Protocol ALO-KNT-301)

	Screening Visit	Washout Period	Baseline Visit	Titration Phase (Weekly visits up to 6 weeks)	Maintenance Phase ¹ (12 weeks total. Visits every week for 2 weeks, then every 2 weeks up to 12 weeks)					Post-Tx Follow-Up	Early Termination
	Day -14 to Day -1	Day 1 to Day 7 of Screening	Visit X (Day 0)	Visits X + 1, 2, 3, 4, 5 & 6 Weeks	Visit Y	Visit Y + 1 Week	Visits Y + 2, 6, & 10 Weeks	Visits Y + 4 & 8 Weeks	Visit Y + 12 Weeks		
Informed consent	X										
Inclusion/exclusion	X		X								
Medical history (incl. chronic pain history)	X										
12-lead ECG	X										
Urine drug screen	X		X								
Physical examination and weight	X								X		X
Height, weight, and BMI	X										
Vital signs	X		X	X	X	X	X	X	X	X	X
Clinical laboratory tests	X		X						X		X
Urine pregnancy test	X		X								
Experience minimum pain flare score ²		X									
Dispense electronic diary	X		X	X	X	X	X	X			
Dispense study drug and/or rescue medication	X		X	X	X		X	X	X		X
Collect and review electronic diary			X	X	X	X	X	X	X		X
Collect study drug and/or rescue medication			X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X	X
Concomitant medications			X	X	X	X	X	X	X	X	X
Beck Depression Inventory			X					X	X		X ³
MOS Sleep Scale			X		X			X	X		X ³
In-clinic pain assessment (BPI)			X	X	X	X	X	X	X		X
WOMAC Osteoarthritis Index			X		X		X	X	X		X ³
Brief Pain Inventory (BPI) ⁴			X	X	X	X	X	X	X		X
Patient Global Impression of Change					X		X	X	X		X
Clinical Opiate Withdrawal Scale					X	X	X ⁵		X		X
Subjective Opiate Withdrawal Scale ⁶					X	X	X ⁵				

1. Visit Y = first day of the Maintenance Phase.
2. Minimum Pain Flare Score = average 24-hour pain intensity of ≥ 5 on the 11-point BPI scale.
3. Subjects who prematurely withdrew from the Titration Phase of the study were not to complete this assessment.
4. BPI included in daily electronic diary completion only.
5. Performed at the Visit Y + 2 weeks only.
6. Included in the daily electronic diary completion; completed daily for the first 2 weeks of the Maintenance Phase.

Visit windows:

The visit numbers were defined based on the specified windows of time (days), as shown in Table 2.

**Table 2. Visit Window Definition
(From the Applicant's Table 4)**

Phase/Visit	Visit Label	Smallest study day ¹	Largest study day ¹	Rules ²
Screening	S	-14	-1	The last value in the window was used
Titration				
Baseline/Visit X	X0	0	0	The first day of titration was used.
Visit X + 1 week	X1	1	9	The visit closest to Day 6 was used. ³
Visit X + 2 weeks	X2	10	16	The visit closest to Day 13 was used. ³
Visit X + 3 weeks	X3	17	23	The visit closest to Day 20 was used. ³
Visit X + 4 weeks	X4	24	30	The visit closest to Day 27 was used. ³
Visit X + 5 weeks	X5	31	37	The visit closest to Day 34 was used. ³
Visit X + 6 weeks ⁴	X6	38	44	The visit closest to Day 41 was used. ³
Maintenance				
Baseline/Visit Y	Y0	0	0	The first day of maintenance was used.
Visit Y + 1 week	Y1	1	9	The visit closest to Day 6 was used. ³
Visit Y + 2 weeks	Y2	10	16	The visit closest to Day 13 was used. ³
Visit Y + 4 weeks	Y3	17	30	The visit closest to Day 27 was used. ³
Visit Y + 6 weeks	Y4	31	44	The visit closest to Day 41 was used. ³
Visit Y + 8 weeks	Y5	45	58	The visit closest to Day 55 was used. ³
Visit Y + 10 weeks	Y6	59	72	The visit closest to Day 69 was used. ³
Visit Y + 12 weeks	Y7	73	86	The visit closest to Day 83 was used. ³

¹ For the Screening and Titration Phases, study day 0 was the day of the first dose of titration drug was taken, and day -1 was the day immediately preceding study day 0. For the Maintenance Phase, study day 0 was the day of the first dose of maintenance

² For subjects who prematurely discontinued, efficacy evaluations performed >2 days beyond last dose were excluded.

³ In the event of ties, the earlier study day was used.

⁴ If a subject finished titration early, visits past the study day of titration discontinuation were not created.

Concomitant Medications

- **Rescue medication:** acetaminophen up to 500 mg every 6 hours as needed during the Washout, Titration, and Maintenance Phases; but not within 24 hours prior to any clinical visit.
- **Concomitant therapy:** the following therapies were allowed:
 - Daily prophylactic bowel regimen to all subjects for opioid-associated constipation

- Low-dose aspirin (≤ 325 mg/day) if the subject had been on a stable dose regimen for ≥ 30 days prior to screening
- Anti-depressant at a stable dose for at least one month prior to screening

OUTCOME MEASURES

Efficacy assessments

Pain intensity (PI): the PI was rated on 11-point BPI (Brief Pain Inventory)

- In-clinic Pain Assessment: at all clinical visits (*average pain* in the past 24 hours)
- At-Home Pain Assessment: electronic BPI diary pain score recorded by subjects between visits, including
 - *Worst pain* in the last 24 hours
 - *Least pain* in the last 24 hours
 - *Average pain* in the last 24 hours
 - *Pain right now*

Medical Outcome Study (MOS) Sleep Scale: 12-item questionnaire

- Seven subscale scores: sleep disturbance, snoring, awaken short of breath or with a headache, quantity of sleep, optimal sleep, sleep adequacy, and somnolence
- 9-item overall sleep problems index

Beck Depression Inventory: 21-item questionnaire on 4-point score (0=minimal and 3=severe).

- Score < 15 : mild depression
- Score 15-30: moderate depression
- Score > 30 : severe depression

WOMAC Index:

- Standardize each of three subscales (Pain, Function and Stiffness), which was a total score of each subscale was divided by the number of questions and then multiplied by 25
- Calculate a composite score: $= 0.42x \text{ Pain} + 0.21x \text{ Stiffness} + 0.37x \text{ Physical}$

Patient global impression of change: on 7-point scale (1=very much improved and 7=very much worse)

Safety assessments

Vital signs (all visits), **physical examination** (screening and Visit Y+12 weeks or early termination), and **clinical laboratory test** (hematology, blood chemistry and urinalysis at screening, baseline and visit Y+12 weeks or early termination)

Clinical Opiate withdrawal scale (COWS) inventory scoring: to assess 11 common opiate signs and symptoms at visit Y, visit Y+1 week, Visit Y+2 weeks and Visit Y+12 weeks (or early termination). The COWS score was the sum of all item scores and categorized to four levels of severity:

- 5-12 = mild
- 13-24 = moderate

- 25-36 = moderately severe
- >36 = severe withdrawal

Subjective Opiate Withdrawal Scale (SOWS) inventory scoring: 16 withdrawal symptoms on 5-point scale (0=not at all and 4=extremely) daily in the electronic diary for first 2 weeks of Maintenance Phase. The SOWS score was the sum of all item scores.

Adverse events: Starting from the time the subject signed the informed consent through follow-up visit (the end of 2-week tapering period)

STATISTICAL ANALYSIS

Analysis population

- Titration Phase population: all subjects who were administered any amount of ALO - 01 in the Titration Phase.
- Intent to Treat (ITT) population: all subjects who were randomized into the Maintenance Phase of the study and took at least one dose of double-blind study medication after randomization. ITT population was used for primary efficacy analysis.
- Safety population: all subjects who were administered any amount of double blind study medication in the Maintenance Phase.
- Completer population: all subjects who completed the 12-week Maintenance Phase of the study without major protocol violations.

Baseline definition

- Screening baseline: the in-clinic BPI obtained at Visit X (the worst pain)
- Randomization baseline: the BPI diary average pain score averaged over the last seven days of the Titration Phase (the least pain)

Primary endpoint:

The mean change of weekly BPI diary average pain score from the randomization baseline to Week 12 (the end of maintenance treatment)

- Randomization baseline: Average of the BPI diary average pain score from the last 7 days of titration. If there were <7 days but >3 days of titration, the average of the available data was used. If there were ≤ 3 days of titration, the screening baseline (the end of washout) was used.
- The end of treatment (Week 12 of the Maintenance Phase, or Visit Y+12-week): The average of the BPI diary average pain score from the last 7 days of maintenance was used for completers.
- BOCF (Baseline Observation Carried Forward) or LOCF (Last Observation Carried Forward) for imputation of dropouts using either the Screening Baseline, the Randomization Baseline, or the average of last 7-day observation (dependent on dropout reasons), see the Primary Analysis.

Primary analysis:

- Differences in the efficacy endpoints between Kadian NT and placebo were analyzed using ANCOVA with treatment as categorical factor and the Visit Y value (randomization baseline) as covariate.
- BOCF/LOCF mixed method (Method #1, as the Applicant referred to in the summary tables) was used to impute dropouts to the end of treatment (week 12) by the following rules:
 - For drop-outs due to opiate withdrawal symptoms (COWS > randomization baseline COWS, and COWS ≥13), imputing the Randomization Baseline for placebo group and the Screening Baseline for Kadian NT group. (BOCF)
 - For drop-outs due to AEs, imputing the Screening Baseline. (BOCF)
 - For dropouts due to any other reason (non-AE and non-COWS), imputing the average of the last seven days of maintenance phase. (LOCF)

Table 2b. BOCF/LOCF imputation of PI scores for dropouts for primary analysis

Reason for Dropout	Placebo	Kadian NT
COWS > Randomization Baseline & COWS ≥ 13	BOCF: Randomization Baseline (<i>least pain</i>)	BOCF: Screening Baseline (<i>worst pain</i>)
AEs	BOCF: Screening Baseline for both groups	
LOE Administrative Investigator, Patient WD Others	LOCF: average of BPI diary average pain score from the last 7-day observations	

Screening baseline was defined as the *in-clinic pain intensity score* at the end of washout.

Randomization baseline was defined as average of the *BPI diary average pain* scores from the last seven days of the Titration Phase. **BPI:** 11-point Brief Pain Inventory scale

COWS: clinical opiate withdrawal scale (11-item questionnaire)

Alternative analysis (post-hoc):

The Applicant also analyzed the efficacy data with the following LOCF (last observation carried forward) imputation methods for dropouts, as alternative analyses. Both methods were not protocol-specified, nor described in the study report, instead briefed in the legends of semi-summary tables (in Appendices of the report):

- LOCF Method #1 (the Applicant referred to Method #2): The average of the last 7 days of available diary data (but not more than 2 days past drug discontinuation) was used to impute dropouts due to lock of efficacy or administrative reasons.
- LOCF Method #2 (the Applicant referred to Method #2): The last diary entry (but not more than 2 days past drug discontinuation) was used to impute dropouts due to lock of efficacy or administrative reasons.

Sensitivity analysis (alternate imputation for drop-outs):

Three alternate imputation methods using the Randomization Baseline or the Screening Baseline to impute dropouts from both treatment and placebo groups:

- Alternate Method #1: imputing the Randomization Baseline for all drop-outs
- Alternate Method #2: imputing the Screening Baseline for drop-outs due to AEs and the Randomization Baseline for dropouts due to other reasons
- Alternate Method #3: imputing the Screening Baseline for all drop-outs

Cumulative responder analysis:

The responder was defined based on the In-Clinic pain score (average pain in the last 24 hours) during the Maintenance Phase, and the dropouts were defined as non-responders.

Secondary efficacy endpoints

The following nine secondary endpoints were assessed during the 12-week Maintenance Phase. The analyses of the secondary endpoints were conducted in the ITT population with the same imputation method as in primary analysis for dropouts except where specified.

- 10) Diary BPI average pain averaged over the entire Maintenance Phase;
- 11) In-clinic BPI
- 12) Weekly diary BPI worst, least, and current pain (daily scores averaged over 7-day intervals to obtain weekly scores);
- 13) WOMAC Index Pain Subscale, Stiffness Subscale, Physical Function Subscale, and Composite Index
- 14) MOS Sleep Scale subscale scores
- 15) Beck Depression Inventory score
- 16) Amount of rescue medication (pill counts summed over 7-day intervals to obtain weekly counts)
- 17) PGIC (patient global impression of change)
- 18) Responders at Week 12 based on in-clinic BPI

PROTOCOL AMENDMENTS

The original protocol dated on November 3, 2006 was approved a Special Protocol Assessment (SPA). The protocol was amended three times during the study and the amended SPA protocols were not resubmitted for review. The detailed amendments were provided in the study report and all appear to not significantly impact the primary efficacy outcome (measures and/or analyses).

Changes in Statistical Analysis Plan

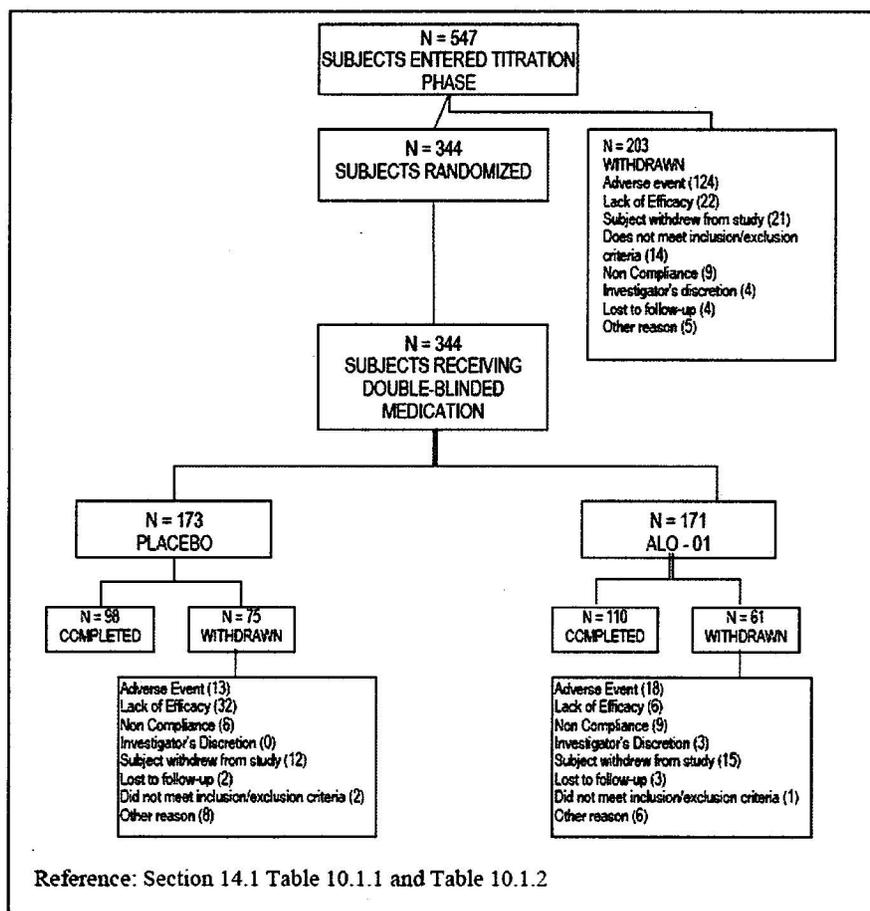
- Weekly diary BPI average pain score: for dropouts, the last diary entry was imputed until the last visit (in-clinic BPI score).
- Modified ITT population: all subjects who were randomized into the Maintenance Phase of the study and took at least 1 dose of double-blind study medication after randomization, *as well as at least one post baseline evaluation* (not included in the SPA-approved SAP).

RESULTS

Disposition of patients

Of a total of 547 patients enrolled in the Titration Phase, 62.9% (n=344) completed the titration and randomized into Kadian NT group (n=171) and placebo group (n=173) for the 12-week Maintenance Phase (Figure 1).

Figure 1. Disposition of subjects (from the Applicant's Figure 1)



Analysis population (Table 3):

- Safety population
 - for the Titration phase: n=547 (all enrollee)
 - for the Maintenance Phase: n=173 on placebo and n=171 on Kadian NT (all randomized patients)
- ITT population: n=173 on placebo and n=170 on Kadian NT (from 171 randomized patients). The one subject excluded from the Kadian NT group was

due to no diary data, which was the protocol amendment to SAP (see the above Change in Statistical Analysis Plan).

- Completer population: n=98 on placebo and n=110 on Kadian NT

**Table 3. Analysis population
(From Applicant's Table 13 in Study ALO-KNT-301)**

Titration Phase		
Population	ALO - 01	
Subjects in Safety Population	547	
Maintenance Phase		
Population	Treatment Group	
	Placebo	ALO - 01
Subjects in Safety Population	173	171
Subjects in ITT Population	173	170 ^a
Subjects in Completer Population	98	110

a. Subject 159-0007 did not have diary data after randomization.

Reference: Section 14.1 Table 11.2.3, Section 14.2 Table 11.4.2.1, Section 14.3.1 Table 12.2.1.1, and Section 14.3.1 Table 12.2.1.2

Section 14.1 Table 11.1.1 summarizes the number of subjects in each analysis population by site. No one site contributed more than 15% of subjects to any analysis population.

Dropout rate during the Maintenance Phase: 36% on Kadian NT and 43% on placebo. Major reasons for dropouts were (Kadian NT vs. placebo, Table 4):

- Adverse events (AEs): 10.5% vs. 7.5% (morphine-related common AEs: nausea, vomiting, hyperhidrosis, diarrhea, constipation or somnolence; only one patient with withdrawal syndrome in Kadian NT group)
- Lack of efficacy (LOE): 3.5% vs. 18.5%
- Subject withdrew from study: 8.8% vs. 6.9%

No dropouts were due to opiate withdrawal **symptoms as per the Applicant's report**. However, in the safety evaluation section of the report, there were three patients in the placebo group who had COWS score ≥ 23 (moderate withdrawal)

The Applicant stated in the report that during the Maintenance Phase, 13 placebo subjects and 18 Kadian NT subjects marked adverse event as the reason for discontinuation on the study completion CRF page; however, 11 placebo subjects and 14 Kadian NT subjects had premature discontinuation of study drug indicated as the action taken on the adverse event CRF page. The Applicant did not provide justification on this difference.

In addition, the Applicant did not present a dropout profile across time (visits) during the Maintenance Phase. The data can not be found in the submission, either.

**Table 4. Subject disposition in Maintenance Phase
(From the Applicant's Table 12 in Study ALO-KNT-301)**

	Treatment Group n (%)		p-value ^a
	Placebo N = 173	ALO - 01 N = 171	
Subjects Enrolled in Maintenance Phase	173 (100.0)	171 (100.0)	
Subjects Completing Maintenance Phase	98 (56.6)	110 (64.3)	0.1531
Subjects Withdrawn from Maintenance Phase	75 (43.4)	61 (35.7)	
Reasons for Withdrawal			
Adverse Event	13 (7.5)	18 (10.5)	
Lack of Efficacy	32 (18.5)	6 (3.5)	
Non Compliance	6 (3.5)	9 (5.3)	
Investigator's Discretion	0	3 (1.8)	
Subject withdrew from study	12 (6.9)	15 (8.8)	
Lost to follow-up	2 (1.2)	3 (1.8)	
Did not meet inclusion/exclusion criteria	2 (1.2)	1 (0.6)	
Other reason	8 (4.6)	6 (3.5)	

a. P-value from Fisher's exact test to compare proportion of subjects between treatment groups.
Reference: Section 14.1 Table 10.1.2

Protocol deviation

A total of 88 subjects failed to meet ≥ 1 entrance criteria:

- N=51 non-randomized subjects (for Titration Phase)
- N=37 randomized subjects (n=15 on placebo and n=22 on Kadian NT)

Demographic characteristics (ITT population)

Titration phase (n=547): Most subjects enrolled to the Titration phase were White (75.5%) with 61% females. Mean age was 55.7 years (21 to 85 years).

Maintenance phase (n=344): Most subjects entered to this phase were White (72.4%) with 58% females. Mean age was 54.4 years (21 to 85 years). The mean BMI was 32.15 kg/m² (7.1 to 52.5 kg/m²). However, a slight unbalance is noted between Kadian NT and placebo groups: subjects in Kadian NT group were younger, heavier (higher BMI) and more females (Table 5) as well as less Hispanic ethnicity (for completer population).

**Table 5. Demographic characteristics in Maintenance Phase (ITT population)
(From the Applicant's Table 14 in Study ALO-KNT-301)**

Category	Treatment Group n (%)		p-value ^a
	Placebo N = 173	ALO - 01 N = 171	
Gender			0.1910
Male	78 (45.1)	65 (38.0)	
Female	95 (54.9)	106 (62.0)	
Age (years)			0.7025
Mean (SD)	54.7 (12.92)	54.2 (11.62)	
Median	56.0	54.0	
Minimum, Maximum	21, 85	24, 81	
Hispanic Ethnicity	40 (23.1)	36 (21.1)	0.6973
Race			0.3358
White	121 (69.9)	128 (74.9)	
Black or African American	30 (17.3)	29 (17.0)	
American Indian or Alaska Native	4 (2.3)	2 (1.2)	
Asian	15 (8.7)	9 (5.3)	
Native Hawaiian or Other Pacific Islander	0	1 (0.6)	
Other	3 (1.7)	2 (1.2)	
BMI (kg/m²)	N = 167	N = 167	0.3099
Mean (SD)	31.78 (6.317)	32.52 (6.927)	
Median	31.00	31.90	
Minimum, Maximum	17.4, 44.9	17.1, 52.5	

a. P-value from Fisher's exact test for categorical variables and ANOVA for continuous variables.

P-values for race compared White vs non-White.

Reference: Section 14.1 Table 11.2.1

Baseline characteristics (ITT population)

Titration phase: the majority were opiate naïve (75.4%). The mean pain intensity score (in last 24 hours) on the 11-point BPI scale at the entrance (the end of washout, or the titration baseline, or the *screening baseline*) was 6.1 ±1.87 (Table 5).

Maintenance phase: the majority were opiate naïve (75.1%). The mean pain intensity score on the 11-point BPI scale at entrance (the randomization baseline) was 2.5±1.2 in the placebo group and 2.7±1.3 in the Kadian NT group (Table 5).

**Table 5. Baseline characteristics in Titration and Maintenance Phases (ITT population)
(From the Applicant's Table 15 for Maintenance and Table 21 for Titration)**

Characteristic	Titration Phase N=547	Maintenance Phase	
		Placebo N=173	Kadian NT N=171
Prior Opiate Use	N=540	N = 171	N = 167
Opiate Naïve	407 (75.4%)	129 (75.4)	125 (74.9)
Opiate Experienced	133 (24.6%)	42 (24.6)	42 (25.1)
Worst Pain in last 24 Hours		N = 142	N = 139
Mean (SD)	N=277	3.34 (1.597)	3.65 (1.693)
Median	6.8 (1.67)	3.00	4.00
Minimum, Maximum		0.0, 9.0	0.0, 8.0
Least Pain in last 24 Hours		N = 142	N = 139
Mean (SD)	N=277	1.85 (1.271)	2.09 (1.383)
Median	5.3 (2.16)	2.00	2.00
Minimum, Maximum		0.0, 5.0	0.0, 6.0
Average Pain in last 24 Hours		N = 142	N = 139
Mean (SD)	N=278	2.50 (1.231)	2.71 (1.336)
Median	6.1 (1.87)	3.00	3.00
Minimum, Maximum		0.0, 6.0	0.0, 6.0
Current Pain		N = 142	N = 138
Mean (SD)	N=276	2.31 (1.488)	2.58 (1.616)
Median	5.9 (2.09)	2.00	3.00
Minimum, Maximum		0.0, 7.0	0.0, 7.0

Note: Pain intensity scale: 0-10 (11-point scale, 0 = no pain and 10 = worst pain ["pain as bad as you can imagine"]).

Reference: Section 14.1 Table 11.2.1 and Table 11.2.4; Section 14.2 Table 11.4.1

Medical history

Approximately 92% of the randomized patients (n=344, in the Maintenance Phase) had one or more medical conditions other than chronic pain in their medical history. Overall medical conditions in the ITT population were balanced between placebo and Kadian NT groups (Table 6).

Chronic pain history in the ITT population of the Maintenance Phase appears well-balanced between placebo and Kadian NT groups (Table 7), with mostly pain due to right knee (46%) followed by left knee (31%) and hips (13% on right and 10% on left). However, the Applicant did not indicate if patients with pain due multiple joints and were balanced between two groups; also the duration of the OA condition was not reported.

**Table 6. Medical conditions ($\geq 5\%$ of patients) at Baseline in Maintenance Phase (ITT)
(From the Applicant's Table 16 in Study ALO-KNT-301)**

Category	Treatment Group n (%)	
	Placebo N = 173	ALO - 01 N = 171
No Relevant Medical History or Current Medical Condition other than Chronic Pain	13 (7.5)	13 (7.6)
Subjects with Relevant Medical History or Current Medical Condition other than Chronic Pain	160 (92.5)	158 (92.4)
Endocrine/Metabolic Disorders	65 (37.6)	75 (43.9)
Hypothyroidism	12 (6.9)	19 (11.1)
Gastrointestinal Disorders	55 (31.8)	55 (32.2)
Constipation	14 (8.1)	15 (8.8)
Dyspepsia	17 (9.8)	13 (7.6)
Gastroesophageal Reflux Disease	24 (13.9)	21 (12.3)
Immune System Disorders	37 (21.4)	42 (24.6)
Drug Hypersensitivity	12 (6.9)	16 (9.4)
Seasonal Allergies	23 (13.3)	24 (14.0)
Metabolism and Nutritional Disorders	73 (42.2)	73 (42.7)
Diabetes Mellitus	17 (9.8)	15 (8.8)
Diabetes Mellitus Non-Insulin-Dependent	12 (6.9)	19 (11.1)
Hypercholesterolemia	20 (11.6)	30 (17.5)
Hyperlipidemia	29 (16.8)	22 (12.9)
Obesity	11 (6.4)	7 (4.1)
Musculoskeletal and Connective Tissue Disorders	51 (29.5)	44 (25.7)
Back Pain	20 (11.6)	14 (8.2)
Osteoarthritis	6 (3.5)	14 (8.2)
Nervous System Disorders	46 (26.6)	46 (26.9)
Headache	19 (11.0)	20 (11.7)
Migraine	8 (4.6)	15 (8.8)
Psychiatric Disorders	52 (30.1)	49 (28.7)
Anxiety	17 (9.8)	15 (8.8)
Depression	27 (15.6)	26 (15.2)
Insomnia	26 (15.0)	19 (11.1)
Respiratory, Thoracic, and Mediastinal Disorders	34 (19.7)	32 (18.7)
Asthma	16 (9.2)	16 (9.4)
Social Circumstances	31 (17.9)	40 (23.4)
Menopause	26 (15.0)	37 (21.6)
Surgical and Medical Procedures	62 (35.8)	78 (45.6)
Cholecystectomy	9 (5.2)	11 (6.4)
Hysterectomy	26 (15.0)	34 (19.9)
Vascular Disorders	77 (44.5)	74 (43.3)
Hypertension	74 (42.8)	67 (39.2)

Reference: Section 14.1 Table 11.2.7

**Table 7. Source of chronic pain (reported $\geq 2\%$ patients) at Baseline during Maintenance Phase (ITT)
(From the Applicant's Table 17 in Study ALO-KNT-301)**

Primary area of OA Sources of Chronic Pain	Treatment Group n (%)	
	Placebo N = 173	ALO - 01 N = 171
Right Hip	24 (13.9)	20 (11.7)
Arthralgia	22 (12.7)	19 (11.1)
Back Pain	10 (5.8)	2 (1.2)
Left Hip Pain	16 (9.2)	17 (9.9)
Arthralgia	16 (9.2)	17 (9.9)
Back Pain	7 (4.0)	1 (0.6)
Right Knee	83 (48.0)	77 (45.0)
Arthralgia	83 (48.0)	77 (45.0)
Back Pain	15 (8.7)	13 (7.6)
Musculoskeletal Pain	2 (1.2)	5 (2.9)
Pain in Extremity	4 (2.3)	4 (2.3)
Left Knee	50 (28.9)	57 (33.3)
Arthralgia	50 (28.9)	57 (33.3)
Back Pain	9 (5.2)	10 (5.8)
Pain in Extremity	1 (0.6)	4 (2.3)

Reference: Section 14.1 Table 11.2.10

Prior Medications

The proportion of patients taking medication prior to the study was similar between the placebo and Kadian NT groups (93.6% and 94.2%, respectively) (Table 8). The most frequently reported prior medications were NSAIDs (63%), followed by acetaminophen (33%) and opioids (23%).

Concomitant medications

During the Titration phase, most patients (89%) took at least one concomitant medication. The most common ($\geq 10\%$ of all subjects) concomitant medications were paracetamol (14.8%) and acetylsalicylic acid (for cardiac prophylaxis) (13.9%). Not all acetaminophen users took it as a rescue medication for breakthrough pain.

During the Maintenance Phase, overall concomitant medications were similar between placebo and Kadian NT groups. However, slightly more patients in the Kadian NT group took **“other analgesics and antipyretics”** and **“antihistamine (systemic)”** than those in the placebo group, particularly acetaminophen (17.5% vs. 11.0%). Conversely, use of the

following agents were slightly more common in the placebo treatment group, primarily ibuprofen and naproxen (see Table 9).

**Table 8. Prior medications (reported by $\geq 5\%$ patients) in Maintenance Phase (ITT)
(From the Applicant's Table 18 in Study ALO-KNT-301)**

Anatomical Therapeutic Chemical Term Preferred Term	Treatment Group n (%)	
	Placebo N = 173	ALO - 01 N = 171
Any Prior Medication/Therapy	162 (93.6)	161 (94.2)
Antiinflammatory/antirheumatic products, non-steroids	109 (63.0)	109 (63.7)
Celecoxib	13 (7.5)	8 (4.7)
Ibuprofen	57 (32.9)	66 (38.6)
Naproxen	9 (5.2)	14 (8.2)
Naproxen sodium	19 (11.0)	17 (9.9)
Opioids	40 (23.1)	38 (22.2)
Vicodin	14 (8.1)	19 (11.1)
Other analgesics and antipyretics	58 (33.5)	55 (32.2)
Paracetamol	43 (24.9)	44 (25.7)

Reference: Section 14.1 Table 11.2.13

**Table 9. Mostly relevant concomitant medications during the Maintenance Phase
(From the Applicant's Table 11.2.16 of Section 14.1 in Study ALO-KNT-301)**

Medications	Titration Phase N=547	Maintenance Phase		
		Placebo N=173	Kadian NT N=171	Overall N=344
Other analgesics & Antipyretics	104 (19.0%)	27 (15.6%)	35 (20.5%)	62 (18.0%)
acetaminophen	81 (14.8%)	19 (11.0%)	30 (17.5%)	49 (14.2%)
vicodin*	4 (0.7%)	0	3 (1.8%)	3 (0.9%)
Antihistamine (systemic)	70 (12.8%)	17 (9.8%)	22 (12.9%)	39 (11.3%)
cetirizine	20 (3.7%)	3 (1.7%)	8 (4.7%)	11 (3.2%)
diphenhydramine	20 (3.7%)	6 (3.5%)	5 (2.9%)	11 (3.2%)
loratadine	12 (2.4%)	5 (2.9%)	4 (2.3%)	9 (2.6%)
fexofendadine	11 (2.0%)	1 (0.6%)	5 (2.9%)	6 (1.7%)
NSAIDs	118 (21.6%)	32 (18.5%)	26 (15.2%)	58 (16.9%)
ibuprofen	37 (6.8%)	10 (5.8%)	7 (4.1%)	17 (4.9%)
naproxen	31 (5.7%)	10 (5.8%)	5 (2.9%)	15 (4.4%)
celecoxib	14 (2.6%)	5 (2.9%)	1 (0.6%)	6 (1.7%)
Opioids	41 (7.5%)	12 (6.9%)	9 (5.3%)	21 (6.1%)
morphine	8 (1.4%)	3 (1.8%)	2 (1.2%)	5 (1.5%)
vicodin*	14 (2.6%)	4 (2.3%)	4 (2.3%)	8 (2.3%)

* It is unclear if Vicodin usage under two categories were overlapped.

Treatment compliance

Treatment compliance was determined at each visit by tablet count for Kadian NT, placebo and acetaminophen, which was verified against the electronic diary. No results were presented in the report. The Applicant referred to a listing table for study drug accountability

Efficacy results - primary endpoint

Primary analysis: Kadian NT was statistically superior to placebo in the mean change of *weekly diary BPI average score* from the randomization baseline to week 12 (Table 10) using the protocol-specified (SPA) imputation for dropouts:

- Kadian NT (n=170): -0.2 ± 1.94 ($p=0.045$ vs. placebo)
- Placebo (n=173): 0.3 ± 2.05

Sensitivity analyses: The following three SPA-agreed imputation methods were planned for the sensitivity analysis of the primary imputation method. One sensitivity analysis (imputation of dropouts with Randomization Baseline) failed statistical superiority of Kadian NT over placebo (Table 10).

- Method #1: Randomization Baseline for all dropouts in both treatment groups
 - Kadian NT (n=170): -0.4 ± 1.34 ($p=0.1223$ vs. placebo)
 - Placebo (n=173): -0.2 ± 1.32
- Method #2: Screening Baseline for drop-outs due to AEs and Randomization Baseline for dropouts due to other reasons in both treatment groups
 - Kadian NT (n=170): 0.0 ± 1.91 ($p=0.0051$ vs. placebo)
 - Placebo (n=173): 0.7 ± 2.17
- Method #3: Screening Baseline (the end of washout right before titration, the worst pain) for all drop-outs in both treatment groups
 - Kadian NT (n=170): 0.6 ± 2.31 ($p=0.0489$ vs. placebo)
 - Placebo (n=173): 1.1 ± 2.37

Post hoc analysis or alternative imputation methods as shown in Table 10: Kadian NT failed statistical superiority to placebo when dropouts were imputed with *the average of last 7 days of diary BPI* for dropouts due to lack of efficacy or administrative reasons.

- Average LOCF (last 7-day mean PI):
 - Kadian NT (n=170): -0.2 ± 1.92 ($p=0.104$ vs. placebo)
 - Placebo (n=173): 0.2 ± 1.97
- Single entry LOCF (last diary entry):
 - Kadian NT (n=170): -0.1 ± 1.97 ($p=0.035$ vs. placebo)
 - Placebo (n=173): 0.3 ± 2.13

**Table 10. Analysis results of primary efficacy endpoint in ITT population
(Reproduced from the Applicant's Table 20 in Study ALO-KNT-301)**

Analysis method	Pain Intensity, mean(SD)		P-value ^a
	Placebo N=173	Kadian NT N=170	
Primary Imputation Method			
Baseline	3.2 (1.07)	3.3 (1.30)	
Visit Y+12 Weeks ^b	3.5 (2.13)	3.1 (1.99)	
Change from Baseline to Visit Y+12 Weeks	0.3 (2.05)	-0.2 (1.94)	0.0445
LOCF Imputation Methods (not protocol-specified)			
Baseline	3.2 (1.07)	3.3 (1.30)	
Visit Y+12 Weeks ^c	3.4 (2.05)	3.1 (1.97)	
Change from Baseline to Visit Y+12 Weeks	0.2 (1.97)	-0.2 (1.92)	0.1041
Visit Y+12 Weeks ^d	3.6 (2.19)	3.2 (2.03)	
Change from Baseline to Visit Y+12 Weeks	0.3 (2.13)	-0.1 (1.97)	0.0347
Sensitivity Analyses (protocol-specified)^e			
Randomization Baseline			
Visit Y + 12 Weeks	3.1 (1.58)	2.9 (1.59)	
Change from Baseline to Visit Y+12 Weeks	-0.2 (1.32)	-0.4 (1.34)	0.1223
Screening or Randomization Baseline			
Visit Y + 12 Weeks	3.9 (2.38)	3.3 (2.13)	
Change from Baseline to Visit Y+12 Weeks	0.7 (2.17)	0.0 (1.91)	0.0051
Screening Baseline			
Visit Y + 12 Weeks	4.3 (2.49)	3.9 (2.54)	
Change from Baseline to Visit Y+12 Weeks	1.1 (2.37)	0.6 (2.31)	0.0489

Reference: Section 14.2 Table 11.4.4.1, Table 11.4.8, Table 11.4.12, and Table 11.4.16

Visit Y: the first day of the Maintenance Phase (the end of the Titration Phase)

Visit Y+12 Weeks: the end of the Maintenance Phase (week 12)

- Means and standard deviations from an ANCOVA model with treatment as categorical factor and randomization baseline score as a covariate.
- Primary imputation method: BOCF or LOCF, dependent on reasons for dropouts (see the STATISTICAL ANALYSIS/Primary Analysis for details).
- Alternative imputation (LOCF): dropouts due to lock of efficacy or administrative reasons were imputed with the average of the last 7 days of available diary data (but not more than 2 days past drug discontinuation)
- Alternative imputation (LOCF): dropouts due to lock of efficacy or administrative reasons were imputed with the last diary entry (but not more than 2 days past drug discontinuation).
- Sensitivity analyses (protocol-specified and SPA agreement):
 - Method 1: **Randomization Baseline** (the end of titration, *the least pain*) for all drop-outs in both groups
 - Method 2: **Screening Baseline** (the end of washout right before titration, *the worst pain*) for all drop-outs in both groups
 - Method 3: **Screening Baseline** for drop-outs due to AEs and **Randomization Baseline** for dropouts due to other reasons in both groups.

Completer analysis: The mean change from baseline to week 12 in the weekly BPI diary average pain scores in the completer population (Table 11) was similar to the primary analysis in the ITT population: -0.3 on Kadian NT vs. 0.4 on placebo (p=0.0012).

Table 11. Analysis results of primary efficacy endpoint in completer population (Reproduced from the Applicant's Table 11.4.5.1 in Study ALO-KNT-301)

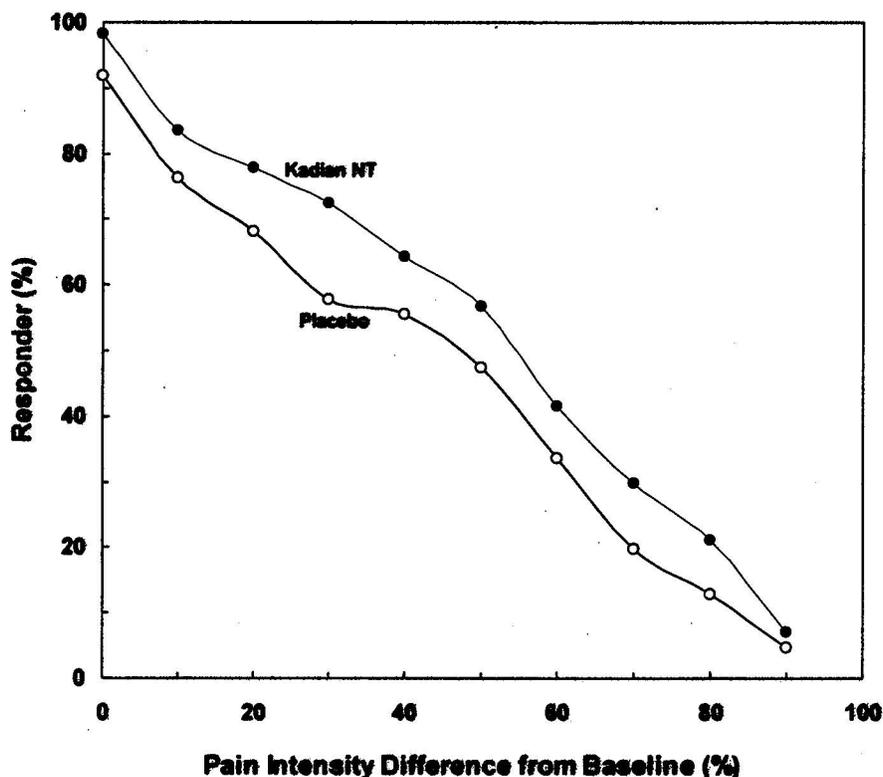
Analysis*	Placebo N=98	Kadian NT N=109	p-value#
Baseline	2.4 ±1.25	2.6 ±1.32	
Week 12	2.8 ±1.85	2.4 ±1.58	
Change from baseline to week 12	0.4 ±1.66	-0.3 ±1.54	0.0012

* The pain intensity score at baseline and week 12 were weekly average of BPI diary daily average pain score.

Differences between treatments were assessed using mixed model random effects ANCOVA with contrasts for by-visit treatment comparisons

Responder analysis: The cumulative responder analysis was based on pain intensity difference (in %) from baseline to week 12 using the in-clinic BPI score and the dropouts were defined as non-responders. The responder curves were separated (Figure 2). The difference in the *only* ≥30% response was statistically significant between Kadian NT (73%) and placebo (58%).

Figure 2. Cumulative responder analysis of pain intensity difference from baseline at week 12 in ITT population. The pain intensity difference from baseline at week 12, expressed as % response, was based on the in-clinic BPI score collected at the baseline and week 12 visits; the dropout was defined as non-responder. (From the Applicant's Table 28 in Study ALO-KNT-301)



Efficacy Results – Secondary endpoints

Secondary endpoints - Titration Phase

- Mean change in weekly PI from baseline to the end of titration: n=278 patients with weekly diary BPI data at the Titration Baseline (Screening Baseline) and Final Visit
 - Worst pain: -3.3 ± 2.07
 - Least pain: -3.3 ± 2.10
 - Average pain: -3.4 ± 1.99
 - Current pain: -3.5 ± 2.27
- WOMAC Index: mean change from baseline in n=313 patients with WOMAC Index scores at the Titration Baseline and Final Visit:
 - Composite: -28.9 ± 16.20
 - Pain: -30.1 ± 17.25
 - Stiffness: -26.8 ± 21.74
 - Physical: -28.6 ± 17.73

- MOS sleep scale: n=313 patients with baseline and final data; overall sleep quality was improved by the end of titration
- Rescue medication: n=482 patients used rescue medication during the titration, average weekly use was 12.45 tablets.
- Responder: 53.6% of patients (n=293) responded to treatment during the titration based on site evaluation of patient response to titration treatment (definition of response was not provided??)

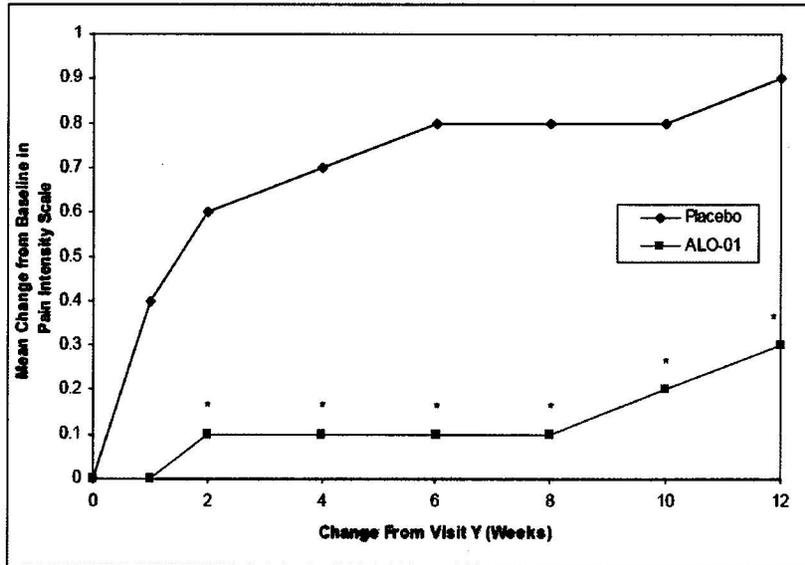
Secondary endpoints - Maintenance Phase

- Time-course of weekly BPI diary pain score: The mean changes from baseline in the *weekly BPI diary average pain score* to each visit (using the primary imputation methods for dropouts) was statistically significantly smaller in the Kadian NT group compared to the placebo group beginning at Week 2 (Figure 2). However, the pain intensity difference values at week 12 are inconsistent with those of the primary efficacy analysis (Table 10): 0.9 vs. 0.3 in placebo and 0.3 vs. -0.2 in Kadian NT; the inconsistency was due to different statistical analysis methods as clarified with the Applicant and the statistical reviewer.

Analyses based on weekly BPI diary *worst, least and current* pain scores were similar to the *average* pain scores.

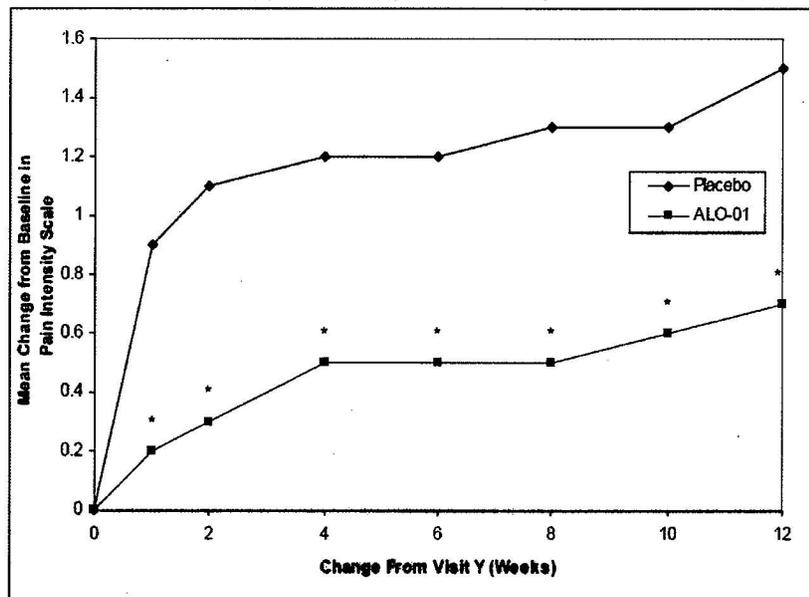
- Time-course of in-clinic BPI pain score: The mean change from baseline to each visit was statistically significantly smaller in the Kadian NT group compared to the placebo group at all visits (Weeks 1 to 12) (Figure 3).
- Time-course of WOMAC Index (Pain, Stiffness and Physical): Kadian NT treatment was statistically superior to placebo in the mean change from baseline to each visit in composite score (Figure 4A). The similar findings were seen in each of WOMAC subscales, such as WOMAC Pain scores (Figure 4B)
- MOS sleep scale: overall, quality of sleep at the end of treatment (week 12) was worse than the baseline in both groups and Kadian NT was slightly better than placebo in the mean change from baseline to Week 12 in the MOS scores but without statistical significance. Some MOS subscales at week 4 or week 8 showed statistically differences between Kadian NT and placebo.

Figure 2. Time-course of mean change from baseline to each visit in the weekly BPI diary average pain intensity (From the Applicant's Figure 2 in Study ALO-KNT-301)



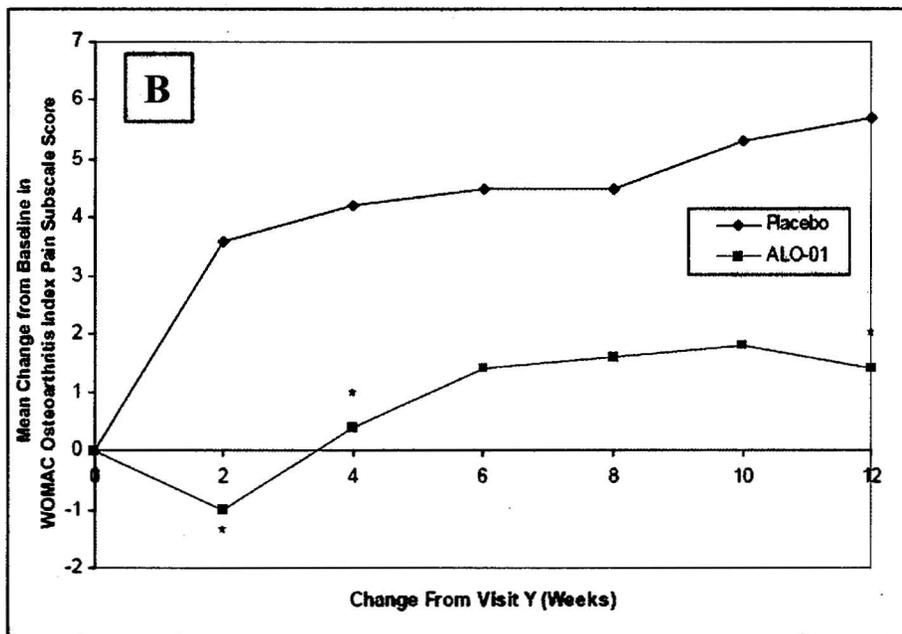
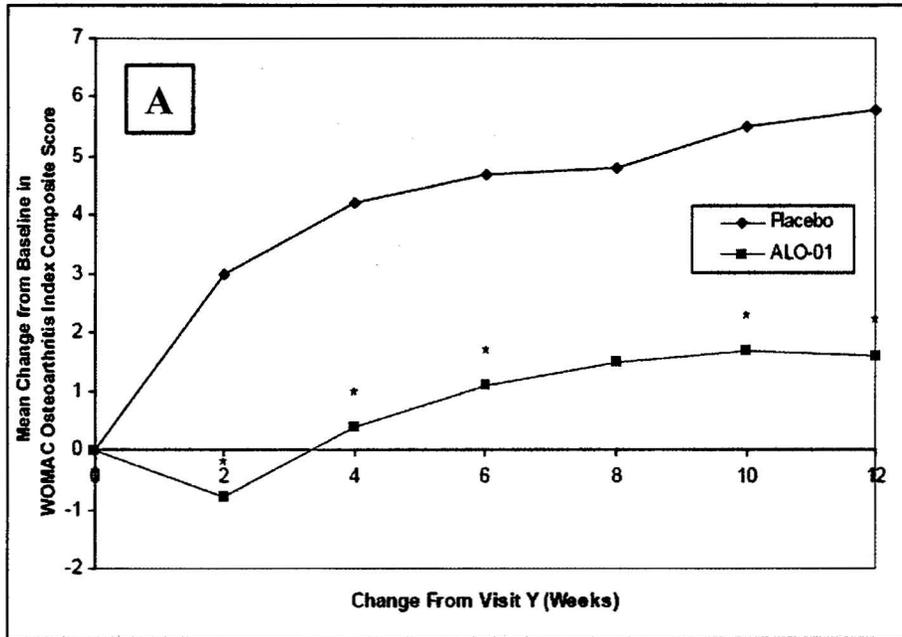
Note: Actual values were derived weekly averages of daily average pain scores.
Reference: Section 14.2 Table 11.4.4.1

Figure 3. Time-course of mean change from baseline to each visit in the in-clinic BPI pain intensity (From the Applicant's Figure 3 in Study ALO-KNT-301)



Note: Pain intensity scale: 0-10 (11-point scale, 0 = no pain and 10 = worst pain ["pain as bad as you can imagine"]).
* $p < 0.05$ for ALO-01 versus placebo using ANCOVA with treatment as a categorical factor and Visit Y as a covariate.
Reference: Section 14.2 Table 11.4.8

Figure 4. Mean change in WOMAC Index composite score (A) and WOMAC Pain score (B) from baseline to each visit (weeks) (From the Applicant's Figures 7 & 8 in Study ALO-KNT-301)



Note: For each subscale, subject's rated pain as none, mild, moderate, severe, or extreme.
 * $p < 0.05$ for ALO-01 versus placebo using ANCOVA with treatment as a categorical factor and Visit Y as a covariate.

Reference: Section 14.2 Table 11.4.16

Secondary endpoints - Maintenance Phase (cont.)

- Beck depression inventory score: The mean decrease from the screening baseline was numerically greater in the Kadian NT treatment group compared to the placebo group at each visit (but no statistically significance).
- Weekly use of Rescue medication: the average weekly number of tablets of rescue medication (acetaminophen) was slightly lower in the Kadian NT group than in the placebo group (Table 12). However, as shown in Table 9, higher percentage of patients in the Kadian NT group used acetaminophen as concomitant medication than in the placebo group (18% vs. 11%); and more patients in the Kadian NT group took other analgesics during the Maintenance Phase.
- Patient global impression of change: more patients in the Kadian NT treatment **reported “very much improved” or “much improved” as compared to placebo** treatment at all visits (44% vs. 38% at week 12) but without statistically significance. The missing data were imputed by LOCF.

**Table 12. Average use of rescue medication during the Maintenance Phase (ITT)
(From the Applicant's Table 27 in Study ALO-KNT-301)**

Category	Treatment Group	
	Placebo N = 173	ALO - 01 N = 171
Overall Maintenance Phase Average Weekly Use (Tablets/Week)^a	N = 125	N = 127
Mean (SD)	6.2 (5.72)	5.3 (6.09)
Median	4.4	2.4
Minimum, Maximum	0, 24	0, 26
Average Daily Use From Visit Y through Visit Y + 2 Weeks (Tablets/Day)	N = 86	N = 85
Mean (SD)	8.0 (7.06)	7.7 (7.88)
Median	5.9	5.0
Minimum, Maximum	0, 28	1, 37
Average Daily Use After Visit Y + 2 Weeks (Tablets/Day)	N = 91	N = 99
Mean (SD)	6.2 (5.84)	4.7 (6.02)
Median	3.8	2.0
Minimum, Maximum	0, 25	0, 25

a. Average weekly use was calculated as $7 \times$ (total tablets of rescue medication during Maintenance/Number of days in Maintenance). Average weekly use in other maintenance intervals is calculated correspondingly.

Reference: Section 14.2 Table 11.3.2

Safety Results

See more detailed review of safety data reported in this study in ISS.

- No deaths were reported during titration and maintenance phases. Three patients during the Titration Phase and nine patients during the Maintenance Phase (n=3 on placebo and n=6 on Kadian NT) experienced SAEs, such as hypotension, atrial fibrillation, chest pain, abdominal pain, tumors, etc. The most of them appear not treatment-related and resolved without discontinuation from the study.
- The common adverse events were associated with class effects of opioids.
- The following review is focusing the formulation-related safety observation: opiate withdrawal syndrome:

Extent of exposure:

Titration Phase: n=547 on open-label Kadian NT treatment

- Starting daily dose: 20-120 mg with a mean 25.3 mg
- Final daily dose: 20-160 mg with a mean of 43.5 mg
- Mean duration of titration: 1-77 days with a mean of 19.6 days

Maintenance Phase:

The Applicant did not provide information of the daily dose of Kadian NT and duration of treatment in the report (main body and appendices). As per protocol, subjects should take the optimal dose from the Titration. The final daily dose from the end of titration was 20-160 mg/day with a mean of 43.5 mg, as shown in the above Titration Phase. The following exposure information was found in the report:

Total cumulative dose (mg):

- Placebo (n=165): 4238.2 ±3112.12
- Kadian NT (n=166): 4597.4 ±3172.58

Duration of exposure (mg):

- Placebo (n=173): 66.4 ±37.1
- Kadian NT (n=171): 74.2 ±33.7

COWS (clinical opiate withdrawal scales): The mean changes from the *randomization baseline* to week 12 in the COWS scores were presented based on the randomization dose levels (≤ 80 mg or > 80 mg morphine) of Kadian NT and showed comparable between Kadian NY and placebo groups (Table 13):

- Patients with dose ≤ 80 mg: -0.3 ± 1.18 (placebo) vs. -0.1 ± 0.87 (Kadian NT)
- Patients with dose > 80 mg: -0.1 ± 1.00 (placebo) vs. 0.2 ± 0.64 (Kadian NT)

**Table 13. Mean Change from Baseline to week 12 for COWS scores
(From the Applicant's Table 48 in Study ALO-KNT-301)**

Total Score	ALO - 01 Dose at Randomization ≤80 mg			
		Placebo N = 126		ALO - 01 N = 127
Visit Y Mean (SD)	N = 118	0.7 (1.34)	N = 125	0.5 (1.17)
Visit Y + 12 Weeks Mean (SD)	N = 67	0.4 (0.91)	N = 74	0.4 (0.97)
Δ from Visit Y to Visit Y + 12 Weeks Mean (SD)	N = 67	-0.3 (1.18)	N = 74	-0.1 (0.87)
	ALO - 01 Dose at Randomization >80 mg			
		Placebo N = 47		ALO - 01 N = 44
Visit Y Mean (SD)	N = 47	0.6 (1.15)	N = 44	0.4 (0.79)
Visit Y + 12 Weeks Mean (SD)	N = 23	0.5 (0.59)	N = 24	0.4 (0.65)
Δ from Visit Y to Visit Y + 12 Weeks Mean (SD)	N = 23	-0.1 (1.00)	N = 24	0.2 (0.64)

Reference: Section 14.3.5 Table 12.5.5

Three patients with COWS of ≥ 23 during the study:

- n=2 on placebo:
 - Subject 121-0016 was an opioid-experienced patient on 120 mg total daily dose at randomization, had COWS of 23 at week 2 of Maintenance Phase and discontinued from the study at week 6 due to LOE.
 - Subject 173-0004 was an opioid-naïve patient on 60 mg total daily dose at randomization, had COWS of 23 at week 1 and discontinued from the study at day 7 due to LOE.
- n=1 on Kadian NT
 - Subject 126-0026 was an opioid-naïve patients on 120 mg total daily dose at the randomization, had COWS of 28 at week 2, and discontinued from the study at day 52 due to withdrawal syndrome.

SOWS (Subjective opiate withdrawal scale): the mean change in the worst SOWS scores from baseline to days 4-6 (reported the most severe score):

- Patients with dose ≤ 80 mg: 4.6 ± 6.9 (placebo) vs. 4.4 ± 5.9 (Kadian NT)
- Patients with dose ≤ 80 mg: 5.4 ± 9.1 (placebo) vs. 3.8 ± 7.5 (Kadian NT)

SUMMARY

This was a randomized, double-blind, placebo-controlled trial (using randomized **withdrawal design**) trial in patients with moderate-to-severe pain due to osteoarthritis. The study protocol was reviewed under a Special Protocol Assessment (SPA); the final agreement on the protocol was reached between the Division and the Applicant on December 14, 2006. However, the Applicant made three amendments to the protocol, including changes to the statistical analysis plan during the study without concurrence from the Division.

A total 547 patients were enrolled and titrated with an open-label treatment of Kadian NT (20 mg to 80 mg BID) for up to six weeks. Patients with pre-specified analgesic response from the titration were randomized to placebo (n=173) or Kadian NT (n=171) groups and immediately entered the 12-week Maintenance treatment at the fixed dose (the effective dose from the titration). Following the maintenance phase, patients completed a 2-week tapering period with a post-treatment follow-up visit at the end of the taper.

The majority (75%) of patients were opioid-naïve (no opioids within the last 30 days) in both the titration and maintenance phases. Slightly more patients in the Kadian NT group took **“other analgesics and antipyretics”** than in the placebo group (21% vs. 16%), primarily acetaminophen (18% vs. 11%) during the maintenance phase.

Dropout rate during the 12-week maintenance phase was 43% in the placebo group and 36% in the Kadian NT group; the major reasons for dropouts were **“lack of efficacy”** (18.5% vs. 3.5%), **“adverse events”** (7.5% vs. 10.5%) and **“subject withdrew from study”** (6.9% vs. 8.8%).

Efficacy: Kadian NT treatment was statistically superior to placebo in the primary endpoint (the mean change in average pain intensity from baseline to week 12). The primary analysis was in the ITT population with BOCF imputation for dropouts; either the Screening Baseline (the end of washout) or the Randomization Baseline (end of titration) was used for BOCF, depending on the reason for dropout. The overall profile of other secondary efficacy endpoints was consistent with the primary endpoint analysis, including the continuous responder analysis (by defining dropouts as non-responders) and WOMAC Pain assessments. However, one of three sensitivity analyses (SPA-agreed) failed to support the primary analysis. The statistic review team confirmed the **Applicant’s primary analysis and commented that the failed sensitivity analysis was due** to high conservative imputation method for dropouts.

Safety: The overall safety profile of Kadian NT is consistent with other opioid products. No deaths occurred during the study and a few patients experienced serious adverse events, which were either resolved or ongoing (such as tumors) by the end of study. The overall profile of opiate withdrawal symptoms was comparable between Kadian NT and the placebo group. However, patients in the placebo group showed fewer withdrawal symptoms (based on the mean change of COWS score baseline to week 12) than those in

the Kadian NT group (Table 13), which is inconsistent with the fact “force tapered” for placebo patients from the Titration Phase to the Maintenance Phase.

CONCLUSION

Kadian NT (up to 80 mg BID) treatment appears statistically superior to placebo in the SPA-agreed primary endpoint and primary analysis, which was supported by the SPA-agreed secondary endpoints and secondary analyses (sensitivity analysis and responder analysis).

Kadian NT treatment was comparable to placebo in the overall profile of opiate withdrawal symptoms assessed during the 12-week double-blind maintenance phase. However, the majority of patients in this study were opiate-naïve (>75%) and all patients were titrated before randomized to the 12-week maintenance phase. The opiate withdrawal syndrome data collected from the maintenance phase have very limited value to assess precipitation of opiate withdrawal syndrome associated with naltrexone release from Kadian NT capsules.

Comments and Clarifications

The following questions were sent to the sponsor by an email on Oct 21, 2008, which were appropriately addressed by the sponsor

1. Why are the primary analysis results in Table 20 (Table 11.4.2.1) different from the results from Week 12 in Table 11.4.4.1 (Fig 2)? ITT population with imputation method 1 was used for both tables.
2. The study population was OA patients (as one of inclusion criteria); why only 3.5% patients on the placebo group and 8.2% patients in Kadian NT group were OA in Table 16 (p78)?
3. In completer population (Tables 11.4.5.1-3), placebo n=98, Kadian NT n=109 at week 12, but why was completer n=110 for Kadian NT in Table 12.
4. Why were imputation methods used for completer population analysis (e.g. p92, 3rd paragraph)?
5. Were safety data from the post-treatment follow-up reported?
6. ITT population was n=173 on placebo and n=170 on Kadian NT, as shown in Table 13; why were n=171 on Kadian NT for all ITT analyses?
7. How were dropouts imputed for the In-Clinic BPI analysis in Table 11.4.8 (Fig 3)?

9.4.2 Study ALO-KNT-202

A Phase II Multi-dose, Double-blind, Crossover Study to Assess the Safety, Efficacy, and Pharmacokinetics of Kadian NT (Morphine Sulfate Plus Naltrexone Hydrochloride Extended-release Capsules) in Subjects with Chronic Pain Due to Osteoarthritis of the Hip or Knee

STUDY OBJECTIVES

Primary: To characterize and assess the PK of Kadian NT following multiple doses in subjects with chronic pain due to OA of the hip or knee.

Secondary: To assess the safety and efficacy of Kadian NT following multiple doses in subjects with chronic pain due to OA of the hip or knee.

STUDY DESIGN

This was a Phase II, multi-center, randomized, active-controlled, double-blind, cross-over study in subjects with chronic pain due to OA of the hip or knee.

Crossover the following five distinct treatment periods:

- Period 1 for titration with Kadian
- Period 2 to be randomized to double-blind treatment with Kadian or Kadian NT
- Period 3 to receive open-label Kadian only
- Period 4 for crossover to alternate medication of Period 2
- Period 5 to receive open-label Kadian only

Study procedure (Table 1):

Screening: washout of all pain medication, acetaminophen (up to 2 g/day as a rescue medication), patients with flaring pain intensity ≥ 5 on 11-point numerical rating scale (NRS) with completed baseline visit were enrolled to Day 1 of Period 1.

Period 1 (Kadian titration): Subjects were to have started with 20 mg Kadian (bid) and titrated weekly up or down; the maximum allowable dose was to have been 160 mg bid. **The subjects were considered “stabilized” on a Kadian dose within 28 days when:**

- pain intensity score ≤ 3 on 11-point NRS
- on the same BID dose for four consecutive days with no unacceptable AEs

Period 2 (randomization): the “stabilized” subjects from Period 1 were to have been randomized to two groups and received Kadian or Kadian NT for 14 days on the stabilized dose established from Period 1. Blood samples were to have been taken on day 7 and day 14 for PK assessment.

Period 3 (open-label Kadian): patients from Period 3 received Kadian BID (on the stabilized dose from Period 1) for seven days.

Table 1. Schedule of Assessment
(From the Applicant's Table 9-2 in study ALO-KNT-202)

	Screening	Washout	Period 1 Titration to Open-Label Kadian		Period 2 Blinded Kadian or Kadian NT (14 D)			Period 3 Open-label Kadian (7 [± 1] D)	Period 4 Crossover to Blinded Kadian or Kadian NT (14 D)			Period 5		Follow Up Telephone Call
			BL Day	7 (± 1) to 28 (-1) Days Weekly (1 - 4 visits) ^a	D 1 (± 1)	D 7 (± 1)	D 14 (± 1)		D 1 (± 1)	D 7 (± 1)	D 14 (± 1)	Open-Label Kadian (7 [± 1] D)	Day 7 (± 2) or Early Term.	
Informed consent	X													
Inclusion/exclusion	X		X											
Washout of previous pain medication(s)		X												
Medical history	X													
Chronic pain history	X													
12-lead ECG	X												X	
Drug and alcohol screen	X		X											
Physical examination	X												X	
Height and BMI	X													
Vital signs	X		X	X	X	X	X		X	X	X		X	
Body weight	X													
Clinical laboratory tests	X		X		X		X		X		X		X	
Urine pregnancy test	X		X										X	
Dispense daily diary			X	X	X		X		X		X			
Dispense rescue meds ^b	X		X	X	X	X	X		X	X	X			
Dispense/Re-dispense study drug				X	X	X	X		X	X	X			
Review daily diary				X	X	X	X		X	X	X		X	
Collect study drug					X	X	X		X	X	X		X	
Adverse events				X	X	X	X		X	X	X		X	
Concomitant medications			X	X	X	X	X		X	X	X		X	
Trough PK blood sample					X	X	X		X	X	X		X	

Continued

	Screening	Washout	Period 1 Titration to Open-Label Kadian		Period 2 Blinded Kadian or Kadian NT (14 D)			Period 3 Open-label Kadian (7 [± 1] D)	Period 4 Crossover to Blinded Kadian or Kadian NT (14 D)			Period 5		Follow Up Telephone Call
			BL Day	7 (± 1) to 28 (-1) Days Weekly (1 - 4 visits) ^a	D 1 (± 1)	D 7 (± 1)	D 14 (± 1)		D 1 (± 1)	D 7 (± 1)	D 14 (± 1)	Open-Label Kadian (7 [± 1] D)	Day 7 (± 2) or Early Term.	
12-hour PK blood sample ^c	Day -14 to -5	Day -7 to -4					X				X			
WOMAC Osteoarthritis Index ^d				X			X				X			
In-clinic pain intensity			X	X	X	X	X		X	X	X		X	
Global assessment of study medication							X				X			
Telephone calls		X ^{e,f}												X ^g

Abbreviations: BL = Baseline, BMI = body mass index, D = day(s), ECG = electrocardiogram; PK = pharmacokinetic, Term. = Termination

a Weekly visits until subject stabilized.

b Rescue medication was dispensed as needed.

c Blood samples for PK analysis were drawn pre-dose and at 1, 3, 4, 5, 6, 8, 10, and 12 hours post dose.

d Western Ontario and MacMaster Universities (WOMAC) Osteoarthritis Index will only be completed by subjects on the last visit of every treatment period and/or at the early termination visit.

e The subject may begin washout after the screening visit procedures are completed (this may require a telephone call to the subject).

f Once the subject feels they have experienced flare, the subject was instructed to contact the clinic site and schedule a clinic visit.

g Adverse events and subject pain were assessed by telephone 7 days after the end of Period 5.

Period 4 (crossover): subjects randomized/designated in Period 2 were to have been switched from Kadian to the alternate medication for 14 days, with the same dosing regimen as used in Period 2. Blood samples were to have been taken on day 7 and day 14 for PK assessment.

Period 5 (open-label Kadian): subjects received open-label Kadian at the stabilized dose (from period 1) for seven days.

Treatment

Kadian and Kadian NT were provided in the form of capsules and orally administered as a BID dose (q12-hr), from initial dose of 20 mg bid to the maximum allowable dose of 160 mg BID (320 mg/day). Subjects were randomly assigned to one of two treatment sequences:

- Sequence 1: Kadian in Period 2 and Kadian NT in Period 4
- Sequence 2: Kadian NT in Period 2 and Kadian in Period 4.

Study Subject

Approximately 60 patients who met the following criteria were to have been enrolled to the study and at least 50 subjects were expected to complete the study:

Key inclusion criteria

- 1) 21 years of age, males/females
- 2) Generally good health at the screening visit
- 3) Primary diagnosis of Functional Class I-III OA of the hip or knee and ACR clinical classification criteria for OA of the hip and knee
- 4) Required treatment of target joint pain within the last 90 days and met at least one of the following criteria:
 - Was unable to consistently control target joint pain with non-opioid analgesics, OR
 - had received chronic opioid treatment (single or combination product) for target joint pain, with the equivalent of \leq 40 mg/day of oral morphine sulfate, inclusive of breakthrough pain medication.
- 5) Pain intensity score \geq 5 on 11-point NRS following washout period.

Key exclusion criteria

- 1) had a documented history of drug abuse/dependence/misuse or narcotic analgesic abuse/dependence/misuse within five years prior to screening.
- 2) was unable to discontinue all formulations of prior analgesics (opioid and/or non-opioid) during the washout period of the study.
- 3) had a primary diagnosis of Functional Class IV OA.
- 4) had a documented history of prior disease (other than OA) and/or surgery at the target joint within the last year prior to enrollment.

- 5) had any chronic pain syndrome (i.e., fibromyalgia) that, in the investigator's opinion, would interfere with the assessment of pain and/or other symptoms of OA.
- 6) had received recent epidural or local corticosteroid injections in target joint within two months of screening, or target joint viscosupplementation within the past three months.

Outcome measures

Efficacy:

- Pain intensity:
 - Clinical visits: average pain within last 24 hours was rated on an 11-point NRS (0= no pain and 10 = worst pain)
 - Daily diary: worst, least, average and right now pain in the last 24 hours on 11-point BPI (Brief Pain Inventory)
- WOMAC index: Pain, Stiffness and Physical Function on 100-mm VAS during the 48 hours at the end of Periods 1, 2, and 4; the composite score was equal to the sum of the three subscales.
- **Patient's global assessment: at the end of treatment** (day 14) of Periods 2 and 4 on 5-point scale
- Rescue medication for breakthrough pain: at each visit for Periods 1, 2, 4 and 5 for usage of acetaminophen.

Safety:

- AE; monitoring of withdrawal symptoms were not planned and specified.
- Physical examination: at screening and day 7 visits on Period 5 or early termination.
- Vital signs: at each visit
- Clinical laboratory: hematology, blood chemistry, urinalysis at Screening, Baseline, Period 2 (day 1), Period 2 (day 14), Period 4 (day 1), Period 4 (day 14) and Period 5 (day 7 or early termination).
- ECG: 12-lead ECG at screening and Period 5 (day 7 or early termination)

PK: Basic PK parameters of morphine, naltrexone and 6- β -naltrexol

Statistical analysis plan

Sample size:

The sample size of 50 subjects who were expected to complete the study:

- 90% power to demonstrate bioequivalence for morphine between Kadian and Kadian NT.
- 90% power to detect a difference of 1 point in mean pain on an 11-point NRS between Kadian and Kadian NT groups, assuming $\alpha=0.05$ and the within-subject SD of 1.5.

Analysis population:

- ITT population: all randomized subjects who received at least one dose or portion of a dose of double-blind Kadian or Kadian NT and for whom at least one efficacy observation is obtained after Period 2, Day 1.
- Completer population: all randomization subjects who completed both Period 2 and Period 4.
- Safety population: all subjects who receive at least one dose or portion of a dose of Kadian or Kadian NT.

Efficacy analysis:

- Only for Periods 2 and 4 (randomized, double-blind treatment)
- Performed on the ITT population and Completer population
- Change from baseline to the end of treatment (Day 14) of Periods 2 and 4
 - Pain intensity (in-clinic pain): baseline at Day 1 of Period 2
 - WOMAC Index: baseline at last day of Period 1
- Analysis: using a mixed linear model for a two-period crossover, including fixed effect terms for treatment, period, and sequence, with a random effect for subject nested within sequence, with Day 0 and Period 2/Day 1 in-clinic pain as covariates.
- LOCF (the last observation carried forward) imputation for missing data

RESULTS

Disposition of subjects

Of a total of 167 patients screened, 113 were enrolled and 72 entered the double-blind treatment periods (Periods 2 and 4) (Table 2):

- N=35 on Kadian to Kadian NT (Sequence 1)
 - N=32 completers
 - N=3 dropouts due to AE (n=1) and non-compliance (n=2)
- N=37 on Kadian NT to Kadian (Sequence 2)
 - N=34 completers
 - N=3 dropouts due to AE (n=1) and non-compliance (n=2)

**Table 2. Analysis population
(From the Applicant's Table 11-1 in Study ALO-KNT-202)**

	Not Randomized	Sequence 1 Kadian to Kadian NT	Sequence 2 Kadian NT to Kadian	Total
Enrolled Patients	41	35	37	113
Safety Population	39	35	37	111
Randomized Patients		35	37	72
ITT Population		35	37	72
Completer Population		32	34	66
PK-BE Population		33	34	67

Source of data: Section 14.1, Table 1

Abbreviations: ITT = intent-to-treat, PK-BE = pharmacokinetic-bioequivalence

Demographics

Overall, the demographics of ITT population were comparable between sequences 1 and 2 except the following differences in the sequence 2 group (vs. sequence 1):

- slightly higher proportion of male subjects (32% vs. 29%)
- slightly higher proportion of black subjects (11% vs. 6%)
- slightly lower proportion of Caucasian subjects (89% vs. 94%)
- information of opiate status (opiate-naïve or opiate-experienced) was not provided in both the study report and appendix.

Baseline characteristics

Overall, mean baseline characteristics (pain intensity and WOMAC index) were comparable between two treatment sequences.

Prior medications and concomitant medications

Overall, no remarkable differences in prior medications and in concomitant medications between treatment sequences.

Extent of exposure

The final titrated doses were similar in safety, ITT and completer populations, as summarized below (based on the Applicant's summary from safety population):

- 60 mg BID:
 - 28.6% in Sequence 1
 - 21.6% in Sequence 2
- 80 mg BID
 - 11.4% in Sequence 1
 - 16.2% in sequence 2

The mean duration of exposure during the periods 2 and 4 was 13.8 to 14.4 days.

Efficacy evaluation

In-clinic pain: the mean changes in pain intensity from baseline to Day 7 or Day 14 were not statistically different between Kadian and Kadian NT (Table 3):

Day 7:

Kadian (n=71): 0.2 ±1.15
Kadian NT (n=70): 0.0 ±1.36 (p=0.692 vs. Kadian)

Day 14:

Kadian (n=71): 0.3 ±1.26
Kadian NT (n=70): 0.1 ±1.51 (p=0.308 vs. Kadian)

Table 3. Comparison of in-clinic pain intensity between Kadian and Kadian NT in ITT Population (From the Applicant's Table 11-5)

Statistic	-----Kadian-----		-----Kadian NT-----		Treatment	p-value ^e Treatment		
	Baseline ^a	Observed ^b	CFB ^c	Observed ^b	CFB ^c		Difference ^d	
Day 7								
N	71	71	70	70	69	69	0.6919	
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 ^a								(-0.27, 0.41)
Day 14								
N		71	70	71	70	70	0.3079	
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 ^a								(-0.54, 0.17)

Source of data: Section 14.2.2, Table 14.1

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 subject 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 (Kadian NT – Kadian) was calculated on an individual subject 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 Kadian NT.
- e ANOVA model with CFB as response; Sequence, Period, and Treatment as fixed effects; Subject within Sequence as random effect; Day 0 and Baseline in-clinic pain as covariates.

Diary Pain: the mean changes from baseline (last day of Period 1) to Day 14 in *worst*, *least*, *average*, and *current* pain (BPI diary pain score) were slightly smaller in Kadian NT treatment than in Kadian treatment, although there was no statistically significance (Table 4).

Time-course of mean changes of diary pain intensity... (Applicant's Table 16.1)

WOMAC Index: the mean changes in three WOMAC subscales (Pain, Stiffness and Physical Function) and composite score were smaller in Kadian NT treatment than in Kadian treatment (Table 5). The variations (SD) were very high in all measures (3-14 times mean); only a statistically significance was shown for Stiffness (p=0.022).

Subject's global assessment of study medication: over all, 91.5% subjects rated the study medication as at least good (good, very good or excellent) during Kadian NT treatment compared with 78.9% subjects during Kadian treatment.

Rescue medication: the majority of subjects used rescue medication during the double-blind treatment periods for both study medications and slightly higher proportion of subjects during Kadian treatment (57.7%) than during Kadian NT treatment (50.7%).

**Table 4. Mean change in diary pain intensity from baseline to Day 14
(From the Applicant's Table 11-6 in Study ALO-KNT-202)**

Time point	-----Kadian-----		-----Kadian NT---		Treatment	p-value*	
Statistic	Baseline ^a	Observed ^b	CFB ^c	Observed ^b	CFB ^c	Difference ^d	Treatment ^e
Sum of Worst Pain							
N	72	70	70	70	70	69	0.5667
Mean	3.2	44.6	1.2	43.6	0.0	-0.9	
SD	1.61	23.37	17.68	24.69	17.99	13.68	
Minimum	1	2	-70	0	-42	-36	
Median	3.0	42.0	0.0	42.0	2.0	0.0	
Maximum	7	100	52	109	48	40	
95% CI ^e						(-4.26, 2.35)	
Sum of Least Pain							
N	72	70	70	70	70	69	0.2492
Mean	1.6	22.0	0.6	20.7	-0.9	-1.4	
SD	1.16	17.43	14.46	16.53	14.98	10.06	
Minimum	0	0	-28	0	-34	-28	
Median	2.0	19.0	0.0	19.5	0.0	0.0	
Maximum	6	74	46	73	45	26	
95% CI ^e						(-3.84, 1.01)	
Sum of Average Pain							
N	72	70	70	70	70	69	0.2551
Mean	2.2	31.0	1.2	29.6	-0.2	-1.4	
SD	1.24	17.90	13.01	16.83	12.40	10.07	
Minimum	0	0	-28	0	-41	-27	
Median	2.0	30.0	0.5	30.0	1.0	0.0	
Maximum	6	81	39	73	23	18	
95% CI ^e						(-3.82, 1.03)	
Sum of Current Pain							
N	72	70	70	70	70	69	0.7724
Mean	2.1	28.1	-0.5	27.6	-1.0	-0.5	
SD	1.52	18.58	17.87	19.26	18.08	12.84	
Minimum	0	0	-70	0	-53	-31	
Median	2.0	28.0	0.0	28.5	0.0	0.0	
Maximum	6	79	50	80	48	39	
95% CI ^e						(-3.54, 2.64)	

Source of data: Section 14.2.2, Table 15.1

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

- Baseline is the last day of Period 1.
- Higher scores indicate greater severity of symptoms.
- CFB = the observed value at the current time point - the observed value at baseline. CFB was calculated on an individual subject 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.
- Treatment difference (Kadian NT - Kadian) was calculated on an individual subject 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 Kadian NT.
- ANOVA model with CFB as response; Sequence, Period, and Treatment as fixed effects; Subject within Sequence as random effect; Baseline value as the covariate.

**Table 5. Mean change in WOMAC Index from baseline to Day 14
(From the Applicant's Table 11-6 in Study ALO-KNT-202)**

Subscale	Kadian		Kadian NT		Treatment Difference ^d	p-value ^e Treatment ^t	
	Baseline ^a	Observed ^b	CFB ^c	Observed ^b			CFB ^c
Pain Subscale							
N	72	69	69	70	70	69	0.0956
Mean	98.6	116.2	18.1	104.8	5.8	-12.1	
SD	58.23	75.16	77.03	76.35	73.50	58.69	
Minimum	3	9	-184	0	-232	-242	
Median	94.0	116.0	15.0	98.5	1.0	-5.0	
Maximum	232	319	263	343	259	118	
95% CI ^e							(-25.90, 2.15)
Stiffness Subscale							
N	72	69	69	70	70	69	0.0219 ^f
Mean	51.0	63.4	12.3	53.7	2.5	-10.1	
SD	32.74	41.75	38.05	40.46	35.10	35.04	
Minimum	0	0	-66	0	-77	-107	
Median	46.5	60.0	4.0	45.5	1.0	-3.0	
Maximum	127	163	119	157	134	92	
95% CI ^e							(-18.41, -1.49)
Physical Function Subscale							
N	72	68	68	70	70	68	0.1570
Mean	399.7	461.5	68.9	430.5	31.7	-39.3	
SD	227.65	297.73	240.83	298.27	218.34	220.67	
Minimum	14	18	-356	1	-605	-856	
Median	380.0	425.0	37.5	398.0	31.0	5.9	
Maximum	1095	1224	851	1204	791	403	
95% CI ^e							(-90.59, 14.93)
Composite Index							
N	72	68	68	70	70	68	0.1041
Mean	549.3	638.7	98.4	589.1	40.0	-60.5	
SD	292.85	399.59	335.86	402.58	303.72	297.59	
Minimum	39	50	-505	1	-745	-1E3	
Median	524.5	591.5	52.5	537.0	33.5	4.5	
Maximum	1355	1678	1189	1703	1184	533	
95% CI ^e							(-130.28, 12.46)

Source of data: Section 14.2.2, Table 17.1

Abbreviations: ANOVA = analysis of variance; CI = Confidence interval; CFB = Change from baseline; ITT = intent-to-treat; SD = standard deviation; WOMAC = Western Ontario and MacMaster Universities.

- a Baseline is the last day of Period 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 subject 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 (Kadian NT - Kadian) was calculated on an individual subject 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 Kadian NT.
- e ANOVA model with CFB as response; Sequence, Period, and Treatment as fixed effects; Subject within Sequence as random effect; Baseline value as the covariate.
- f p-value is statistically significant (≤ 0.0500).

PK analysis

See the PK review for details.

Morphine: Kadian NT was bioequivalent to Kadian in AUC but with slight higher C_{max} than Kadian.

- The 95% CI for the AUC₀₋₁₂ of Kadian/AUC₀₋₁₂ of Kadian NT was 0.824 to 1.069, and thus demonstrated bioequivalence limited to the extent of exposure at steady state for Kadian NT and Kadian.
- The mean steady state C_{max} of morphine was approximately 12% greater for Kadian NT treatment compared with Kadian treatment.

Naltrexone: Only 7/67 subjects during Kadian NT treatment and 1/67 subjects during Kadian treatment had a sufficient number of time points with detectable naltrexone concentrations to estimate an AUC. Pharmacokinetic parameters for these subjects were:

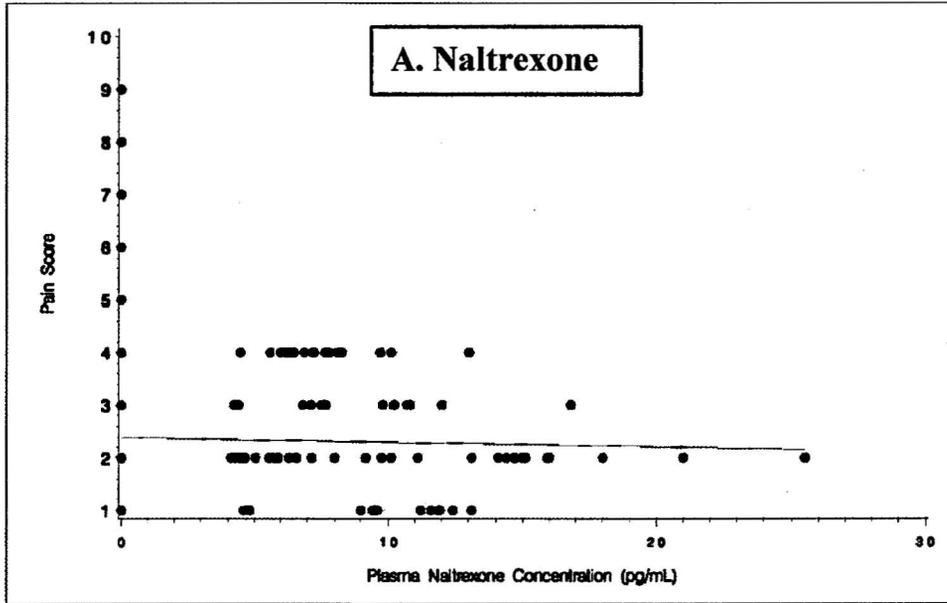
- The mean AUC₀₋₁₂ of naltrexone:
 - 106.8 pg.h/mL (± 48.79 pg.h/mL) for Kadian NT treatment
 - 99.9 pg.h/mL for one subject during Kadian treatment
- The mean C_{max} of naltrexone:
 - 12.0 pg/mL (± 5.25 pg/mL) for Kadian NT treatment
 - 13.0 pg/mL for one subject during Kadian treatment
- The median t_{max} of naltrexone:
 - 1.0 hours (range, 0.0 hours to 10.0 hours) for Kadian NT treatment
 - 3.0 hours for one subject during Kadian treatment

6-β-naltrexol: A total of 55/67 subjects during Kadian NT treatment and 7/67 subjects during Kadian treatment had a sufficient number of time points with detectable 6-β-naltrexol concentrations to estimate an AUC. Pharmacokinetic parameters for these subjects were:

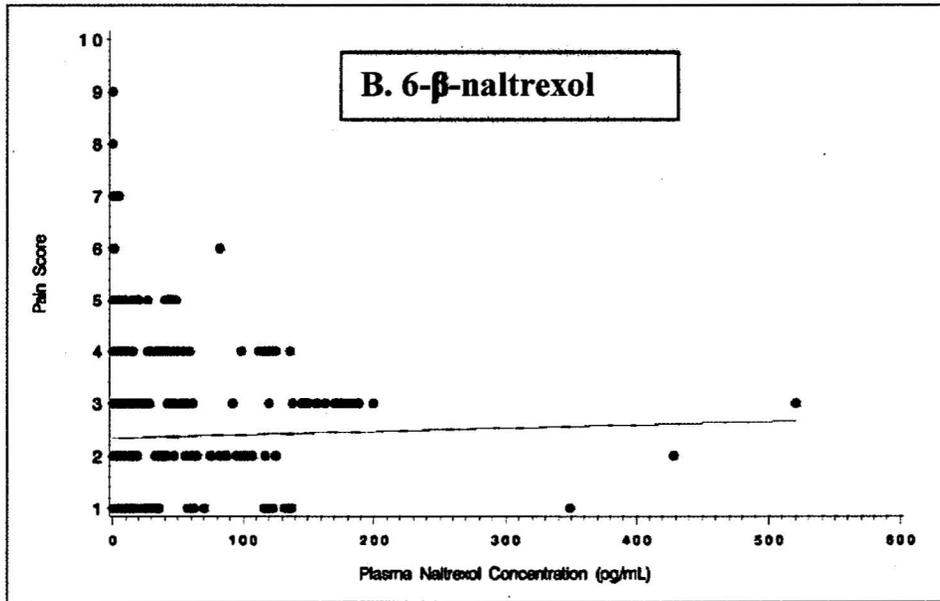
- The mean AUC₀₋₁₂ of 6-β-naltrexol
 - 308.6 pg.h/mL (± 470.96 pg.h/mL) for Kadian NT treatment
 - 40.7 pg.h/mL (± 67.43 pg.h/mL) for Kadian treatment
- The mean C_{max} of 6-β-naltrexol
 - 31.3 pg/mL (± 45.83 pg/mL) for Kadian NT treatment
 - 5.3 pg/mL (± 7.58 pg/mL) for Kadian treatment
- The median t_{max} of 6-β-naltrexol:
 - 3.0 hours (range, 0.0 hours to 12.0 hours) for Kadian NT treatment
 - 4.0 hours (range, 0.0 hours to 12.0 hours) for Kadian treatment

Naltrexone and 6-β-naltrexol Concentrations vs. Pain Scores:

Comparisons of the detectable naltrexone and/or 6-β-naltrexol concentrations with the time-matched pain score showed that there was no correlation of pain scores to naltrexone (Figure 1A) but slight correlation to 6-β-naltrexol (Figure 1B).



Source of data: Section 14.2.1, Ad Hoc Figure 2.



Source of data: Section 14.2.1, Ad Hoc Figure 1.

Figure 1. Correlation of naltrexone (A) or 6-β-naltrexol (B) concentration in plasma with the time-matched pain intensity score. (From the Applicant's Figure 11-4 and Figure 11-5 in Study ALO-KNT-202).

SUMMARY/CONCLUSION OF EFFICACY:

Kadian NT appears comparable to Kadian in analgesic effects in OA patients treated at similar doses for two weeks. However, the efficacy assessment was not a primary objective for this study and the crossover design may confound the comparability between Kadian NT and Kadian due to potential carry-over effects.

Plasma naltrexone and 6- β -naltrexol were detectable in some subjects and apparently the plasma level was not correlated with changes in analgesic response to Kadian NT.

9.4.3 Study ALO-KNT-302

A Long-Term, Open-Label Safety Study of ALO-01 (Morphine Sulfate Plus Naltrexone Hydrochloride Extended-Release) Capsules in Subjects With Chronic Moderate to Severe Nonmalignant Pain

Study location: 58 sites in US

Study period: Dec 07, 2006 to March 07, 2008

Study objective:

Primary: To evaluate the long-term safety of ALO-01 administered for up to 12 months

Secondary:

- 1) To evaluate the long-term efficacy of ALO-01 during a 12-month period by assessing pain intensity (PI) in the last 24 hours using the Brief Pain Inventory (BPI) Short Form, the Global Assessment of Study Drug and use of rescue medication (acetaminophen) for break-through pain
- 2) To evaluate opioid withdrawal symptoms in subjects who receive ALO-01 upon completion of 12 months exposure or early termination from the study using the Clinical Opiate Withdrawal Scale (COWS),
- 3) To evaluate plasma naltrexone, 6- β -naltrexol, and morphine concentrations at Visits 2 through 15 in selected male and female subjects for sparse pharmacokinetic (PK) sampling

Study design:

This was an open-label, 12-month treatment (Kadian NT qd or bid) trial in patients with moderate to severe nonmalignant pain.

There were 15 in-treatment visits and one post-treatment follow-up visit (2-32 days after the final dose). The in-treatment visits were monthly except visit 2 which was one week after the baseline visit (visit 1).

The schedule of visit and assessments are presented in Table 1.

Table 1. Schedule of Assessment
(From the Applicant's Table 3 in the Study ALO-KNT-302 report)

Evaluation	Visit 1 Baseline Day -7 to Day 0	Drug Dispensing Visit Day 0	Visits 2-3 End of Wks 1 & 4 (±2 days)	Unscheduled Visits ^{1,2} Dose Adjust/ Tx of AEs	Visits 4-14 End of Months 2-11 Wks 8 – 48 (±3 days)	Visit 15 End of Month 12 (Wk 52)/Early Termination (±3 days)	Follow-up Telephone Call Opioid Withdrawal Monitoring (Days 1-4) ³	Visit 16 ⁴ Post Treatment Follow-up
Written Informed Consent	X							
Inclusion/Exclusion Criteria	X							
Vital Signs ⁵	X		X	X	X	X		
Height, Weight, and body mass index	X							
Complete Physical Exam	X				X ⁶	X		
Chronic Pain History	X							
Medical History	X							
12-lead Electrocardiogram	X				X ⁶	X		
Clinical Laboratory Tests ⁷	X				X ⁸	X		
Pharmacokinetic Sampling ⁹			X		X	X		
Urine Drug Screen	X		X ¹⁰	X ¹⁰	X ¹⁰	X ¹⁰		
Urine Pregnancy Test ¹¹	X		X ¹²	X	X	X		
Clinical Pain Intensity	X		X	X	X	X		
Clinic Global Assessment of Study Drug			X		X	X		
Dispense Study drug		X	X	X	X			
Study/Rescue Drug Accountability			X	X	X	X		
Clinical Opiate Withdrawal Scale			X ¹²	X	X	X		X
Concomitant Medications	X		X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X

1. Assess subject's current pain intensity at unscheduled visits for inadequate pain relief (to enter in IWRS).
2. A subject converting from another opioid to ALO-01 could return in ≥24 hours of the Drug Dispensing Visit for an unscheduled visit for a dose increment if the initial dose conversion leads to inadequate pain relief. In addition, if a subject who converted from another opioid experiences symptoms of opioid withdrawal after dose conversion, Alpharma/ INC Research was contacted for approval to allow the subject to return in <24 hours of the Baseline Visit for a dose increase, if necessary. All other visits for dose increases could only occur if a subject had been on current dose for ≥3 days.
3. Subjects were to be converted to approved extended-release opioid or tapered per Investigator discretion. If necessary, a clinic visit was scheduled for subjects experiencing clinically significant symptoms of opioid withdrawal.
4. Visit 16 to be conducted 28 to 32 days after the last dose of study medication.
5. Vital signs included heart rate, respiratory rate, blood pressure after sitting for 3 minutes, and oral temperature.
6. Completed at Visit 8/Month 6 only.
7. Included chemistry, hematology, and urinalysis.
8. Completed at Visits 5, 8, and 11 (End of Months 3, 6, and 9) only.
9. For subjects in the PK population only.
10. Included reflex testing to identify specific opiates used.
11. For women of child-bearing potential.
12. Completed at Visit 3 only.

Treatment

- Dosing regimen:
 - Opioid naïve: started 20 mg bid
 - Opioid experienced: converted the current opioid dose to starting dose equivalent to 50-75% of current opioid requirements.
- Dose titration up or down was allowed throughout the duration of the study. Patients could be dosed either qd or bid based on their individual tolerability.
- No maximum allowable daily dose was set during the study.
- Tapering at end of treatment: to take half of last effective dose in divided doses of Kadian (BID) for 3 days, and then to take half of that reduced dose in divided doses (BID) for the next 3 days; on the seventh day, all dosing was to be discontinued. Alternatively, some subjects converted to currently approved extended release opioids, at the discretion of the Investigator.

Study subject:

Approximately 400 subjects met the following criteria were to be enrolled to achieve goals of 100 subjects retained for 6 months and 50 retained for the entire 12-month study.

Key inclusion criteria

- 1) Males and females between 18 and 70 years of age
- 2) History of chronic moderate to severe pain caused by a nonmalignant condition for at least 3 months, including (but not limited to) osteoarthritis of any joint, chronic low back pain with or without radiculopathy, diabetic peripheral neuropathy, and post-herpetic neuralgia.
- 3) Subject agreed to refrain from taking any opioid medications other than study drug during the study period.

Key exclusion criteria

- 1) Documented history of drug abuse/dependence/misuse or narcotic analgesic abuse/dependence/misuse within 5 years prior to the Baseline Visit.
- 2) Clinically significant abnormalities in clinical chemistry, hematology or urinalysis.
- 3) Pain in the target area due to conditions such as malignancy, fibromyalgia, migraine, recent trauma or fracture, or infection.
- 4) History of severe impairment of pulmonary function, hypercarbia, hypoxia, chronic obstructive pulmonary disease, cor pulmonale, uncontrolled asthma, sleep apnea syndrome, or respiratory depression.

Safety evaluation:

- Treatment-emergent adverse events (TEAEs)
- Vital signs (all visits); physical examination and 12-lead ECG (Visits 1, 5 and 15 or early termination)

- Clinical laboratory tests (hematology, chemistry and urinalysis) (Visits 5, 8, 11 and 15 or at early termination)
- Qualitative urine drug screens (monthly), including alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, methamphetamines, opiates, phencyclidine (PCP), tetrahydrocannabinol (THC).
- Opiate withdrawal symptoms assessed by Clinical Opiate Withdrawal Scale (COWS: an 11-item opiate withdrawal signs and symptoms) (all Visits 3 to 16, or at early termination)
 - The total COWS score summarized by visit and by average daily dose range.
 - The total COWS score at the final treatment visit, either Visit 15 or early termination
 - Actual values, values for subjects at Visit 3, and change from the first evaluation (Visit 3) were summarized at each time point.

PK evaluation

Sparse blood samples were collected (prior to dosing or trough) from pre-determined subset of subjects at Visits 2-15 (monthly after the Baseline Visit) for plasma naltrexone, 6- β -naltrexol and morphine.

A total of 93 subjects were selected from 34 study sites to participate in the PK sample collection, with approximately 20 subjects each from three daily dosing groups (20-60 mg, 80-120 mg, and >120 mg) and one age group (≥ 65 years).

Individual and mean plasma morphine, naltrexone, and 6- β -naltrexol concentrations were presented in tabular and graphical format for all blood sampling time points.

Efficacy evaluation (ITT Population)

- Pain intensity using the BPI Short Form questionnaire
- Global Assessment of Study Drug
- the use of rescue medication (acetaminophen)

Disposition of subjects

A total of 467 subjects were enrolled and 465 received at least one dose of study drug. Overall dropout rate was 65.7% (n=307 of 467). The most common reason for dropout was due to AE (23.7%) (Figure 1 and Table 2)

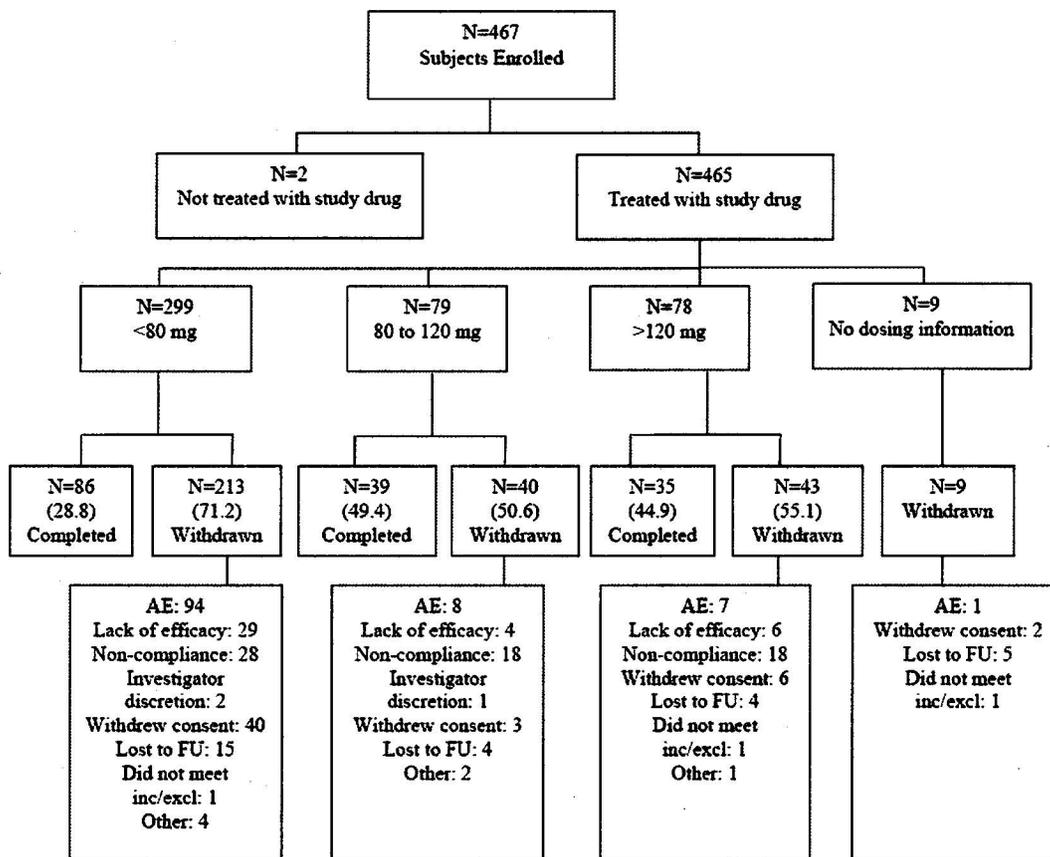
Of these 465 subjects, 208 (44.7%) completed 6 months and 160 (34.4%) completed 12 months.

Disposition by daily dosing group:

- The percentage of dropouts was highest in the <80 mg dose group, intermediate in the >120 mg dose group and lowest in the 80-120 mg dose group (Figure 1).

- The <80 mg dose group had a higher incidence of adverse events and lack of efficacy than the 80-120 mg and >120 mg dose groups.

Figure 1. Disposition of Subjects by Daily Dosing Level
(From the Applicant's Figure 1 in the Study ALO-KNT-302 report)



Note: Study completers were defined as those subjects with a positive response for 'Did the subject complete study?' on End of Study CRF.

Reference: Section 14 Table 1.1 and Section 16.2.1 Listing 1

Table 2. Subject Disposition
(From the Applicant's Table 4 in the Study ALO-KNT-302 report)

	Overall
Subjects Enrolled	467
Subjects who received study drug	465 ^a
Subjects completed	160
Discontinuations from Study	307 (65.7)
Reasons for Discontinuation	
Adverse Event ^b	110 (23.7)
Lack of Efficacy	39 (8.4)
Non Compliance	64 (13.7)
Investigator's Discretion	3 (0.6)
Subject withdrew from study	52 (11.1)
Lost to follow-up	28 (6.0)
Did not meet inclusion/exclusion criteria	4 (0.9)
Other reason	7 (1.5)

a. There were 2 subjects who were not treated with study drug.

b. Listing 15.2 erroneously included Subject 260-2012 as an AE leading to study drug discontinuation; however, this subject actually completed study.

Note: Other reasons for discontinuation included positive urine drug screens for prohibited substances, family illness, negative urine drug screens for study drug, sponsor decision in light of subject's medical condition, travel, lack of efficacy and sedation, and relocation.

Reference: Section 14.1, Table 1.1 and Table 1.2

Disposition by opioid status: Of the 465 subjects treated, 246 were opioid-naïve and 219 were opioid-experienced (Table 3). Overall dropout rate was comparable between opioid naïve (63%) and opioid-experienced subjects (64%).

**Table 3. Disposition of subjects by Opioid experience and daily dosing level
(From the Applicant's Study ALO-KNT-302 report)**

	Opioid-Naïve N = 246 n (%)			Opioid-Experienced N = 219 n (%)		
	<80 mg	80-120 mg	>120 mg	<80 mg	80-120 mg	>120 mg
Subjects Enrolled	177	34	31	122	45	47
Subjects Treated	177	34	31	122	45	47
Subjects Completed	55	18	13	31	21	22
Discontinuations from Study	122	16	18	91	24	25
Reasons for Discontinuation						
Adverse Event	59	5	2	35	3	5
Lack of Efficacy	11	0	2	18	4	4
Non Compliance	15	7	6	13	11	12
Investigator's Discretion	2	0	0	0	1	0
Subject withdrew from study	26	1	3	14	2	3
Lost to follow-up	8	1	3	7	3	1
Did not meet inclusion/exclusion criteria	0	0	1	1	0	0
Other reason	1	2	1	3	0	0

Note: Other reasons for discontinuation included positive drug screens for prohibited substances, family illness, negative drug screens for study drug, sponsor decision in light of subject's medical condition, travel, lack of efficacy and sedation, and relocation.

Reference: Section 14.1, Table 1.2

Demographic characteristics:

Approximately 47% of subjects were males. The mean age was 51.7 years (19-74 years). The majority of subjects were white (88.2%), followed by Black/African American (8.8%) and Hispanic ethnicity (7.7%). The mean BMI was 30.18 kg/m² (16.5 to 51.0 kg/m²).

Opioid status: Of the 465 treated subjects, 47% (n=219) had previously used opioids. The opioid-experienced subjects tended to take higher dose of Kadian NT (Table 4):

- <80 mg dose group: 40.8%
- 80-120 mg dose group: 57.0%
- >120 mg dose group: 60.3%

Opioid naïve was defined as “subjects who used opioids within the 30-day window but discontinued prior to the day of first dose of study drug”. (Opioid-experienced was not defined)

Table 4. Demographic Characteristics
(From the Applicant's Table 6 in the Study ALO-KNT-302 report)

Category	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 (%)	
Gender				
Male	127 (42.5)	37 (46.8)	52 (66.7)	220 (47.3)
Female	172 (57.5)	42 (53.2)	26 (33.3)	245 (52.7)
Age (years)				
Mean (SD)	52.6 (10.68)	50.6 (10.47)	50.4 (9.32)	51.7 (10.56)
Median	53.0	50.0	51.5	53.0
Min, Max	19, 74	24, 68	28, 68	19, 74
Number (%) ≥65 years	39 (13.0)	5 (6.3)	4 (5.1)	48 (10.3)
Hispanic Ethnicity	30 (10.0)	4 (5.1)	2 (2.6)	36 (7.7)
Race				
White	263 (88.0)	70 (88.6)	69 (88.5)	410 (88.2)
Black or African American	27 (9.0)	5 (6.3)	8 (10.3)	41 (8.8)
American Indian or Alaska Native	3 (1.0)	0	0	3 (0.6)
Asian	3 (1.0)	1 (1.3)	0	4 (0.9)
Native Hawaiian or other Pacific Islander	0	0	0	0
Other	3 (1.0)	3 (3.8)	1 (1.3)	7 (1.5)
BMI (kg/m²)				
Mean (SD)	30.34 (5.744)	31.09 (6.835)	28.64 (6.125)	30.18 (3.026)
Median	29.90	29.80	27.60	29.60
Min, Max	17.9, 51.0	19.0, 44.6	16.5, 44.1	16.5, 51.0
Opioid Experienced				
n (%)	122 (40.8)	45 (57.0)	47 (60.3)	219 (47.1)

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

Reference: Section 14.1, Table 3.1 and Table 4.1

Chronic pain history (Table 5): The most common site of pain was the lower back (57%), followed by arthralgia (22%; knees or hips) and posterior neck/middle back pain (8%).

**Table 5. Source of chronic pain reported by $\geq 2\%$ of Patients in the any dose group
(From Applicant's Table 9 in the Study ALO-KNT-302 report)**

Category	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 (%)	
Knee, anterior right	23 (7.7)	5 (6.3)	5 (6.4)	33 (7.1)
Arthralgia	23 (7.7)	5 (6.3)	5 (6.4)	33 (7.1)
Knee, anterior left	14 (4.7)	2 (2.5)	1 (1.3)	17 (3.7)
Arthralgia	14 (4.7)	2 (2.5)	1 (1.3)	17 (3.7)
Neck, posterior	15 (5.0)	3 (3.8)	6 (7.7)	25 (5.4)
Neck pain	12 (4.0)	2 (2.5)	6 (7.7)	21 (4.5)
Middle Back	8 (2.7)	3 (3.8)	3 (3.8)	14 (3.0)
Back pain	8 (2.7)	3 (3.8)	2 (2.6)	13 (2.8)
Hip, right	20 (6.7)	4 (5.1)	4 (5.1)	29 (6.2)
Arthralgia	17 (5.7)	4 (5.1)	3 (3.8)	25 (5.4)
Lower back	157 (52.5)	54 (68.4)	49 (62.8)	265 (57.0)
Back pain	151 (50.5)	52 (65.8)	49 (62.8)	257 (55.3)
Hip, left	19 (6.4)	1 (1.3)	2 (2.6)	23 (4.9)
Arthralgia	14 (4.7)	1 (1.3)	2 (2.6)	18 (3.9)

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

Reference: Section 14.1, Table 6.1

Extent of exposure

The Applicant reported, as shown in Table 6, that mean total dose of Kadian NT was 17,238.2 mg (20 to 247,840 mg). The average daily dose was 84.56 mg (1.2 to 963.6 mg). The mean duration of exposure was 180 ± 152 days.

The average daily dose across 15 visits showed in Table 7 increased duration of treatment at the first four months and stayed stable during the rest of eight months. The overall mean daily dose was 85 mg, ranged from 45 to 222 mg.

Table 6. Extent of exposure by dose group
(From the Applicant's Table 12 in the Study ALO-KNT-302 report)

Category	Statistic	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 (%)	
Total Dose (mg)	Mean (SD)	7,914.8 (8,746.31)	24,512.8 (13,731.33)	45,609.9 (41,164.45)	17,238.2 (23,947.66)
	Median	3,360.0	30,200.0	43,730.0	10,435.0
	Min, Max	20, 29,670	80, 44,590	360, 247,840	20, 247,840
Average Daily Dose (mg)	Mean (SD)	45.39 (17.835)	97.34 (11.287)	221.79 (142.282)	84.56 (89.000)
	Median	42.50	97.42	179.33	58.58
	Min, Max	1.2, 79.0	80.0, 119.5	121.3, 963.6	1.2, 963.6
Duration of Exposure (days)	Mean (SD)	152.8 (149.69)	250.4 (135.95)	221.7 (145.41)	180.3 (152.05)
	Median	77.0	316.0	228.0	135.0
	Min, Max	1, 378	1, 380	1, 375	1, 380

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.

Reference: Section 14.1, Table 10

Table 7. Average daily dose of Kadian NT across all visits
 (From the Applicant's Section 14.1/Table 11 in Study ALO-KNT-302 report)

Visit Schedule	Average Daily Dose of Kadian NT						Overall N=465	
	<80 mg N=299		80-120 mg N=79		>120 mg N=78		n	Mean (SD)
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)		
Visit 1 (Baseline)	293	40.91 (20.57)	75	61.25 (41.21)	75	157.93 (172.67)	443	64.16 (86.066)
Visit 2 (Week 1)	231	47.73 (21.55)	73	73.27 (34.77)	69	165.83 (163.17)	373	74.57 (85.891)
Visit 3 (Week 4)	172	50.34 (17.63)	62	81.80 (24.97)	58	168.82 (115.07)	292	80.55 (70.697)
Visit 4 (Month 2)	147	54.61 (20.98)	62	92.59 (18.15)	56	171.78 (91.94)	265	88.26 (64.770)
Visit 5 (Month 3)	133	54.51 (19.26)	59	107.15 (61.78)	55	192.79 (87.38)	247	97.87 (76.331)
Visit 6 (Month 4)	120	56.14 (18.58)	58	106.04 (30.05)	50	235.51 (203.36)	228	108.17 (119.72)
Visit 7 (Month 5)	112	56.16 (17.68)	50	100.13 (22.23)	47	370.47 (861.69)	209	137.36 (425.03)
Visit 8 (Month 6)	105	56.59 (19.29)	51	111.58 (24.76)	44	243.66 (245.06)	200	111.77 (137.03)
Visit 9 (Month 7)	94	57.45 (18.73)	50	111.54 (18.21)	40	223.72 (120.26)	184	108.30 (87.13)
Visit 10 (Month 8)	95	57.19 (21.83)	47	111.95 (15.80)	37	231.82 (134.22)	179	107.67 (92.35)
Visit 11 (Month 9)	91	57.90 (20.58)	45	108.78 (18.60)	35	237.81 (127.15)	171	108.11 (91.43)
Visit 12 (Month 10)	88	59.93 (21.21)	42	109.69 (17.94)	37	249.20 (135.13)	167	114.38 (99.51)
Visit 13 (Month 11)	86	57.55 (25.07)	39	114.46 (25.42)	36	262.84 (149.61)	161	117.24 (109.86)
Visit 14 (Month 12)	84	59.69 (21.72)	37	167.85 (328.90)	35	256.23 (160.37)	156	129.44 (194.00)
Visit 15 (Month 13)	1	30.00 (N/A)	1	101.70 (N/A)	0		2	65.85 (50.70)
Overall	299	45.39 (17.84)	79	97.34 (11.28)	78	221.79 (142.28)	456	84.56 (89.00)

Efficacy results

Subjects who received higher doses of Kadian NT tended to have smaller analgesic responses than subjects at lower doses. The Applicant interpreted “possibly due to more intractable pain at Baseline”.

PK results

- **Naltrexone:** The frequency (%) of detectable naltrexone concentrations was low (11%) and did not increase across visits (up to 12 months).
- **6- β -naltrexol:** The frequency of detectable 6- β -naltrexol concentrations was consistently higher than naltrexone at approximately 60% to 80% throughout the study.
- **Morphine:** 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 subjects $<$ 65 yrs.

Safety results

See the ISS of this review.

Correlation between PK and analgesic response

There were no observational correlations between plasma concentrations of morphine, naltrexone or 6- β -naltrexone and the pain intensity change from baseline across all visits (by time-matching analysis).

Correlation between PK and COWS scores

There were no observational correlations between plasma concentrations of morphine, naltrexone or 6- β -naltrexone and the COWS scores or the mean COWS change from baseline across all visits (by time-matching analysis). See more details in ISS of the review.

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

/s/

Jin Chen
11/30/2008 09:24:04 PM
MEDICAL OFFICER

Ellen Fields
11/30/2008 10:28:09 PM
MEDICAL OFFICER