

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-321

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

BIOPHARMACEUTICS REVIEW

NDA: 22321

Submission date: February 28, 2008
October 7, 2008

Morphine Sulfate Extended Release
With sequestered Naltrexone HCL Capsules
20, 30, 50, 60, 80 and 100 mg capsules
Reviewer: Patrick J Marroum.

Type of submission: In Vivo Bioequivalence/Bioavailability Waiver Request.

Background:

Embeda is a capsule comprised of pellets containing morphine sulfate with a sequestered naltrexone HCL inner core. If taken as prescribed, only morphine sulfate is liberated in an extended release profile to provide relief of moderate to severe chronic pain for up to 24 hours. The opioid antagonist naltrexone is designed to remain sequestered in the core of each pellet. This review deals with the biowaiver request for the lower strengths. The sponsor provided dissolution profile comparison in the proposed media for each of the lower strength compared to the highest strength. Figures 1 to 5 show the dissolution profile comparison for the various strengths. The results show that the dissolution of the lower strengths are identical to the highest strength.

RECOMMENDATION:

Since the dissolution profiles are identical to the dissolution profile of the highest strength, an in vivo bioavailability/bioequivalence waiver is granted. No further action is required at this time.

CC: Hakim A, Chikhale E

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/s/

Patrick Marroum
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BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY REVIEW

NDA: 22-321 N000	Submission Date(s): 6/30/2008
Brand Name	EMBEDA capsules
Generic Name	Morphine sulfate extended release capsules with sequestered naltrexone
Clinical Pharmacology Reviewer	Srikanth C. Nallani, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND Division	Anesthesia, Analgesia and Rheumatology Products
Sponsor	Alpharma LLC
Relevant IND(s)	70,853
Formulation; Strength(s)	Capsule; 20, 30, 50, 60, 80, and 100 mg Morphine Sulfate
Indication	Management of moderate to severe chronic pain
Proposed Dosage Regimen	Once or twice daily dosing titrated to achieve balance between effective analgesia and opioid side effects such as confusion, sedation and constipation.

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1 Executive Summary

1.1 Recommendation

The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology Findings

Alpharma Pharmaceuticals LLC (Alpharma) submitted this NDA for EMBEDA (morphine sulfate extended-release with sequestered naltrexone hydrochloride Capsules 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, and 100 mg) for the management of moderate to severe pain. This product is a reformulation of Alpharma's previously approved (7/03/1996) Kadian NDA 20-616 (morphine sulfate extended release capsules 10, 20, 30, 50, 60, 80, 100 and 200 mg).

The abuse of prescription opioid products is a recognized public health problem in the United States. In light of this, FDA has encouraged drug companies to develop novel interventions to prevent this abuse, while recognizing the importance of maintaining the availability of these important drug products for the millions of patients in this country who suffer from chronic pain. Alpharma indicates that EMBEDA addresses the need for a new opioid drug product that resists or deters tampering and abuse of morphine extended-release prescription product. Alpharma maintains that the data they provided indicates that EMBEDA is a significant improvement with greater safety profile compared to existing modified-release morphine products in that subset of legitimate pain patients who will attempt to abuse this drug by various known routes.

Embeda is a capsule comprised of individual pellets containing morphine sulfate with a sequestered naltrexone HCl inner core. The sponsor indicates that if the product is taken orally as prescribed, morphine is released in an extended-release profile bioequivalent (100 mg strength) to Kadian, thus providing relief of moderate to severe chronic pain for up to 24 hours. EMBEDA capsules at different strength are compositionally proportional with higher strengths consisting of proportionally higher number of drug containing pellets. Biowaiver is sought for EMBEDA strengths below 100 mg. The opioid antagonist naltrexone is designed to remain sequestered in the core of each pellet. However, upon crushing or chewing of the pellets, both the morphine and naltrexone would be available and absorbed as an immediate-release dosage form. The released naltrexone is to be absorbed thereby mitigating the drug liking and euphoric effects of the morphine and deter drug tampering and diversion.

Twelve clinical and clinical pharmacology studies were conducted to evaluate pharmacokinetics of morphine and naltrexone with normal use (1.3.1) and abuse (1.3.2) of EMBEDA, long-term safety in patients, efficacy in osteoarthritis patients requiring an opioid for pain management.

1.3.1 Clinical Pharmacokinetics of Morphine and Naltrexone under normal use of EMBEDA

Bioequivalence of EMBEDA to previously approved KADIAN

Study # 101 established bioequivalence of systemic levels of morphine between 100 mg strength of EMBEDA and previously approved product KADIAN.

In an open-label, randomized, single-dose, 2-way cross over study conducted in healthy adult subjects (n=34) under fasted condition, Embeda (morphine sulfate and naltrexone core extended-release) 100 mg strength capsule was shown to be bioequivalent to Kadian (morphine sulfate extended-release) 100 mg strength. Pharmacokinetic parameters of serum morphine from both products are tabulated below. Tmax of morphine is earlier in subjects receiving Embeda when compared to Kadian.

Summary of Pharmacokinetic Results for Morphine from EMBEDA vs. KADIAN (N=34)

Parameter*	EMBEDA (A)	KADIAN® (B)
AUC _{0-t} (ng·h/mL)	310.9 (25.30%)	304.52 (25.8)
AUC _{inf} (ng·h/mL)	384.01 (24.10%)	390.98 (29.90%)
C _{max} (ng/mL)	12.31 (36.80%)	13.19 (45.70%)
T _{max} (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 C_{max}, median (range) for T_{max} and arithmetic mean (CV%) for half-life.

Plasma Profile of Morphine (EMBEDA vs KADIAN)

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

Bioequivalence Analysis Results for Serum Morphine PK parameters

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

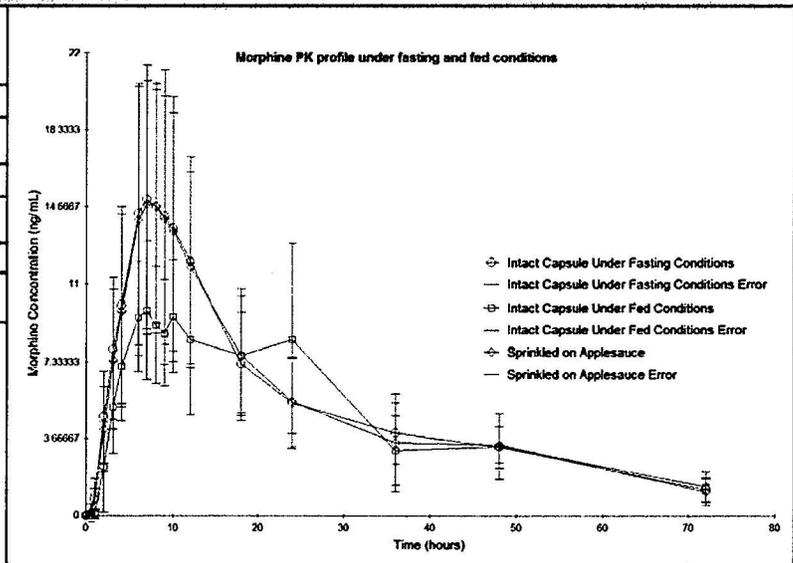
Food effect: EMBEDA may be taken with or without food. EMBEDA may be taken by sprinkling the contents over applesauce.

Study # 103 was conducted to assess the relative bioavailability of EMBEDA capsules when administered sprinkled on applesauce (A), intact under fed conditions (B) and intact under fasting (C) conditions. This study had an open-label, randomized, single-dose, 3-way crossover, 6-sequence design where 100 mg EMBEDA capsules was administered in healthy adult volunteers. Morphine plasma levels with EMBEDA were bioequivalent under fasted (C) vs. sprinkled over applesauce (B) conditions as evidenced by the ratio of least square means of C_{max} and AUC within 90% CI (see table below). However, a 22% decrease in C_{max} was noted when EMBEDA capsules were taken with food compared to fasting condition. It should be noted that the efficacy study # 302 allowed the patients to take EMBEDA with or without food (See Medical officer review for conclusions on efficacy). Twelve subjects vomited, a known major adverse effect of morphine, during the study approximately at the time to peak plasma morphine levels. Since it is safe to assume that the gastric emptying time is complete (, i.e. > 4 hours), the PK data was not deleted from the analysis.

Summary of Pharmacokinetic Results for Morphine from EMBEDA taken with or without food, sprinkled on applesauce (N=34)

Parameter	Trt	Ratio of LSM (%)	90% CI
AUC _{0-t} (ng·h/mL) N=34	A/C	98.8	93.5 - 104.4
	B/C	90.3	85.4 - 95.5
AUC _{inf} (ng·h/mL) N=30	A/C	97.5	89.8 - 105.9
	B/C	92.0	84.2 - 100.5
C _{max} (ng/mL) N=34	A/C	99.0	90.4 - 108.3
	B/C	77.8	71.0 - 85.1

A = EMBEDA sprinkled on applesauce
 B = EMBEDA intact fed
 C = EMBEDA intact fasting



1.3.2 Clinical pharmacokinetics of Morphine and Naltrexone under EMBEDA abuse

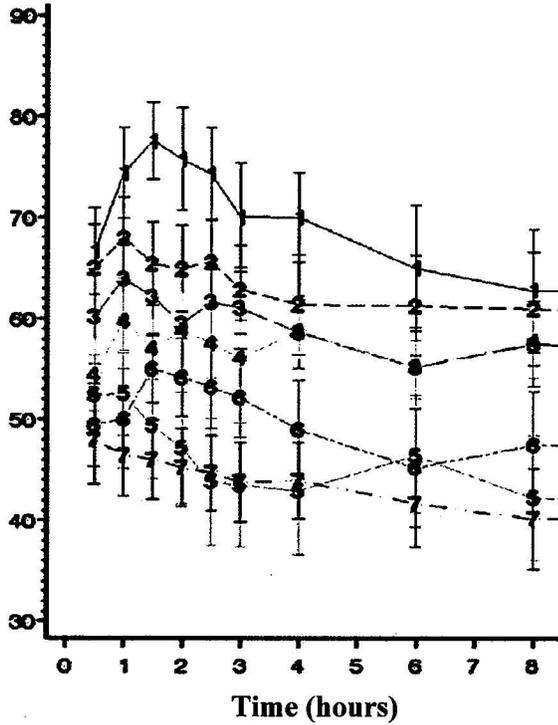
In the clinical development plan, studies (# 106, 107, 201, and 205) were aimed at demonstrating the utility of naltrexone sequestered in the EMBEDA pellets to deter drug tampering and diversion.

Clinical pharmacology study # 201 was conducted to establish the appropriate pharmacological ratio of naltrexone to morphine (1:25) that would mitigate the drug liking and euphoric effects of morphine released by crushing or chewing EMBEDA. Study # 201 is a restricted-randomized, double-blind, cross-over, placebo-controlled trial evaluating the effect of dose ranging of naltrexone (naltrexone to morphine ratios of 1:50, 1:25 and 1:12.5, 1:6.25, 1:3.125) on the morphine (100 mg)-induced euphoria in non-dependent, opioid experienced subjects under fasting conditions. The primary objective of this study was to assess the appropriate naltrexone to morphine ratio required to abate the euphoric effects of morphine in opiate experienced nondependent recreational drug users. Pharmacokinetics of morphine and naltrexone were determined as an exploratory endpoint.

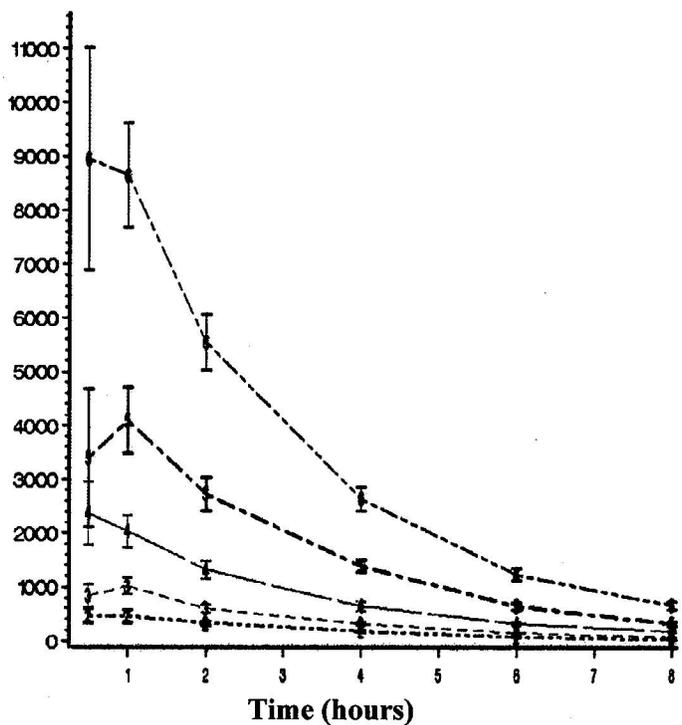
Morphine administration resulted in a characteristic and expected increase for the Drug Liking. Co-administration of naltrexone with morphine reduced morphine-induced positive effects in a dose-dependent fashion up to the 1: 25 ratio of naltrexone to morphine, there after the reduction induced by the two highest naltrexone doses (19.2 mg or 1: 6.25 ratio and 38.4 mg or 1: 3.125 ratio) was similar. Hence, the sponsor decided to use 1:25 naltrexone to morphine ratio for EMBEDA formulation. Although the average decrease in drug liking response appears to be dose-dependent, noteworthy is the fact that the drug liking effects are highly variable in individuals. Some subjects liked the drug (VAS = 100) even after receiving 9.6 - 38.4 mg naltrexone. On the other hand, some individuals (n= 11, subject# 052, 010, 038, 048, 083, 069, 049, 077, 016, 029, 007) receiving 120 mg morphine had a drug liking VAS score of less than the average (83.8). Hence, considering the high variability in pharmacodynamic response to morphine with and without naltrexone, the results should be viewed with caution when claiming abuse deterrence.

Pharmacodynamic profile of morphine "Drug Liking" following morphine solution administered with or without naltrexone oral solution (2.4 – 38.4 mg) administered orally

Profile of morphine pharmacodynamic effect "Drug Liking VAS (0 - 100)"



Pharmacokinetic profile (mean ± SD, pg/mL) of naltrexone

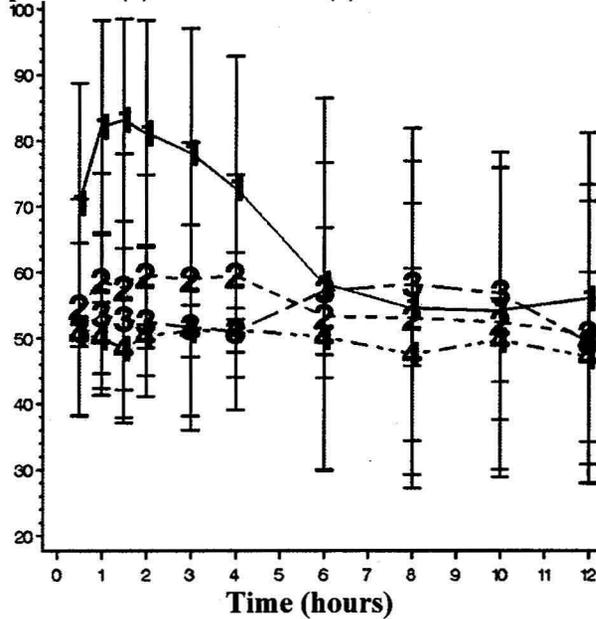


1: Morphine 120 mg	2: Morphine+ Naltr 2.4 mg	3: Morphine+ Naltr 4.8 mg
4: Morphine+ Naltr 9.6 mg	5: Morphine+ Naltr 19.2 mg	6: Morphine+ Naltr 38.4 mg
7: Placebo		

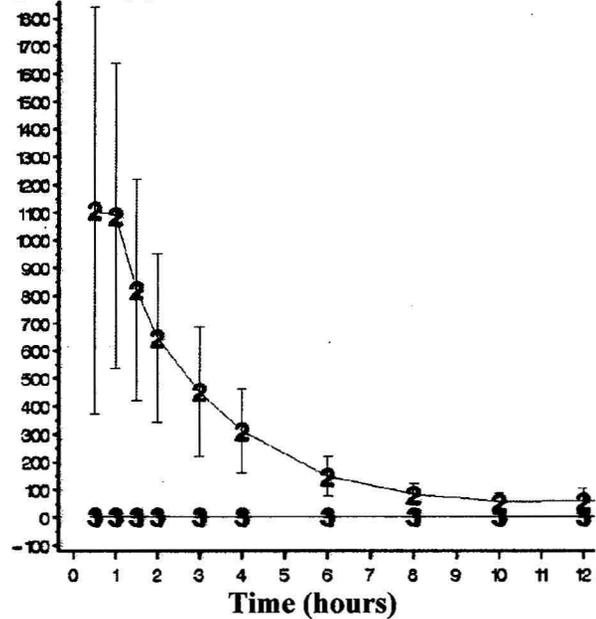
Employing the 1:25 ratio of naltrexone to morphine, EMBEDA was tested for its abuse liability in study # 205. Study # 205 evaluated the pharmacodynamic effects and safety of equivalent oral doses of whole and crushed EMBEDA versus morphine IR solution in opioid experienced, non-dependent subjects. Crushing EMBEDA results in (a) Release of morphine comparable to an immediate release morphine oral solution (b) Release of naltrexone comparable to an oral solution (see figure below).

As shown in the figure below, large variability in pharmacodynamic response is noted in each treatment; however, average drug liking scores were lower in EMBEDA intact and crushed treatments when compared to morphine sulfate IR solution treatment. Some individuals (n=4, subject #9002, 9009, 9015, 9034) receiving crushed EMBEDA product demonstrated strong liking (VAS score = 100) at few time points, despite the release and absorption of naltrexone from the crushed pellets.

VAS scores (0 -100) for Drug Liking (mean±SD) in subjects in subjects receiving Morphine sulfate IR solution (1), EMBEDA crushed product (2) and EMBEDA intact product (3) and Placebo (4)

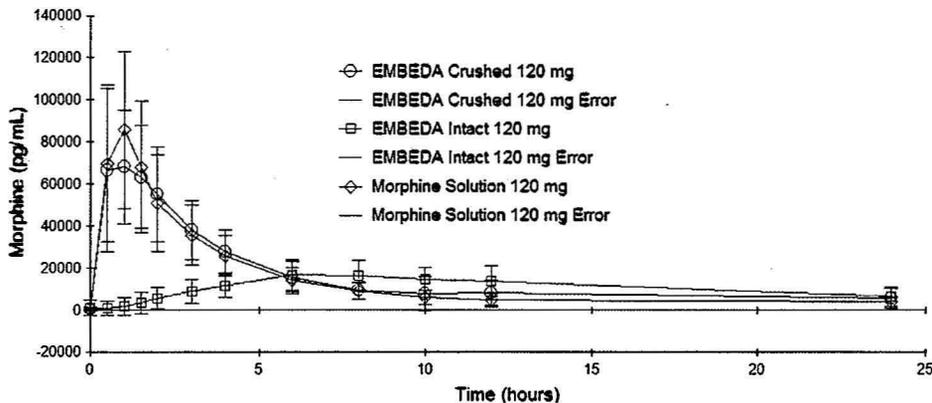


Pharmacokinetic profile of plasma naltrexone in subjects receiving Morphine sulfate IR solution (1), EMBEDA crushed product (2) and EMBEDA intact product (3)



On an average, peak morphine levels were 4-fold higher (range 1.4- to 7-fold) and achieved quickly (shorter T_{max}) in subjects receiving crushed EMBEDA compared to intact product. AUC levels were higher by 12% in crushed EMBEDA treatment compared to intact product. The plasma morphine profile was comparable between crushed EMBEDA and morphine sulfate oral solution treatment. C_{max} for all the treatments were significantly different from each other, in comparison to morphine sulfate oral solution C_{max} of EMBEDA crushed was 94.3%, while C_{max} with EMBEDA whole was 23.4%. Relative bioavailability of morphine, in terms of AUC, was 115% in EMBEDA crushed group compared to morphine oral solution, while EMBEDA intact capsules had a relative bioavailability of 83%. Median T_{max} was approximately 1 hour for EMBEDA crushed and morphine sulfate oral solution and 8 hours for EMBEDA whole.

Morphine Pharmacokinetics



It is noteworthy that despite the high variability, the median peak was similar between morphine peak plasma levels and pharmacodynamic response (see table above). The proportion of subjects who had any reduction in post-dose Drug Liking E_{max} compared to MSIR 120 mg are listed in the Table below. Generally, majority of the subjects (presented as percentage [number of subjects/total number of subjects]) had at least a 20% minimum reduction in E_{max} following EMBEDA whole administration (65.1% [21/32]) and at least a 30% minimum reduction following EMBEDA crushed administration (53.1% [17/32]) relative to MSIR. The highest percent reductions observed were in the 40-49% range, occurring at an incidence of 15.6% (5/32 subjects) following EMBEDA whole administration and in 25.0% (8/32) of subjects following EMBEDA crushed administration.

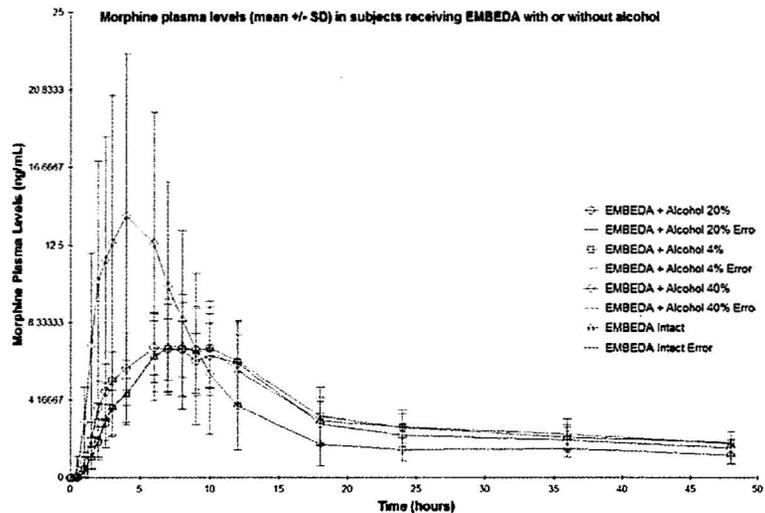
Proportion of subjects (per protocol population) who had a 10-100% reduction in post-dose Drug Liking E_{max} compared to Morphine Sulfate IR 120 mg

Change in E_{max} of Drug Liking	EMBEDA (2 x 60 mg) crushed (N=32)	EMBEDA (2 x 60 mg) whole (N=32)
At least 10% reduction	23 (71.9%)	26 (81.3%)
At least 20% reduction	21 (65.6%)	21 (65.6%)
At least 30% reduction	17 (53.1%)	12 (37.5%)
At least 40% reduction	8 (25.0%)	5 (15.6%)
At least 50% reduction	0 (0.0%)	0 (0.0%)
At least 60% reduction	0 (0.0%)	0 (0.0%)
At least 70% reduction	0 (0.0%)	0 (0.0%)
At least 80% reduction	0 (0.0%)	0 (0.0%)
At least 90% reduction	0 (0.0%)	0 (0.0%)
At least 100% reduction	0 (0.0%)	0 (0.0%)

It should be noted that this study was conducted following single dose administration. When subjects have already received multiple doses of EMBEDA or morphine the amount of naltrexone released following consumption of one crushed EMBEDA capsule may not be adequate to block drug liking effects. Hence, the abuse liability of crushing EMBEDA product while patients are at steady-state cannot be determined based on results from this study.

Alcohol drug interaction

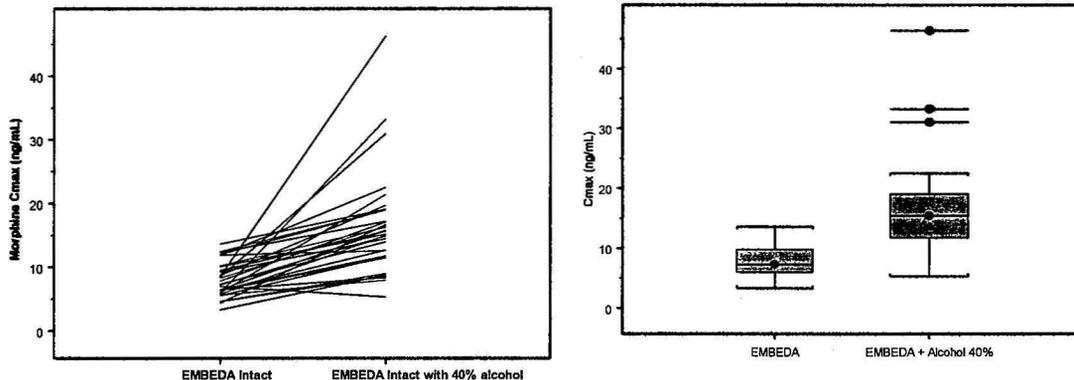
Previously in KADIAN NDA 20-616 S-021 (approved date 2/27/2007), an alcohol interaction study showed that KADIAN did not dose-dump morphine from the formulation when dosed with 40% alcohol. In the current NDA, alcohol interaction study # 103 was



conducted to compare single-dose bioavailability of EMBEDA capsules when dosed with water, 4%, 20% and 40% alcohol. Compared to intact EMBEDA consumed with water under fasting condition, pharmacokinetics of morphine were not significantly altered when EMBEDA was coadministered with 4% and 20% alcohol (see figure).

However, coadministration with 40% alcohol resulted in morphine dose-dumping from EMBEDA, where on an average 2-fold higher C_{max} of morphine was noted compared to EMBEDA consumed with water (See individual line plots below showing a range of 1.4 – to 5-fold increase in C_{max}; five individuals with 2-fold increase, two individuals with 3.5-fold, two individuals with 5-fold higher, out of n=30). Plasma AUC of morphine was not significantly different between the different treatments. The number of subjects experiencing adverse events (nausea, vomiting, dizziness and headache) increased when EMBEDA 60 mg was consumed with increasing amount of alcohol. Because plasma naltrexone was a key pharmacokinetic measurement for the study, naltrexone block (50 mg naltrexone tablet) could not be administered as a μ -opioid antagonist prior to dosing. Results indicated that co-administration of alcohol had no effect on the sequestration of naltrexone.

Morphine C_{max} when EMBEDA is consumed with 40% alcohol (individuals (left) and in a box plot (right))



In subjects receiving intact EMBEDA capsules with or without any alcohol treatment, pharmacokinetic analysis was not performed for naltrexone in plasma because most concentration values in most subjects were below the limit of quantitation. Four subjects had very low naltrexone plasma levels (6.8 – 9 pg/mL) at single time point following EMBEDA intact treatment. Five subjects had very low naltrexone plasma levels (4.4 – 7.7 pg/mL) at single time point following EMBEDA + 4% alcohol treatment. Seven subjects had very low naltrexone plasma levels (5.1 – 14.6 pg/mL) at single time point following EMBEDA + 20% alcohol treatment. Three subjects had very low naltrexone plasma levels (4.5 – 11.6 pg/mL) at single time point following EMBEDA + 40% alcohol treatment.

These results are in line with the in vitro dissolution experiments where morphine but not naltrexone was released following treatment of EMBEDA capsules with (b) (4)

Overall, the clinical pharmacology database is acceptable.

2 QBR

2.1 General Attributes

1. What regulatory background or history information contributes to the assessment of the clinical pharmacology and biopharmaceutics of this drug?

Alpharma Pharmaceuticals LLC (Alpharma) submitted this NDA for EMBEDA (morphine sulfate extended-release with sequestered naltrexone hydrochloride Capsules 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, and 100 mg) for the management of moderate to severe pain. This product is a reformulation of previously approved (7/03/1996) **Alpharma's Kadian NDA 20-616 (morphine sulfate extended release capsules 10, 20, 30, 50, 60, 80, 100 and 200 mg).**

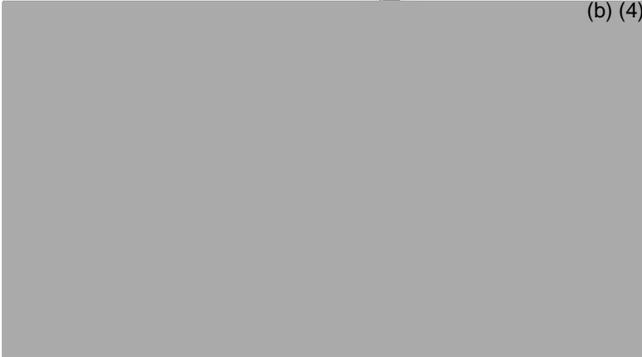
AlPharma indicates that EMBEDA addresses the need for a new opioid drug product that resists or deters tampering and abuse of morphine extended-release prescription product. Alpharm maintains that the data they provided indicates that EMBEDA is a significant improvement with greater safety profile compared to existing modified-release morphine products in that subset of legitimate pain patients who will attempt to abuse this drug by various known routes.

2. What are the highlights of the formulation of the drug product?

EMBEDA is a capsule comprised of individual pellets containing morphine sulfate with a sequestered naltrexone HCl inner core. The sponsor indicates that if the product is taken orally as prescribed, morphine is released in an extended-release profile bioequivalent (100 mg strength) to KADIAN, thus providing relief of moderate to severe chronic pain. EMBEDA capsules at different strength are compositionally proportional with higher strengths consisting of proportionally higher number of drug containing pellets. Biowaiver is sought for EMBEDA strengths below 100 mg. The opioid antagonist naltrexone is designed to remain sequestered in the core of each pellet. However, upon

Schematic Diagram of Morphine Sulfate Extended-release with Sequestered Naltrexone Hydrochloride Pellet

(b) (4)



(b) (4)



crushing or chewing of the pellets, both the morphine and naltrexone would be available and absorbed as an immediate-release dosage form. The released naltrexone is to be absorbed thereby mitigating the liking and euphoric effects of the morphine and deter drug tampering and diversion.

2.2 General Clinical Pharmacology

Clinical pharmacology program was geared towards comparing systemic levels of morphine between EMBEDA and previously approved similar product KADIAN. One bioequivalence study # 101 was conducted to bridge EMBEDA with KADIAN. In addition, the clinical development plan was aimed to demonstrate the utility of naltrexone sequestered in the EMBEDA pellets to deter drug tampering and diversion. Clinical pharmacology studies were conducted to establish the appropriate pharmacological ratio of naltrexone to morphine (1:25). The established ratio would mitigate the drug liking and euphoric effects of morphine released by crushing or chewing EMBEDA.

Release of the opiate-receptor antagonist, naltrexone, from the sequestered pellets under prescribed use may have effects on product performance with regard to precipitating opiate withdrawal effects and decrease efficacy. Hence, the Agency mentioned at a Pre-IND meeting that if any systemic exposure of naltrexone is noted in the early clinical pharmacology studies, Alpharma would have to conduct a safety and efficacy study. Accordingly, based on the naltrexone systemic levels noted in the initial PK studies, study #302 was conducted comparing safety and efficacy of EMBEDA capsules with KADIAN capsules. Patients were monitored for opiate withdrawal symptoms in this study.

In addition, the biopharmaceutics studies were conducted characterizing the pharmacokinetics of morphine with the normal use and abuse of EMBEDA. Clinical pharmacology studies were also conducted to determine the effective naltrexone-to-morphine ratio that provides mitigation of positive subjective effects of morphine (e.g., drug liking) associated with opioid abuse.

Clinical pharmacology studies under normal/prescribed use situations

- Bioequivalence (BE) study comparing 100 mg of EMBEDA with KADIAN (ALO-01-07-101)
 - Alpharma is seeking biowaiver for 20 - 80 mg strengths (See ONDQA review for more details).
- Bioavailability study for 100 mg on effect of a high fat meal and sprinkling pellets on applesauce (ALO-01-07-102)
- Single dose, double-blind, placebo-controlled PD and PK studies in nondependent, recreational opioid drug users (Protocols ALO-KNT-201, ALO-01-07-205, and ALO-01-07-106)
- Multiple dose, double-blind, placebo-controlled safety, efficacy and PK studies in patients with osteoarthritis pain of the hip and knee (Protocols ALO-KNT-202)

and ALO-KNT-302 (EMBEDA 20 -80 mg) and ALO-01-07-107 (EMBEDA 20 – 100 mg)

Clinical pharmacology studies under abuse situations

- Single dose (EMBEDA 60 mg) PK alcohol interaction study in healthy volunteers who were moderate drinkers (ALO-01-07-103).
- Bioavailability study with EMBEDA 60 mg administered whole and crushed and with an oral solution of naltrexone (ALO-01-07-104)
- Randomized, double-blind, triple-dummy, single-dose, four-way crossover study to determine the relative bioavailability, pharmacodynamic effects and safety of equivalent oral doses of whole and crushed EMEDA (2 X 60 mg capsules) versus morphine IR solution in opioid experienced, non-dependent subjects (ALO-01-07-205).

Plasma samples were collected in clinical pharmacology and biopharmaceutics studies and analyzed for determination of morphine, naltrexone and its metabolite 6 β -naltrexol concentrations.

2.2.1 Is EMBEDA bioequivalent to KADIAN?

EMBEDA is bioequivalent to KADIAN with respect to C_{max} and AUC after single dose administration. However, morphine T_{max} was earlier (Median 7.5 hrs, range 2.5– 18 hrs) for EMBEDA compared to KADIAN (Median T_{max} 10 hrs, range 6– 24 hrs).

In an open-label, randomized, single-dose, 2-way cross over study conducted in healthy adult subjects (n=34) under fasted condition, Embeda (morphine sulfate and naltrexone core extended-release) 100 mg strength capsule was shown to be bioequivalent to Kadian (morphine sulfate extended-release) 100 mg strength. Pharmacokinetic parameters of serum morphine from both products are tabulated below. T_{max} of morphine is earlier in subjects receiving Embeda when compared to Kadian.

Summary of Pharmacokinetic Results for Morphine (N=34)

Parameter*	EMBEDA (A)	KADIAN® (B)
AUC _{0-t} (ng·h/mL)	310.9 (25.30%)	304.52 (25.8)
AUC _{inf} (ng·h/mL)	384.01 (24.10%)	390.98 (29.90%)
C _{max} (ng/mL)	12.31 (36.80%)	13.19 (45.70%)
T _{max} (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 C_{max}, median (range) for T_{max} and arithmetic mean (CV%) for half-life.

As shown in the table below, the confidence intervals for the ratios of least-squares means derived from the analyses of the ln-transformed pharmacokinetic parameters AUC 0-t, AUCinf and Cmax for morphine in serum following oral administration of EMBEDA as compared to KADIAN under fasting conditions were within the 80-125% range.

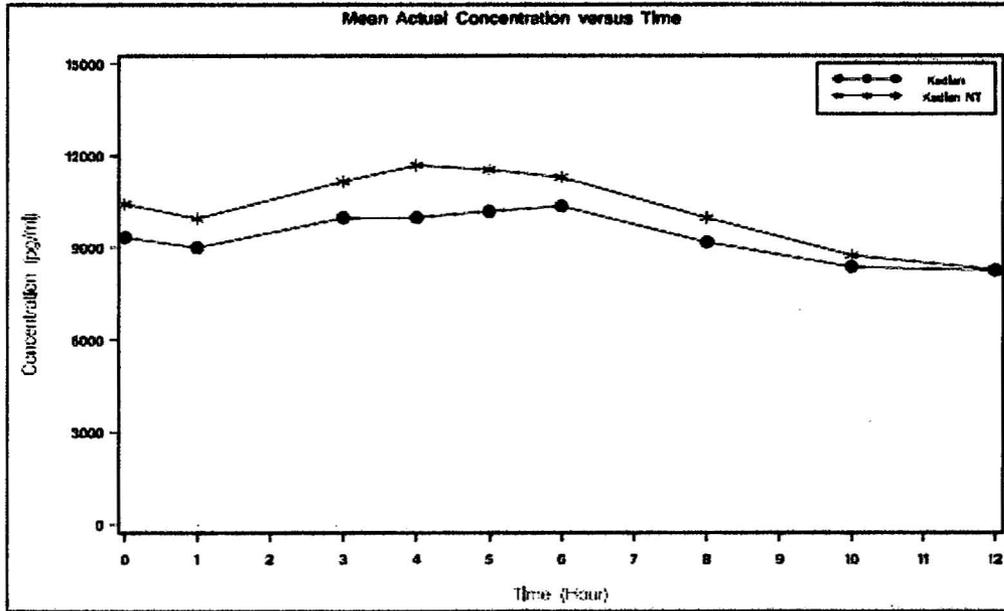
Bioequivalence Analysis Results for Serum Morphine PK parameters

	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

The sponsor noted that twelve subjects vomited during the study. Upon closer examination, the time to vomiting coincided with the Tmax (~ 7 -10 hours after EMBEDA administration). Since it is reasonable to assume that the gastric emptying may be complete in this duration, the absorption through stomach and duodenum may not have been affected by vomiting. Hence, there was no need exclude data from the twelve subjects and the BE study analysis and results are acceptable.

In one long-term, open-label safety trial (study # 202), osteoarthritis patients requiring opiate medication for pain relief were administered with KADIAN and EMBEDA. This study had a crossover design with five distinct treatment periods: Period 1 for titration with KADIAN, Period 2 to be randomized to double-blind treatment with Kadian or EMBEDA, Period 3 to receive open-label KADIAN only, Period 4 for crossover to alternate medication of Period 2, and Period 5 to receive open-label KADIAN only. In Period 2, subjects were randomly assigned to one of two treatment groups: Sequence 1 (KADIAN followed by EMBEDA) or Sequence 2 (EMBEDA followed by KADIAN). In this study, 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. Additionally, on Day 14 of Period 2, blood samples were collected over 12 hours. Morphine concentrations from serial blood sampling during this period were similar between the KADIAN and EMBEDA (KADIAN NT) treatments (See figure below).

Average Morphine Levels (ng/mL) Over Time

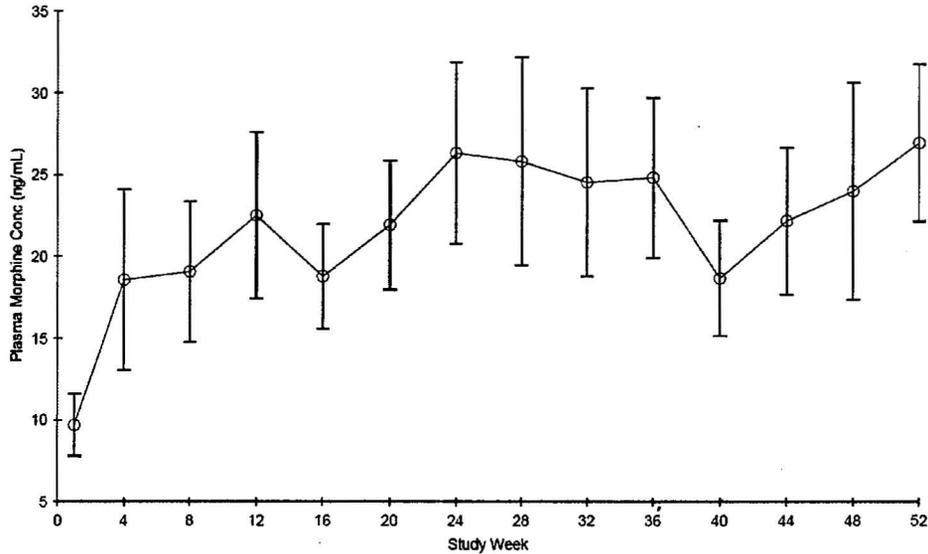


In the long-term safety study#302 (ALO-KNT-302), up to 20 subjects were planned for participation in the PK sub-study within each of the following total daily dose groups: 40 mg to 60 mg, 80 mg to 120 mg, and > 120 mg. An additional group of 20 elderly subjects was recruited for the PK study aged ≥ 65 years. The PK objectives of the study were to evaluate plasma morphine, naltrexone, and 6- β - naltrexol concentrations at visits 2-15 in selected male and female subjects. The PK analysis plan for plasma morphine concentration data was to provide graphical presentation of mean (SE) values by dose and age groups and overall for each study week. Plasma naltrexone and 6- β -naltrexol concentrations were evaluated to determine whether accumulation occurred over the course of the study, and whether dose- and age group changes occurred, and whether the frequency of detectable concentrations increased with time.

All opioid-naïve subjects started at a total daily dose of 40 mg ALO-01 administered as 20 mg BID. The mean duration of drug exposure was 180 days with a range of 1 – 380 days. The mean daily dose was 84.56 mg with a range of 1.2 to 963.6 mg.

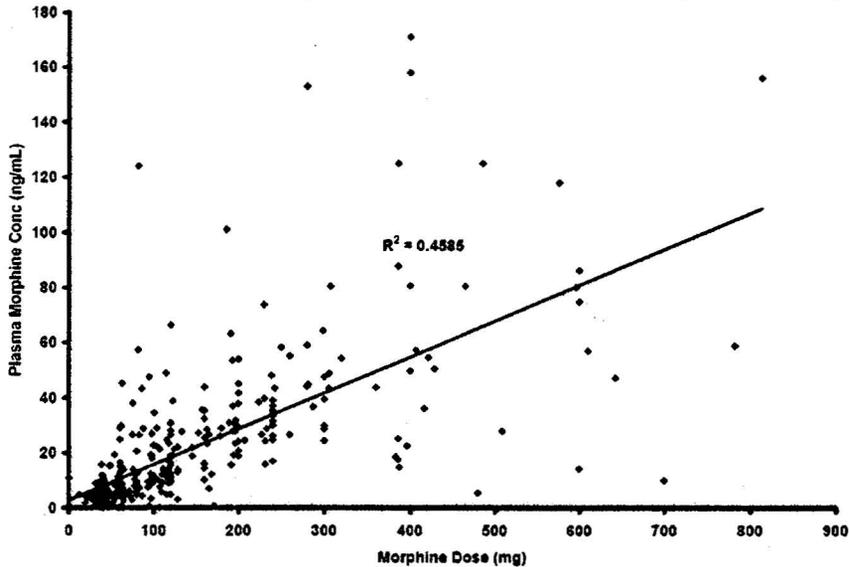
As shown in Figure below, although highly variable, overall mean plasma morphine concentrations remained within the range of 18.6 to 26.9 ng/mL during Weeks 4 to 52. Mean plasma morphine concentrations showed an approximate 2-fold increase from Week 1 (9.85 ng/mL) to Week 4 (18.6 ng/mL). The initial increase may be due to many subjects undergoing titration to higher doses to better control their pain during this time. Up and down titration during the course of the study may also explain the variability of the mean concentrations at each study week.

Mean (SE) Plasma Morphine Concentrations-Time Profiles for All Subjects



Individual patient plasma morphine concentrations appear to increase with increasing total morphine dose (See figure below). This observation supports that plasma morphine concentrations increase in a dose related manner.

Individual Plasma Morphine Concentrations vs. Morphine Dose (N=376)



The low plasma naltrexone levels (range of 4 -145 pg/mL) were detectable in a low percentage (11%) of patients, where as most of the concentrations in others were below the 4.00 pg/mL limit of detection. Of the 338 detectable 6- β -naltrexol concentrations, the median value over all study weeks was 18.5 pg/mL and, including all BLQ's set to zero, the median value was 10.3 pg/mL. The overall mean 6- β -naltrexol concentration was 73.7 pg/mL.

2.2.2 What is the rationale for naltrexone: morphine dose-selection? What are the pharmacokinetic and pharmacodynamic characteristics of the released naltrexone?

When considering average response in non-dependent opioid experienced subjects, it appears that a 1:25 ratio of naltrexone to morphine decreases drug liking effects of morphine compared to morphine alone treatment. However, significant variability in drug liking is noted in response to morphine. For example, the drug liking is not completely suppressed even in those subjects receiving highest doses of naltrexone (1:3.125 ratio with respect to morphine). Hence, caution is warranted when using this information for the purpose of abuse deterrence claims.

Naltrexone is sequestered in pellets and it is not released from EMBEDA capsules significantly when used as prescribed. However, when the EMBEDA pellets are crushed, naltrexone is released from the sequestered pellets and absorbed orally comparable to an oral naltrexone solution of similar dose.

A) Dose-ranging study (#201) to determine the ratio of naltrexone to morphine to reliably mitigate opiate drug liking and euphoric effects.

Study # 201 is a restricted-randomized, double-blind, cross-over, placebo-controlled trial evaluating the effect of dose ranging of naltrexone on the morphine-induced euphoria in non-dependent, opioid experienced subjects under fasting conditions. The primary objective of this study was to assess the appropriate naltrexone to morphine ratio required to abate the euphoric effects of morphine in opiate experienced nondependent recreational drug users. Pharmacokinetics of morphine and naltrexone were determined as an exploratory endpoint.

In Stage 1 Dosing of this study, three naltrexone to morphine ratios were examined (1:50, 1:25 and 1:12.5). During Stage 1 Dosing of the Treatment Period, all eligible subjects (n=19) received each of the five following treatments, one per treatment session, in a five visit, five sequence, double blind, randomized, crossover, single dose design:

- **morphine sulfate 120 mg + naltrexone HCl 2.4 mg (naltrexone/morphine ratio - 1:50)**
- **morphine sulfate 120 mg + naltrexone HCl 4.8 mg (1:25)**
- **morphine sulfate 120 mg + naltrexone HCl 9.6 mg (1:12.5)**
- **morphine sulfate 120 mg + naltrexone HCl placebo**
- **morphine sulfate placebo + naltrexone HCl placebo.**

In Stage 2 Dosing, two naltrexone to morphine ratios were examined (1:6.25 and 1:3.125). All subjects (n=19) who completed Stage 1 Dosing received the following additional treatments, one per treatment session, in a two session, two sequence double blind, randomized, crossover single dose design.

- **morphine sulfate 120 mg + naltrexone HCl 19.2 mg (1:6.25)**
- **morphine sulfate 120 mg + naltrexone HCl 38.4 mg (1:3.125)**

The primary exploratory endpoints were the pharmacodynamic (PD) effects organized primarily by morphine pharmacologic effects, with the emphasis on the drug liking and euphoric effects. For the purpose of this review, Drug Liking is presented in the discussion below. Visual analogue scale (VAS) for Drug Liking is assessed by the

response on a scale of 0 to 100 to the item “Overall, my liking for this drug is”, where 0 is anchored by “Strong disliking”, 50 is anchored by “Neutral”, and 100 is anchored by “Strong liking”.

Drug liking in presence of naltrexone

Morphine administration resulted in a characteristic and expected increase for the Drug Liking. As tabulated below, the mean positive effects for the morphine alone treatment peaked sharply at approximately 1.5 hours post dose. Co-administration of naltrexone with morphine reduced morphine-induced positive effects in a dose-dependent fashion though the reduction induced by the two highest naltrexone doses (19.2 mg and 38.4 mg) was similar. Although the average decrease in drug liking response appears to be dose-dependent, noteworthy is the fact that the drug liking effects are highly variable in individuals. In that regard, even on an average, complete suppression of drug liking could not be achieved following the highest dose (38.4 mg) of naltrexone; and additionally, some individuals (n= 3,) liked the drug effects even after receiving 38.4 mg naltrexone. On the other hand, some individuals (n= 11, subject# 052, 010, 038, 048, 083, 069, 049, 077, 016, 029, 007) receiving 120 mg morphine had a drug liking VAS score of less than the average (83.8). Hence, considering the high variability in pharmacodynamic response to morphine with and without naltrexone, the results should be viewed with caution when claiming abuse deterrence.

Mean (SD) for pharmacodynamic effect “VAS for Drug Liking” in subjects receiving morphine and naltrexone oral solutions (n=19)

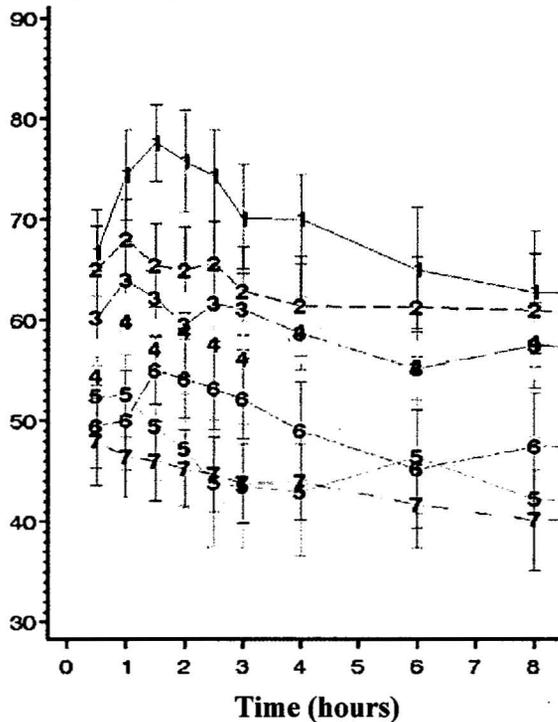
Variable	Morphine	Naltrexone 2.4	Naltrexone 4.8	Naltrexone 9.6	Naltrexone 19.2	Naltrexone 38.4	Placebo
EMAX	83.8 (14.8)	73.7 (16.9)	72.2 (16.1)	66.3 (16.2)	59.2 (15.6)	62.6 (15.8)	48.9 (19.4)
EMAX Range	60 – 100	50 - 100	50 - 100	50 - 100	44 – 100	50 - 100	0 -78
TEMAX (h)	3.50 (5.42)	3.40 (5.48)	1.92 (1.82)	2.32 (2.22)	2.19 (5.31)	3.81 (7.17)	2.32 (5.42)
TEMAX (h) Range	0.5 - 24.0	0.5 – 24.0	0.5 - 8.0	0.5 - 8.0	0.5 - 24.0	0.5 - 24.0	0.5 - 24.0
EMAX reduction compared to morphine		29%	33%	50%	70%	61%	

Emax: Maximum effect on VAS for drug liking

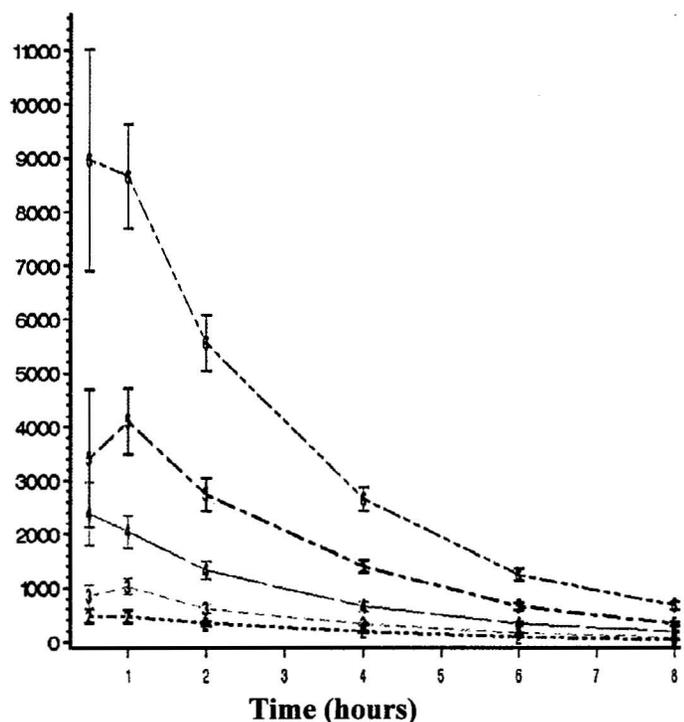
TEmax: Time to maximum effect on VAS for drug liking

Pharmacodynamic profile of morphine “Drug Liking” following morphine solution administered with or without naltrexone oral solution (2.4 – 38.4 mg) administered orally

Profile of morphine pharmacodynamic effect “Drug Liking VAS (0 - 100)”



Pharmacokinetic profile (mean ± SD, pg/mL) of naltrexone



1: Morphine 120 mg	2: Morphine+ Naltrexone 2.4 mg	3: Morphine+ Naltrexone 4.8 mg
4: Morphine+ Naltrexone 9.6 mg	5: Morphine+ Naltrexone 19.2 mg	6: Morphine+ Naltrexone 38.4 mg
7: Placebo		

From the pharmacokinetic perspective, in comparison with administration of morphine alone, an increase in morphine C_{max} by 7.9%, 13.4%, 20.1%, and 35.0% noted when coadministered with for naltrexone 2.4, 9.6, 19.2 and 38.4, respectively (See attached synopsis). The T_{max} was shorter in subjects receiving 38.4 mg naltrexone. With regard to naltrexone pharmacokinetics, a dose-proportional increase in C_{max} and AUC were noted in the dose range of 2.4 – 38.4 mg. After administration of oral naltrexone solution, peak plasma levels were noted around 1 hour and the elimination half-life was about 2 hours.

B) Pharmacodynamic Study # 205, comparing effect of morphine “drug liking” in subjects receiving morphine sulfate immediate release (MSIR) oral solution, EMBEDA whole product or EMBEDA crushed product:

Study # 205 is a randomized, double-blind, triple-dummy, single-dose, four-way crossover study to determine the relative bioavailability, Pharmacodynamic effects and safety of equivalent oral doses of whole and crushed EMEDA versus morphine IR solution in opioid experienced, non-dependent subjects. This study consisted of three periods: a screening/qualifying period, a double-blind treatment period, and a post-

treatment follow-up period. Validity of claims of abuse deterrence based on results from this study is being reviewed by controlled substances staff review Dr. James Tolliver.

During each treatment session, all eligible subjects (n=32 to complete 24) received two whole capsules (with active drug or placebo) and two beverages (with active drug and/or placebo) orally. All eligible subjects received each of the four following treatments, one per treatment session:

Treatment A: 2 x Placebo capsules (whole) + EMEDA 2 x 60 mg capsules (crushed) in apple juice (Beverage 1) + apple juice (MSIR Placebo) (Beverage 2)

Treatment B: 2 x 60 mg EMEDA (whole) + 2 x Placebo capsules (crushed) in apple juice (Beverage 1) + apple juice (MSIR Placebo) (Beverage 2)

Treatment C: 2 x Placebo capsules (whole) + 2 x Placebo capsules (crushed) in apple juice (Beverage 1) + 120 mg Morphine Sulfate IR in apple juice (Beverage 2)

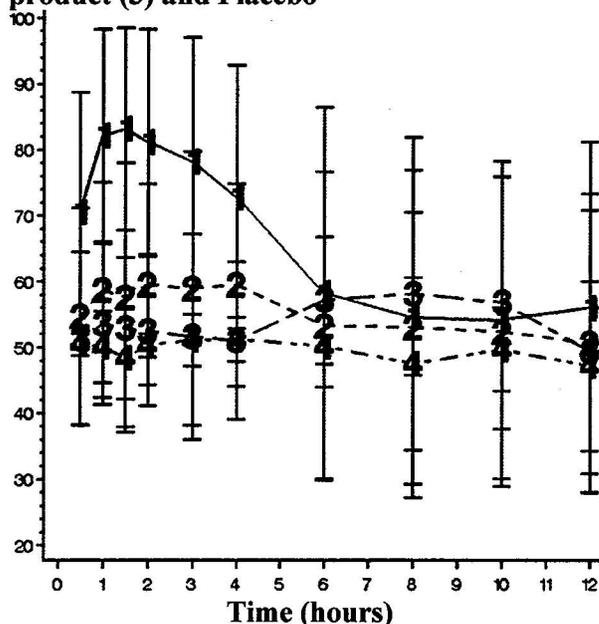
Treatment D: 2 x Placebo capsules (whole) + 2 x Placebo capsules (crushed) in apple juice (Beverage 1) + apple juice (MSIR Placebo) (Beverage 2)

VAS for Drug Liking was chosen as one of the primary measures in the study because the degree of subject liking is one of the most sensitive indicators of abuse liability. VAS for Drug Liking is assessed by the response on a scale of 0 to 100 to the item “Overall, my liking for this drug is”, where 0 is anchored by “Strong disliking”, 50 is anchored by “Neutral”, and 100 is anchored by “Strong liking”.

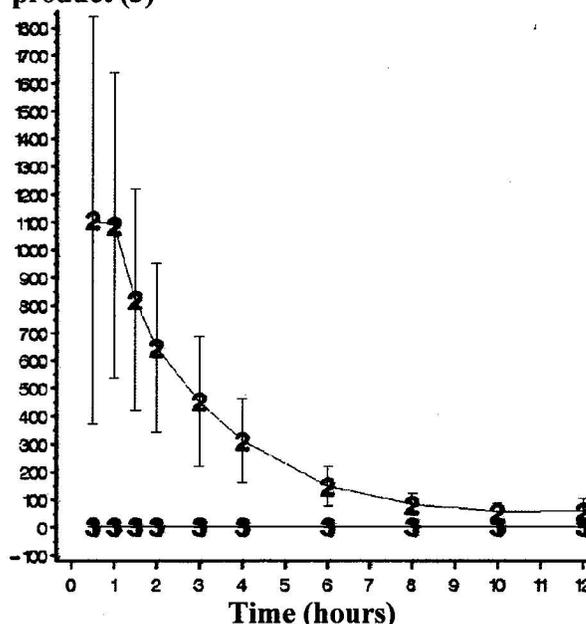
Considering the 1:25 ratio of naltrexone to morphine, 4.8 mg naltrexone dose was sequestered in pellets of two 60 mg EMBEDA capsules. Naltrexone plasma levels could be profiled only in subjects receiving EMEDA crushed treatment, but only trace amounts of naltrexone were detected in 5 of 32 subjects from the EMEDA whole treatment (See figure below). In subjects receiving crushed EMBEDA, peak plasma naltrexone levels were highly variable (mean \pm SD = 265 \pm 706 ng/mL, range= 316 – 3320 ng/mL) and were noted between 0.58 – 1.17 hours of administration.

The figure below shows the pharmacodynamic profile for each treatment group for up to 8 hours (data was collected up to 24 hours).

VAS scores (0 -100) for Drug Liking (mean±SD) in subjects in subjects receiving Morphine sulfate IR solution (1), EMBEDA crushed product (2) and EMBEDA intact product (3) and Placebo



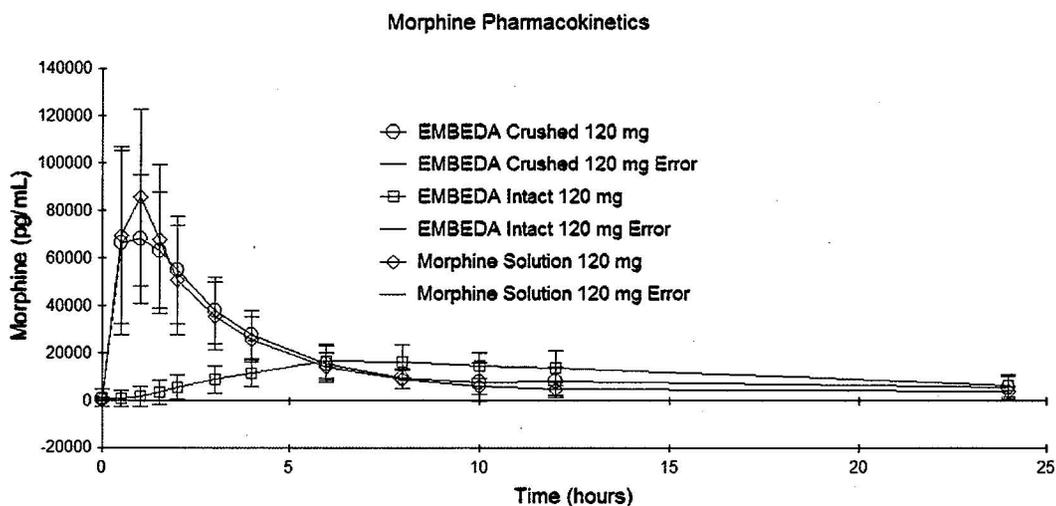
Pharmacokinetic profile of plasma naltrexone in subjects receiving Morphine sulfate IR solution (1), EMBEDA crushed product (2) and EMBEDA intact product (3)



As shown in the figure above and the table below, large variability in pharmacodynamic response is noted in each treatment; however, average drug liking scores were lower in EMBEDA intact and crushed treatments when compared to morphine sulfate IR solution treatment. Some individuals (n=4, subject #9002, 9009, 9015, 9034) receiving crushed EMBEDA product demonstrated strong liking (VAS score = 100), despite the release of naltrexone from the sequestered pellets.

Variable	Placebo	EMBEDA 120 mg whole	EMBEDA 120 mg crushed	Morphine Sulfate IR 120 mg
Morphine Pharmacokinetics				
C_{max} (pg/mL) Mean (SD)	-	19256 (7683)	80587 (38805)	92515 (38051)
T_{max} Median (Range)	-	8.125 (4.1 to 12.2)	1.109 (0.6 to 2.2)	1.150 (0.6 to 2.1)
Morphine Pharmacodynamics (Drug Liking)				
E_{max} Mean (SD)	52.2 (4.5)	67.6 (13.1)	68.1 (17.5)	89.5 (12.6)
Median	51	66	62	92.5
Range	50 - 75	51 - 100	50 - 100	57 - 100
T_{E_{max}} Median (Range)	1.5 (0.5 - 8)	8 (0.5 - 12)	2 (0.5 - 24)	1.5 (0.5 - 24)

On an average, peak morphine levels were 4-fold higher (range 1.4- to 7-fold) and achieved quickly (shorter T_{max}) in subjects receiving crushed EMBEDA compared to intact product. AUC levels were higher by 12% in crushed EMBEDA treatment compared to intact product. The plasma morphine profile was comparable between crushed EMBEDA and morphine sulfate oral solution treatment. C_{max} for all the treatments were significantly different from each other, in comparison to morphine sulfate oral solution C_{max} of EMBEDA crushed was 94.3%, while C_{max} with EMBEDA whole was 23.4%. With regard to AUC (relative bioavailability) of morphine was 115% in EMBEDA crushed group compared to morphine oral solution, while EMBEDA intact capsules had a relative bioavailability of 83%. Median T_{max} was approximately 1 hour for EMBEDA crushed and morphine sulfate oral solution and 8 hours for EMBEDA whole.



It is noteworthy that despite the high variability, the median peak was similar between morphine peak plasma levels and pharmacodynamic response (see table above). The proportion of subjects who had any reduction in post-dose Drug Liking E_{max} compared to MSIR 120 mg are listed in the Table below. Generally, majority of the subjects (presented as percentage [number of subjects/total number of subjects]) had at least a 20% minimum reduction in E_{max} following EMBEDA whole administration (65.1% [21/32]) and at least a 30% minimum reduction following EMBEDA crushed administration (53.1% [17/32]) relative to MSIR. The highest percent reductions observed were in the 40-49% range, occurring at an incidence of 15.6% (5/32 subjects) following EMBEDA whole administration and in 25.0% (8/32) of subjects following EMBEDA crushed administration.

Proportion of subjects (per protocol population) who had a 10-100% reduction in post-dose Drug Liking E_{max} compared to Morphine Sulfate IR 120 mg

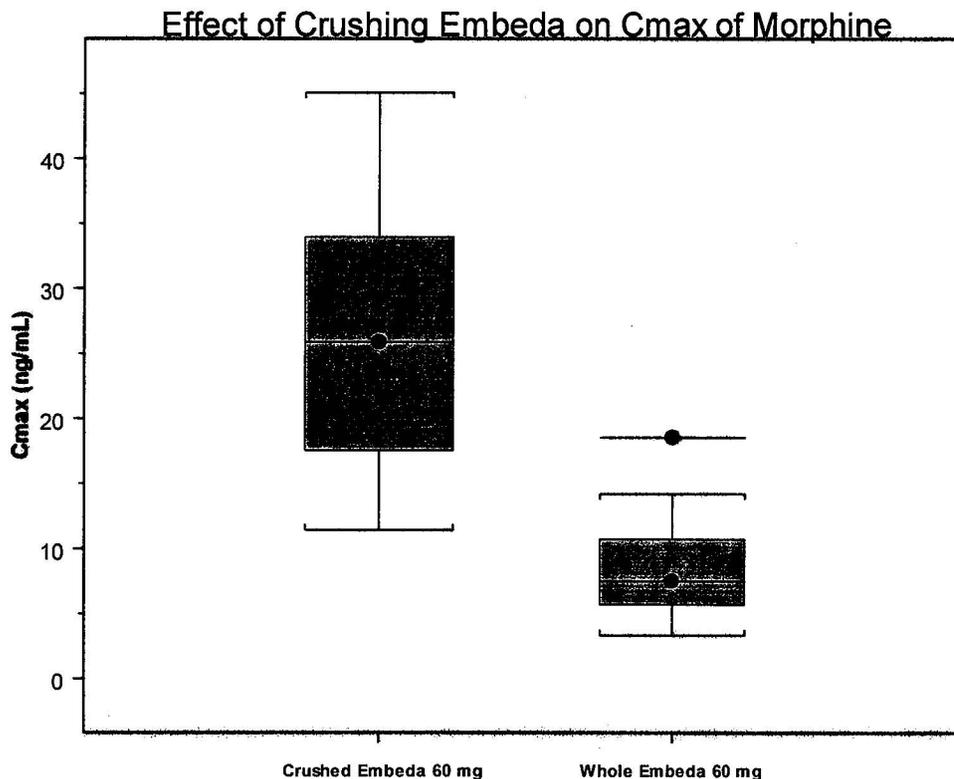
Change in E _{max} of Drug Liking	EMBEDA (2 x 60 mg) crushed (N=32)	EMBEDA (2 x 60 mg) whole (N=32)
At least 10% reduction	23 (71.9%)	26 (81.3%)
At least 20% reduction	21 (65.6%)	21 (65.6%)

At least 30% reduction	17 (53.1%)	12 (37.5%)
At least 40% reduction	8 (25.0%)	5 (15.6%)
At least 50% reduction	0 (0.0%)	0 (0.0%)
At least 60% reduction	0 (0.0%)	0 (0.0%)
At least 70% reduction	0 (0.0%)	0 (0.0%)
At least 80% reduction	0 (0.0%)	0 (0.0%)
At least 90% reduction	0 (0.0%)	0 (0.0%)
At least 100% reduction	0 (0.0%)	0 (0.0%)

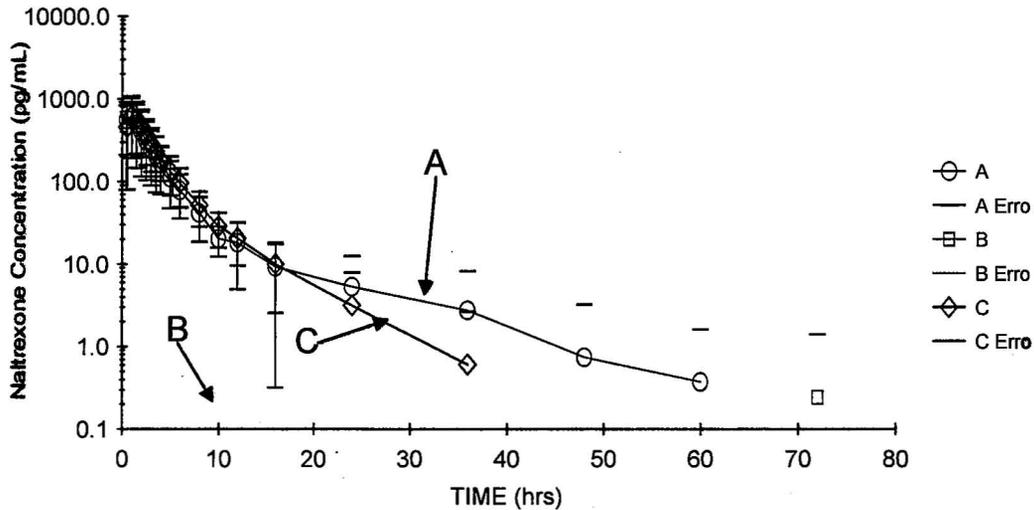
C) Pharmacokinetics of Morphine and Naltrexone following consumption of crushed 60 mg EMBEDA

In addition to study # 205, study # 104 compared pharmacokinetics of morphine and naltrexone in fasting subjects receiving intact and crushed EMBEDA (60 mg capsules) and naltrexone oral solution. Unlike study # 205, pharmacodynamic effects of morphine was not assessed in this study. As noted in study#205, morphine pharmacokinetics were similar between crushed EMBEDA and oral morphine solution, the rate (median Tmax, 2 hrs) and extent (Cmax, 24.5 ng/mL) of exposure being distinctly different from EMBEDA whole (median Tmax, 7.03 hours; Cmax, 7.73 ng/mL).

Box plot showing peak plasma morphine levels in subjects receiving crushed and whole/intact EMBEDA capsules



While naltrexone is not released significantly when EMBEDA intact capsules (60 mg) are consumed, the data also revealed that plasma naltrexone (2.4 mg) sequestered in the core of EMBEDA pellets is completely released upon crushing and comparable to naltrexone oral solution (2.4 mg) (see figure below).



Treatment A: Crushed Embeda 60 mg morphine + 2.4 mg naltrexone sequestered
 Treatment B: Whole Embeda 60 mg + 2.4 mg naltrexone sequestered
 Treatment C: Naltrexone oral solution 2.4 mg

2.2.3 Is naltrexone released from the sequestered pellets when EMBEDA capsule is taken orally as indicated?

Plasma naltrexone concentrations are low and highly variable following single and multiple dose administration of EMBEDA capsules.

Plasma samples were collected in several single and multiple dose biopharmaceutics studies with EMBEDA and analyzed for determination of naltrexone and its metabolite 6 β -naltrexol concentrations. Since naltrexone has a shorter half life (~ 6 hours), its longer half-life metabolite, 6 β -naltrexol, levels may also be a marker of overall naltrexone exposure.

In bioavailability study # 104, only one subject had detectable plasma naltrexone level (5 pg/mL) upon receiving intact EMBEDA (Morphine 60 mg, Sequestered naltrexone 2.4 mg).

In food effect study # 102, plasma levels of naltrexone were analyzed following single dose administration of EMBEDA in healthy volunteers under fasting conditions, fed condition or when capsule contents were sprinkled over apple sauce. Under fasting condition for intact capsule formulation, plasma naltrexone concentrations (fasting: range 4.46 to 20.8 pg/mL) were detected in 11 samples in three subjects; while the rest of the subjects (n=31) had plasma naltrexone levels below the quantitation 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 of the subjects (n=27) did not have naltrexone levels above the analytical method limit of quantitation. In only fifteen subjects (out of n = 34) receiving EMBEDA with high fat meal, plasma naltrexone levels were in the range of 4.05 - 132 pg/mL) at different time points.

In the long-term, open-label safety trial (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 limit of quantitation for the majority of subjects during EMBEDA 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 EMBEDA 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 limit of quantitation for the majority of subjects during EMBEDA treatment (80.6% to 83.6% of subjects). Nine subjects had detectable naltrexone concentrations after dosing with EMBEDA (range 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).

2.3 Intrinsic Factors

No new clinical pharmacology studies were conducted to evaluate the effect of intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ (hepatic or renal) dysfunction) on pharmacokinetics of morphine with EMBEDA administration. This application relies on KADIAN NDA 20-616 for information on use in special populations. This approach is acceptable since morphine levels are bioequivalent between EMBEDA and KADIAN.

2.4 Extrinsic Factors

Except for an alcohol interaction study, no new clinical pharmacology studies were conducted to evaluate the effect of extrinsic factors (drugs, herbal products and smoking) on pharmacokinetics of morphine following EMBEDA administration. Previously, in the submission for KADIAN NDA 20-616/SLR-021 (approved date 2/27/2007), an alcohol interaction study showed that KADIAN did not dose-dump morphine from the formulation when dosed with 40% alcohol.

2.4.1 What is the effect of alcohol consumption with EMBEDA capsules on morphine pharmacokinetics?

In the current NDA, alcohol interaction study (# 103) was conducted to compare single-dose bioavailability of EMBEDA capsules when dosed with water, 4%, 20% and 40% alcohol. This study was an open-label, randomized, single-dose, 4-way crossover, 4-sequence pharmacokinetic drug interaction study between EMBEDA 60 mg capsules and alcohol, following their administration under fasting conditions.

Subjects (n = 32) observed an overnight fast of at least 10 hours. On the morning of Day 1, subjects received the following regimen. Blood samples were collected before dosing (Hour 0) and for up to 168 hours post-dose.

Regimen A: EMBEDA 60 mg capsule with 4% Ethanol

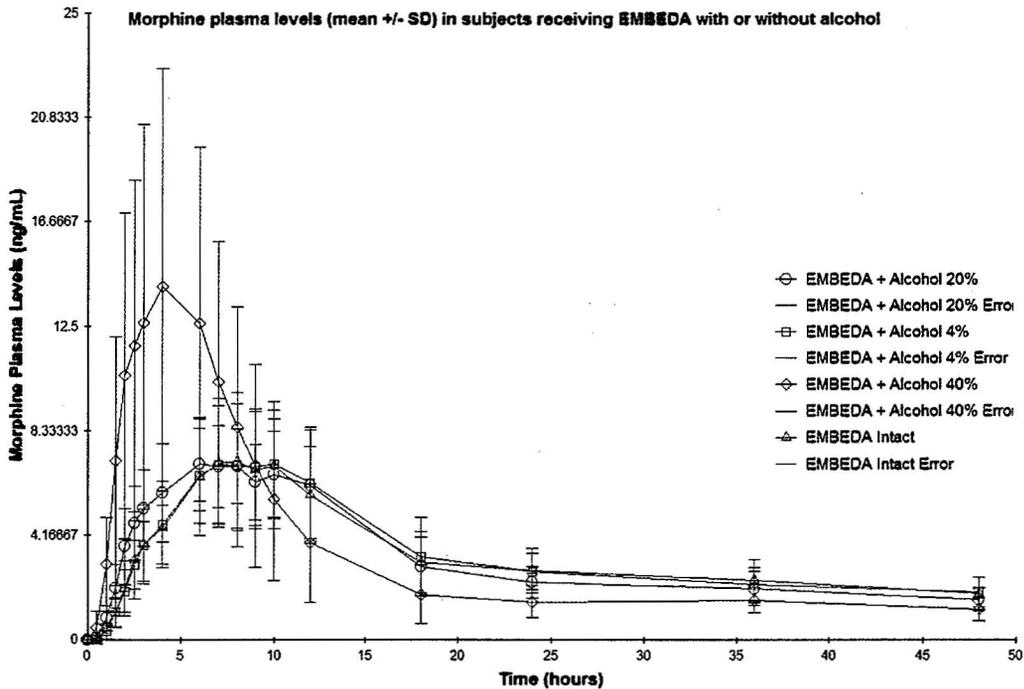
Regimen B: EMBEDA 60 mg capsule with 20% Ethanol

Regimen C: EMBEDA 60 mg capsule with 40% Ethanol

Regimen D: EMBEDA 60 mg capsule with water

The plasma morphine concentration time profiles for EMBEDA with 4% and 20% concomitant alcohol administration were similar to EMBEDA with water. However, EMBEDA consumed with 40% alcohol resulted in morphine dose-dump and the plasma morphine exposure (C_{max} and AUC) was higher compared to all other treatments. As mentioned before, KADIAN did not dose-dump morphine from the formulation when dosed with 40% alcohol (see clinical pharmacology review dated 12/22/2006 by Dr. David Lee).

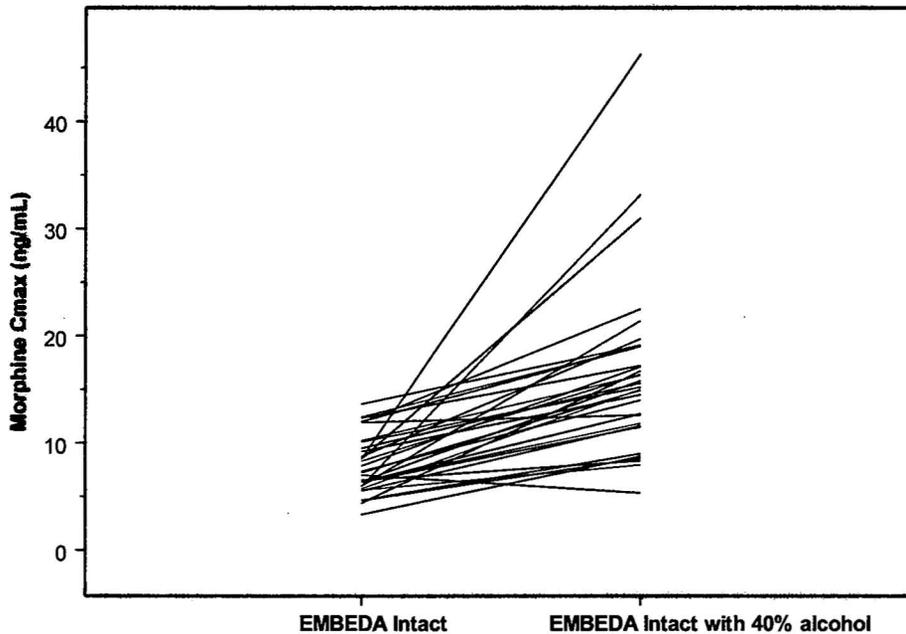
Compared to intact EMBEDA consumed with water under fasting condition, pharmacokinetics of morphine were not significantly altered when EMBEDA was coadministered with 4% and 20% alcohol (see figure below).



However, coadministration with 40% alcohol resulted in morphine dose-dumping from EMBEDA, where on an average 2-fold higher C_{max} of morphine was noted compared to EMBEDA consumed with water (See individual line plots below showing a range of 1.4

– to 5-fold increase in C_{max}; five individuals with 2-fold increase, two individuals with 3.5-fold, two individuals with 5-fold higher, out of n=31). Plasma AUC of morphine was not significantly different between the different treatments.

Morphine C_{max} Following Embeda and Embeda + 40% Alcohol Treatment



In subjects receiving intact EMBEDA capsules with or without any alcohol treatment, pharmacokinetic analysis was not performed for naltrexone in plasma because most concentration values in most subjects were below the limit of quantitation. Four subjects had very low naltrexone plasma levels (6.8 – 9 pg/mL) at a single time point following EMBEDA intact treatment. Five subjects had very low naltrexone plasma levels (4.4 – 7.7 pg/mL) at a single time point following EMBEDA + 4% alcohol treatment. Seven subjects had very low naltrexone plasma levels (5.1 – 14.6 pg/mL) at a single time point following EMBEDA + 20% alcohol treatment. Three subjects had very low naltrexone plasma levels (4.5 – 11.6 pg/mL) at a single time point following EMBEDA + 40% alcohol treatment.

These results are in line with the in vitro dissolution experiments where morphine but not naltrexone was released following various alcohol treatments of EMBEDA capsules in vitro. In vitro dissolution studies were performed using EMBEDA Capsules to evaluate the effect of alcohol on the dissolution profile of morphine sulfate. (b) (4)

This study design was similar to that performed on Alpharma's other extended-release pelletized product KADIAN and previous data generated using KADIAN Capsules is included as a reference.

In Vitro Alcohol Dissolution of EMBEDA Capsule

(b) (4)



(b) (4)

Noteworthy is the increased incidence of adverse events when EMBEDA is consumed with alcohol (See table below). The number of subjects experiencing adverse events increased with increasing amount of alcohol coadministration with EMBEDA. Adverse events commonly noted with morphine/opiates such as nausea, vomiting, dizziness and headache were noted with increased incidence when EMBEDA was consumed with alcohol. Because plasma naltrexone was a key pharmacokinetic measurement for the study, naltrexone block (50 mg naltrexone tablet) could not be administered as a μ -opioid antagonist prior to dosing. Results indicated that co-administration of alcohol had no effect on the sequestration of naltrexone.

Adverse Events in alcohol-EMBEDA drug interaction study

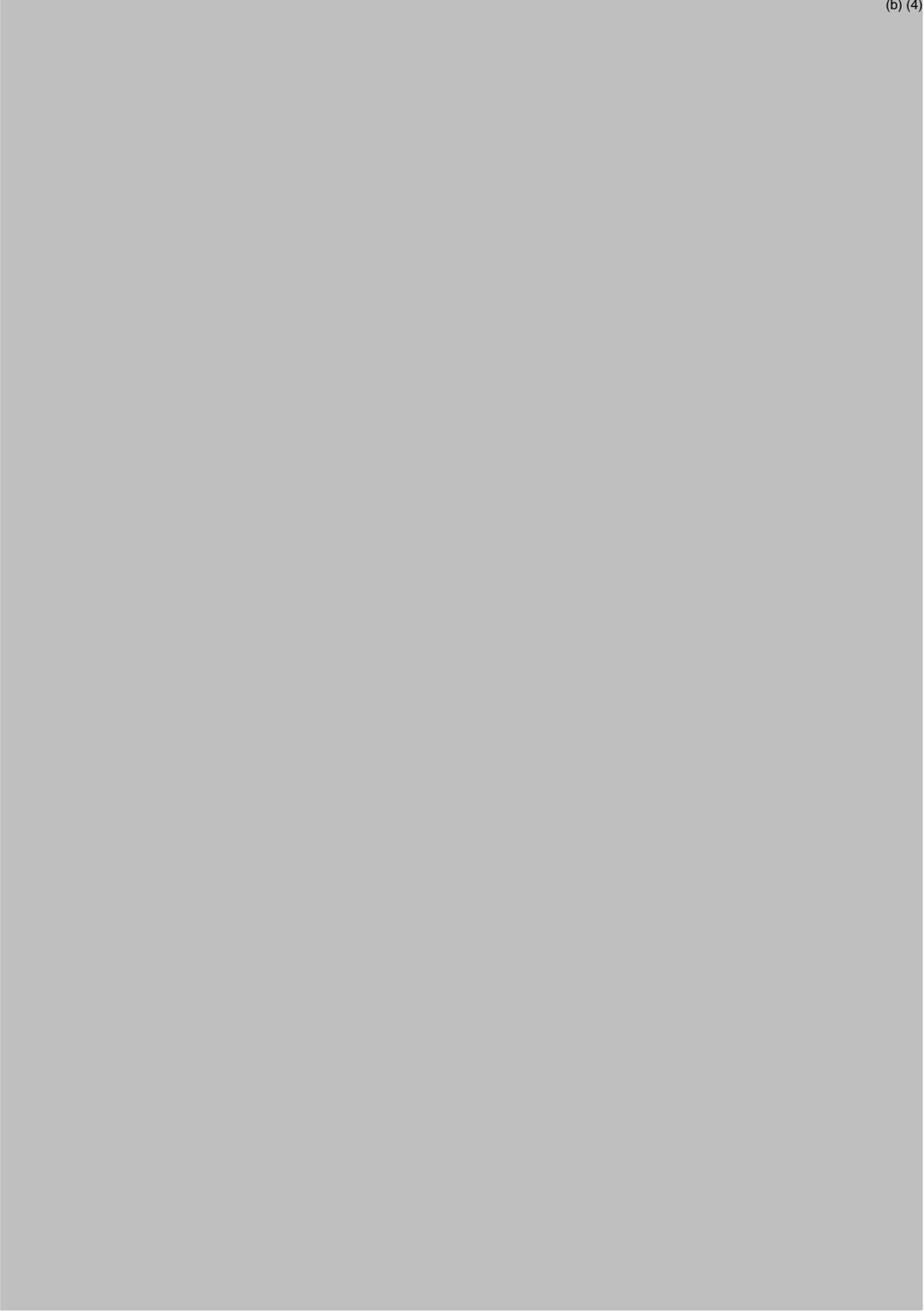
Preferred Term	EMBEDA 60 mg + Water	EMBEDA 60 mg + 4% alcohol	EMBEDA 60 mg + 20% alcohol	EMBEDA 60 mg + 40% alcohol	Total
Number of Subjects Dosed (%)	32(100%)	31 (100%)	31 (100%)	32 (100%)	32 (100%)
Number of Subjects With Adverse Events (%)	12 (37.5%)	11 (35.5%)	16 (51.6%)	20 (62.5%)	23 (71.9%)
Number of Subjects Without Adverse Events (%)	20(62.5%)	20 (64.5%)	15 (48.4%)	12 (37.5%)	9 (28.1%)
Headache	5 (15.6%)	5 (16.1%)	9 (29.0%)	8 (25.0%)	18 (56.3%)
Nausea	0 (0.0%)	3 (9.7%)	6 (19.4%)	12 (37.5%)	12 (37.5%)
Vomiting	1 (3.1%)	0 (0.0%)	2 (6.5%)	12 (37.5%)	12 (37.5%)
Dizziness	1 (3.1%)	2 (6.5%)	2 (6.5%)	9 (28.1%)	10 (31.3%)

2.5 General Biopharmaceutics

The proposed EMBEDA formulation strengths (20 – 100 mg) are compositionally proportional (See table below). The sponsor has compared the dissolution profiles for each strength of EMBEDA and KADIAN employing the f2 test (See ONDQA review). Additionally, the sponsor had demonstrated bioequivalence of the EMBEDA to KADIAN 100 mg strength. Based on this evidence, sponsor is requesting biowaiver for the EMBEDA strengths below 100 mg. The final assessment of these data and a decision on the biowaiver request is deferred to ONDQA.

Ingredient	Function	EMBEDA 20 Weight (mg)	EMBEDA 30 Weight (mg)	EMBEDA 50 Weight (mg)	EMBEDA 60 Weight (mg)	EMBEDA 80 Weight (mg)	EMBEDA 100 Weight (mg)
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(b) (4)



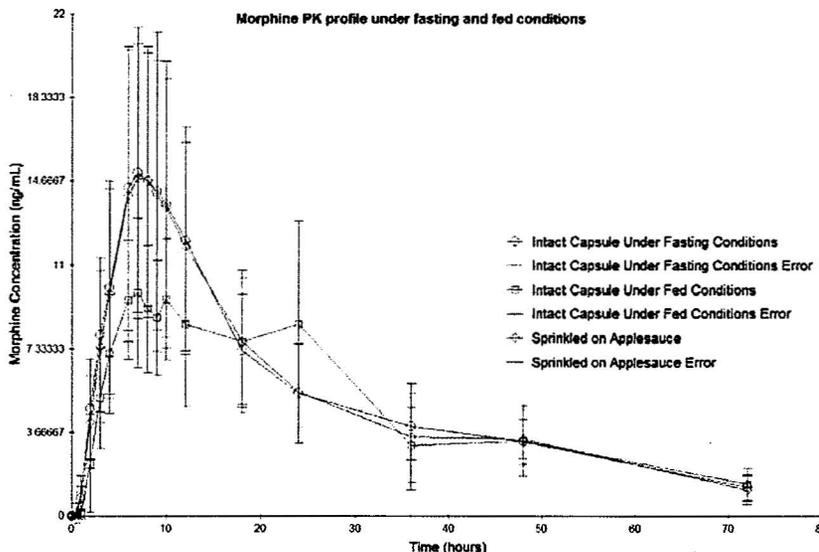
2.5.2 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

EMBEDA may be administered in patients without regard for food consumption. In addition, patients who are unable to take EMBEDA capsules may consume it by sprinkling the capsules contents on applesauce. Consumption of EMBEDA with food decreased the C_{max} of morphine by 22% without a significant change in the AUC compared to fasting condition. Additionally, EMBEDA consumed when sprinkled over applesauce was bioequivalent to fasting condition.

Study # 103 was conducted to assess the relative bioavailability of EMBEDA capsules when administered sprinkled on applesauce (A), intact under fed conditions (B) and intact under fasting (C) conditions. This study had an open-label, randomized, single-dose, 3-way crossover, 6-sequence design where 100 mg EMBEDA capsules was administered in healthy adult volunteers. Morphine plasma levels with EMBEDA were bioequivalent under fasted (C) vs. sprinkled over applesauce (B) conditions as evidenced by the ratio of least square means of C_{max} and AUC within 90% CI (see table below). However, a 22% decrease in C_{max} was noted when EMBEDA capsules were taken with food compared to fasting condition. It should be noted that the efficacy study # 302 allowed the patients to take EMBEDA with or without food (See Medical officer review for conclusions on efficacy). Twelve subjects vomited, a known major adverse effect of morphine, during the study approximately at the time to peak plasma morphine levels. Since it is reasonable to assume that the gastric emptying time is complete (, i.e. > 4 hours), the PK data was not deleted from the analysis.

Parameter	Trt	Ratio of LSM (%)	CI: Lower Limit (%)	CI: Upper Limit (%)
AUC 0-t (ng.h/mL) N=34	A/C	98.8	93.5	104.4
	B/C	90.3	85.4	95.5
AUCinf (ng.h/mL) N=30	A/C	97.5	89.8	105.9
	B/C	92.0	84.2	100.5
C _{max} (ng/mL) N=34	A/C	99.0	90.4	108.3
	B/C	77.8	71.0	85.1

A = EMBEDA sprinkled on applesauce
 B = EMBEDA intact fed
 C = EMBEDA intact fasting



Pharmacokinetics of morphine in subjects receiving EMBEDA

Parameter	EMBEDA sprinkled (A)	EMBEDA fed (B)	EMBEDA fasting (C)
AUC 0-t ^a (ng.h/mL)	358.7 (25.6%)	328.2 (25.7%)	363.0 (23.4%)
AUCinf ^a (ng.h/mL)	390.1 (28.2%)	380.7 (36.1%)	401.5 (26.2%)
Cmax ^a (ng/mL)	15.83 (37.2%)	12.36 (25.9%)	16.03 (37.1%)
Tmax ^b (h)	8.00 (6.00-18.00)	10.00 (6.00-24.00)	7.50 (4.00-18.00)
Half-life ^c (h)	20.12 (43.0%)	24.63 (65.9%)	20.37 (46.5%)
k _{el} ^c (1/h)	0.04207 (50.6%)	0.03532 (39.8%)	0.04029 (41.9%)

^a Geometric mean (CV%), geometric CV calculation retained on file at (b) (4)

^b median (range)

^c arithmetic mean (CV%)

These results are similar to that noted with KADIAN formulation, i.e., decreased Cmax and prolonged Tmax without any change in AUC (based on KADIAN product label). Based on the results from this study#103, patients were instructed to take EMBEDA or other treatment with or without food in clinical efficacy study # 301. The type of food consumed by patients was neither specified nor recorded in the study #301 report.

2.6 Analytical

Sponsor employed validated LC/MS/MS methods for the determination of morphine naltrexone and 6β-naltrexol levels in plasma (see attached summaries).

Morphine and, in some in vivo studies, M3- and M6-glucuronide were measured in plasmasamples. The methods were linear over a range of 0.200 to 60.0 ng/mL for morphine, 3.50 to 1050 ng/mL for morphine-3-glucuronide (M3G) and 1.00 to 300 ng/mL for morphine-6-glucuronide (M6G).

LC-MS/MS development and validation of bioassays with increased sensitivity for naltrexone and its primary metabolite, 6-β-naltrexol, was performed by the (b) (4) performed bioassays for studies ALO-KNT-201, ALO-KNT-202, ALO-01-07-104, ALO-01-07-205, and ALO-KNT-302. The original assay procedure for the determination of naltrexone and 6-β-naltrexol in plasma samples was linear over a range of 4 to 500 pg/mL for naltrexone and 0.25 to 10 pg/mL for 6-β-naltrexol.

Bioanalytical assays for biopharmaceutic studies ALO-01-07-101 and ALO-01-07-102 and clinical pharmacology studies ALO-01-07-103, ALO-01-07-106, and ALO-01-07-107 were performed by (b) (4) The bioanalytical method was LC-MS/MS and bioanalysis for these studies was performed by the (b) (4) at the (b) (4) facility. The assay method range for naltrexone was 4.00 - 500 pg/mL and for 6-β-naltrexol, was 4.00 to 1600 pg/mL. A more sensitive method for the determination of 6-β-naltrexol was developed and validated with an analytical linear range of 0.500 - 25.0 pg/mL.

3 Labeling

Sponsor provided labeling text relevant to clinical pharmacology discipline is presented as regular text (bold or formatted where appropriate). Reviewer edits are provided as bold italic text or strikethrough text for additions and deletions.



(b) (4)

4.2.2 Synopsis of Study ALO-01-07-101

Title: Comparative, Randomized, Single-Dose, 2-way Crossover Bioavailability Study of Alpharma Inc. Abuse Deterrent Kadian NT 100 mg Morphine Sulfate-Naltrexone Core Capsules and (Kadian[®]) 100 mg Morphine Sulfate Extended-Release Capsules in Healthy Adult Volunteers under Fasting Conditions

Objective: The objective of this study was to assess the single-dose relative bioavailability of Alpharma Inc. Abuse Deterrent ALO-01 100 mg (morphine sulfate-naltrexone core) capsules and KADIAN[®] 100 mg (morphine sulfate extended-release) capsules, under fasting conditions.

Study Design: This was an open-label, randomized, single-dose, 2-way crossover, 2-sequence, comparative bioavailability study under fasting conditions. The study was performed on 36 healthy adult volunteers (25 males and 11 females). Thirty-four (34) subjects (25 males and 9 females) completed the study. Subjects were housed from at least 10 hours before dosing until after the 48-hour blood draw and returned for the 72-hour blood sample. Periods were separated by a washout of 14 days.

Subjects randomized to Treatment A (test) received a single oral dose of one ALO-01 100 mg (morphine sulfate-naltrexone core) capsule with 240 mL of water under fasting conditions.

Subjects randomized to Treatment B (reference) received a single oral dose of one KADIAN[®] 100 mg (morphine sulfate extended-release) capsule with 240 mL of water under fasting conditions.

Methods: The AUC 0-t, AUCinf, AUC 0-t/AUCinf, Cmax, tmax, half-life and kel pharmacokinetic (PK) parameters were calculated for morphine in serum. For information purposes only, these parameters were also calculated for morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G).

Analyses of variance (ANOVA) were performed on the ln-transformed AUC 0-t, AUCinf, and Cmax PK parameters. The ANOVA model included group, sequence, period nested within group, formulation, and formulation*group interaction as fixed effects, and subject nested within group*sequence as a random effect. Sequence was tested using subject nested within group*sequence as the error term. If the formulation*group interaction was not statistically significant, at a 5% level, the interaction term was dropped from the model. If a statistically significant interaction was found, results for those pharmacokinetic parameters that show interaction were presented by group as well as combined. Each ANOVA included calculation of least-squares means (LSM), differences between formulation LSM, and the standard error associated with these differences.

Ninety-percent confidence intervals for the ratios of LSM were derived by exponentiation of the confidence intervals obtained for the difference between formulation LSM resulting from the analyses on the ln-transformed AUC 0-t, AUCinf and Cmax PK parameters.

Safety and tolerability were assessed by monitoring adverse events (AEs), clinical laboratory results, vital signs, ECGs and physical examinations.

Results: The ANOVA was performed on the following datasets: 1) including all subjects who had completed the study; and 2) excluding subjects who vomited during the labeled dosing interval (12 hours). Results of the ANOVA are presented below.

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

	Ratio of Least Square Means (%)	CI: Lower Limit (%)	CI: Upper Limit (%)	CV (%)
Including all completed subjects				
AUC _{0-t} (ng-h/mL), N=34	102.2	98.8	105.9	8.6
AUC _{inf} (ng-h/mL), N=30	97.4	91.2	104.1	13.9
C _{max} (ng/mL), N=34	93.8	82.4	106.7	32.2
Excluding subjects who vomited within the labeled dosing interval (12 h)				
AUC _{0-t} (ng-h/mL), N=23	103.6	99.5	107.8	7.6
AUC _{inf} (ng-h/mL), N=21	99.6	94.3	105.1	9.6
C _{max} (ng/mL), N=23	88.8	76.9	102.1	27.4

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

In addition, after excluding subjects who experienced emesis within the labeled dosing interval (12 hours), the confidence intervals for the ratios of least-squares means derived from the analyses of the ln-transformed AUC 0-t and AUC_{inf} were within the 80-125% range. The ratio of least-squares means for the ln-transformed C_{max} was within the 80-125% range. However, the confidence interval of ln-transformed C_{max} was not with a lower limit of 76.9%.

Overall, 34 subjects (94.4%) experienced at least one adverse event possibly, probably or definitely related to study medication (ALO-01 and/or KADIAN[®]); 30 subjects (83.3%) with ALO-01 and 28 subjects (82.4%) with KADIAN[®]. Most of AEs were mild (87%) and the remaining AEs were moderate. There were no serious or severe AEs and all AEs resolved during the study.

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

In addition, after excluding subjects who experienced emesis within the labeled dosing interval (12 hours), the confidence intervals for the ratios of least-squares means derived from the analyses of the ln-transformed AUC 0-t and AUC_{inf} were within the 80-125% range. The ratio of least-squares means for the ln-transformed C_{max} was within the 80-125% range. However, the confidence interval of ln-transformed C_{max} was not with a lower limit of 76.9%.

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

In this study the safety profile of ALO-01 100 mg (morphine sulfate-naltrexone core) capsules was comparable to that of KADIAN[®] 100 mg (morphine sulphate extended-release) capsules under fasting conditions. Both products appear to be generally safe and well tolerated.

Software: The following software were used to generate the report, tables and figures for this study: Microsoft[®] Word 2003, Microsoft[®] Excel 2003, PhAST 2.3-001 and SAS[®] System for Windows[™] releases 6.12 and 8.2.

4.2.3 Synopsis of Study ALO-01-07-102

Title: Comparative, Randomized, Single-Dose, 3-way Crossover Bioavailability Study of Alpharma Pharmaceuticals LLC. Abuse Deterrent KADIAN NT 100 mg Morphine Sulfate-Naltrexone Core Capsules Administered under Fasting and Fed Conditions and Sprinkled on Applesauce in Healthy Adult Volunteers

Objective: The primary objective of this study was to assess the single-dose relative plasma morphine bioavailability of Abuse Deterrent ALO-01 100 mg Morphine Sulfate-Naltrexone Core Capsules (hereafter referred to as ALO-01) administered under fasting and fed conditions and sprinkled on applesauce. The secondary objectives were to evaluate the single-dose plasma naltrexone and 6-beta-naltrexol pharmacokinetics and overall safety of ALO-01 administered under fasting and fed conditions and sprinkled on applesauce.

Study Design: This was an open-label, randomized, single-dose, 3-way crossover, 6-sequence, comparative bioavailability study under fed and fasting conditions, and sprinkled on applesauce. The study was performed on 36 healthy adult non-smoking or light-smoking volunteers (21 males and 15 females). Thirty-two (32) subjects completed the study. Subjects were housed from approximately 10 hours before dosing until after the 168-hour blood draw. Periods were separated by a washout of 14 days.

All subjects received a single oral dose one of ALO-01 100 mg capsule, under the following regimens:

- Regimen A: capsule contents (pellets) sprinkled on applesauce
- Regimen B: intact capsule under fed conditions
- Regimen C: intact capsule under fasting conditions

Methods: The AUC 0-t, AUCinf, AUC 0-t/AUCinf, Cmax, tmax, half-life and kel pharmacokinetic (PK) parameters were calculated for morphine in plasma. For information purposes only, these parameters were also calculated for 6-beta-naltrexol. No pharmacokinetic analysis was performed for naltrexone in plasma, because most concentration values in most subjects were below the limit of quantitation (BLQ).

Analyses of variance (ANOVA) were performed on the ln-transformed AUC 0-t, AUCinf, and Cmax PK parameters for morphine in plasma. Ninety-percent confidence intervals (CI) for the ratios of LSM were derived by exponentiation of the confidence intervals obtained for the difference between regimen LSM resulting from the analyses on the ln-transformed AUC 0-t, AUCinf and Cmax PK parameters for morphine in plasma. The comparisons of interest were: A (sprinkled on applesauce) vs. C (fasted conditions) and B (fed conditions) vs. C (fasted conditions).

Safety and tolerability were assessed by monitoring adverse events (AEs), clinical laboratory results, vital signs, ECGs and physical examinations.

Results: The ANOVA was performed on the following datasets for morphine in plasma: 1) including all subjects who had completed the study and 2) including only those subjects who did not vomit during the labeled dosing interval (12 hours). Results of the ANOVA are presented below.

ANOVA Results for Morphine in Plasma

Parameter	Trt	Ratio of LSM (%)	CI: Lower Limit (%)	CI: Upper Limit (%)	CV (%)
Including subjects with at least one comparison of interest					
AUC 0-t (ng·h/mL) N=34	A/C	98.8	93.5	104.4	13.5
	B/C	90.3	85.4	95.5	

ANALYSIS ALO-01-07-102

Cmax (ng/mL) N=34	A/C	99.0	90.4	108.3	22.2
	B/C	77.8	71.0	85.1	
Including subjects with at least one comparison of interest who did not vomit within the labeled dosing interval (12 h)					
AUC 0-t (ng-h/mL) N=22	A/C	99.6	93.6	106.1	11.1
	B/C	94.2	99.8	99.8	
AUCinf (ng-h/mL) N=18	A/C	104.7	95.0	115.4	15.6
	B/C	102.1	92.6	112.7	
Cmax (ng/mL) N=22	A/C	98.7	87.9	110.7	20.5
	B/C	85.5	76.6	95.1	

A = ALO-01 sprinkled on applesauce; B = ALO-01 intact fed; C = ALO-01 intact fasting

The ratios of LSM and the 90% CI derived from the analyses of the ln-transformed pharmacokinetic parameters AUC 0-t, AUCinf and Cmax for morphine in plasma (ALO-01 pellets sprinkled on applesauce as compared to ALO-01 intact capsules administered under fasting conditions) were within the 80-125% acceptance range in both datasets.

The ratios of LSM and the 90% CI derived from the analyses of the ln-transformed pharmacokinetic parameters AUC 0-t and AUCinf for morphine in plasma (ALO-01 intact capsules administered under fed conditions as compared to fasting conditions) were within the 80-125% acceptance range in both datasets, but not for Cmax.

The median (minimum and maximum) tmax values of morphine in plasma for ALO-01 sprinkled on applesauce, under fed conditions and under fasting conditions including all subjects were 8.00 (6.00 – 18.00) hours, 10.00 (6.00 – 24.00) hours and 7.50 (4.00 – 18.00) hours, respectively.

Single oral doses of 100 mg ALO-01 capsules sprinkled on applesauce and administered under fed and fasted conditions appeared to be generally safe in the healthy adult subjects in this study.

The safety profile of 100 mg ALO-01 capsules sprinkled on apple sauce was comparable to that of 100 mg ALO-01 capsules administered under fasted conditions. Episodes of nausea and vomiting were approximately 2 times less frequent in subjects dosed with ALO-01 under fed conditions, compared to when the capsules were sprinkled on applesauce or administered under fasted conditions. Overall, the frequency of subjects reporting treatment-related AE episodes was slightly lower when ALO-01 capsules were administered under fed conditions as compared to when the capsules were sprinkled on applesauce, or administered under fasted conditions.

Conclusions: The 90% confidence intervals for the ratios of least-squares means derived from the analyses of the ln-transformed pharmacokinetic parameters AUC 0-t, AUCinf and Cmax for morphine in plasma (ALO-01 pellets sprinkled on applesauce as compared to ALO-01 intact capsules administered under fasting conditions) were within the 80-125% acceptance range, indicating that the total extent of exposure and the rate and extent of bioavailability were clinically equivalent for both regimens.

The 90% confidence intervals for the ratios of least-squares means derived from the analyses of the ln-transformed pharmacokinetic parameters AUC 0-t and AUCinf for morphine in plasma (ALO-01 intact capsules administered under fed conditions as compared to fasting conditions) were within the 80-125% acceptance range, but the confidence intervals for Cmax were not, indicating that the administration of food (high-fat breakfast) results in delayed and lower maximum concentrations, as compared to fasting conditions.

Based on these results, ALO-01 100 mg capsules displayed similar pharmacokinetics (AUC, C_{max}) whether the contents of the capsules (pellets) were sprinkled on applesauce or the capsules were administered intact under fasting conditions. A lower rate and extent of bioavailability (C_{max}) was observed after ALO-01 was administered with food as compared to fasting conditions, but the total exposure to the drug (AUC) remained the same. This is consistent with the pharmacokinetics of KADIAN[®].

Single oral doses of 100 mg ALO-01 capsules sprinkled on applesauce and administered under fed and fasted conditions appear to be generally safe in healthy adult subjects in this study.

The safety profile of 100 mg ALO-01 capsules sprinkled on applesauce was comparable to that of 100 mg ALO-01 capsules administered under fasted conditions. The frequency of subjects reporting treatment-related AE episodes was slightly lower when ALO-01 capsules were administered under fed conditions as compared to when the capsules were sprinkled on applesauce, or administered under fasted conditions.

Software: The following software were used to generate the report, tables and figures for this study: Microsoft[®] Word 2003, Microsoft[®] Excel 2003, PhAST 2.3-001, SAS[®] System for Windows[™] releases 6.12 and 8.2, and SAS[®] 8.2 for Open VMS.

4.2.4 Synopsis of Study ALO-01-104

Name of Sponsor/Company: Alpharma Pharmaceuticals LLC		Individual Study Table Referring to Part of the Dossier: Volume: Page:	(For National Authority Use Only)
Name of Finished Product: ALO-01			
Name of Active Ingredients: morphine sulfate and naltrexone hydrochloride			
Title of Study: A Randomized Three-Way Crossover, Single-Dose, Open-Label Study to Evaluate the Relative Bioavailability of a Crushed KADIAN® Abuse Deterrent Product (KADIAN NT) Following Oral Administration to Healthy Adult Subjects Under Fasted Conditions			
Investigators: (b) (4)			
Study Center(s): (b) (4)			
Publication (reference): None			
Study Period (days): 12 February – 19 March 2007		Phase of Development: 1	
<p>Objectives: The primary objectives of this study were to compare the plasma morphine, naltrexone, and 6-β-naltrexol relative bioavailability of a <i>crushed</i> ALO-01 (1 × 60 mg) capsule manufactured by Alpharma Pharmaceuticals LLC to an equivalent oral dose of a <i>whole, intact</i> ALO-01 (1 × 60 mg) capsule manufactured by Alpharma Pharmaceuticals LLC following an overnight fast of 10 hours and to compare the plasma naltrexone, and 6-β-naltrexol relative bioavailability of a <i>crushed</i> ALO-01 (1 × 60 mg) capsule manufactured by Alpharma Pharmaceuticals LLC to a naltrexone oral solution (1 × 2.4 mg naltrexone) (b) (4) following an overnight fast of 10 hours.</p> <p>The secondary objective of this study was to compare the naltrexone and 6-β-naltrexol relative bioavailability of a <i>whole, intact</i> ALO-01 (1 × 60 mg) capsule manufactured by Alpharma Pharmaceuticals LLC to a naltrexone oral solution (1 × 2.4 mg naltrexone hydrochloride) (b) (4) following an overnight fast of at least 10 hours.</p>			
<p>Study Design (Methodology): This was a single-dose, open-label, randomized, three-period, three-treatment crossover study in which 24 healthy adult subjects were scheduled to receive three separate single-dose administrations of study drug, crushed ALO-01 (1 × 60 mg) capsule, whole intact ALO-01 (1 × 60 mg) capsule and naltrexone (1 × 2.4 mg) oral solution, following an overnight fast.</p>			
Number of Subjects:	24	Planned:	24
		Analyzed:	23
<p>Diagnosis and Main Criteria for Inclusion: Healthy adult male or non-pregnant, non-breast-feeding female volunteers, between 18 – 55 years of age, with BMI between 18 – 30 kg/m², inclusive, and body weight of at least 50 kg (110 lbs).</p>			
<p>Treatment A & B, Dose and Mode of Administration, Lot Number: ALO-01 (1 × 60 mg oral capsule) Lot PI-1594</p>			
<p>Duration of Treatment: Three single dose treatments were administered with a 14-day washout period between doses.</p>			

Name of Sponsor/Company: Alpharma Pharmaceuticals LLC	Individual Study Table Referring to Part of the Dossier:	(For National Authority Use Only)
Name of Finished Product: ALO-01	Volume:	
Name of Active Ingredients: morphine sulfate and naltrexone hydrochloride	Page:	
Treatment C, Dose and Mode of Administration, Lot Number: naltrexone hydrochloride (1 × 2.4 mg oral solution) Lot C115850		
Criteria for Evaluation: Efficacy: No efficacy evaluations were performed in this study. Safety: Physical examinations by a qualified investigator as well as clinical laboratory tests and electrocardiograms, were performed and evaluated to monitor subject safety during screening and at study discharge. Subjects were monitored for any adverse events from time of informed consent through the end of the study.		
Pharmacokinetic Analysis and Statistical Methods: <p>Data from 23 subjects who completed the study were included in the pharmacokinetic and statistical analyses. The concentration-time data were transferred from Watson directly to WinNonlin Enterprise Edition (Version 4.0, Pharsight Corporation) using the Custom Query Builder option for analysis. Data were analyzed by noncompartmental methods in WinNonlin. Concentration-time data that were below the limit of quantification (BLQ) were treated as zero (0.00 ng/mL) in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as "missing". Full precision concentration data (not rounded to three significant figures) and actual sample times were used for all pharmacokinetic and statistical analyses.</p> <p>The following pharmacokinetic parameters were calculated: peak concentration in plasma (C_{max}), time to peak concentration (T_{max}), elimination rate constant (k_{el}), terminal half-life ($T_{1/2}$), area under the concentration-time curve from time-zero to the time of the last quantifiable concentration (AUC_{last}), and area under the plasma concentration time curve from time-zero extrapolated to infinity (AUC_{inf}).</p> <p>Analysis of variance (ANOVA) and the Schulmann's two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max}, AUC_{last}, and AUC_{inf}. The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals of the log-transformed parameters were within 80% to 125%.</p>		

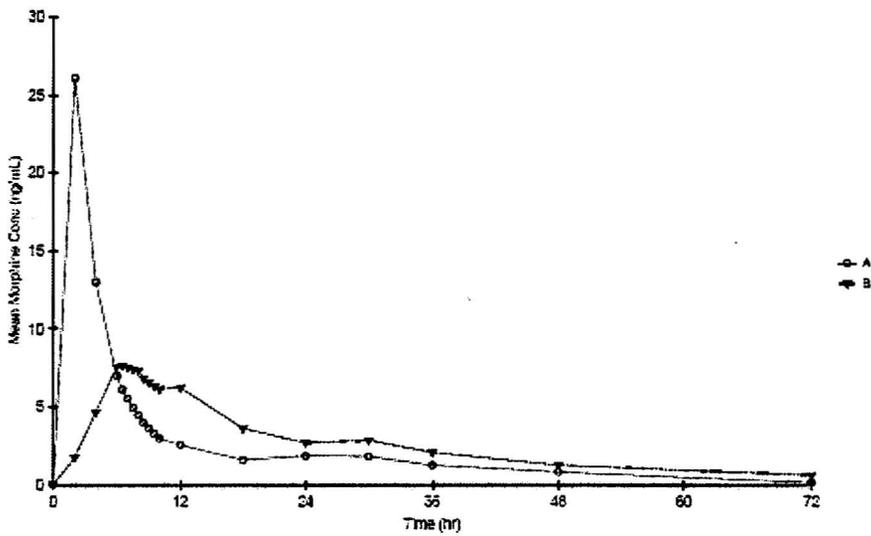
Name of Sponsor/Company: Alpharma Pharmaceuticals LLC	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(For National Authority Use Only)
Name of Finished Product: ALO-01		
Name of Active Ingredients: morphine sulfate and naltrexone hydrochloride		

SUMMARY - CONCLUSIONS

PHARMACOKINETIC RESULTS:

Mean concentration-time data are shown in Synopsis Figures 1 through 3. Results of the pharmacokinetic and statistical analyses are shown below in Synopsis Tables 1 through 6.

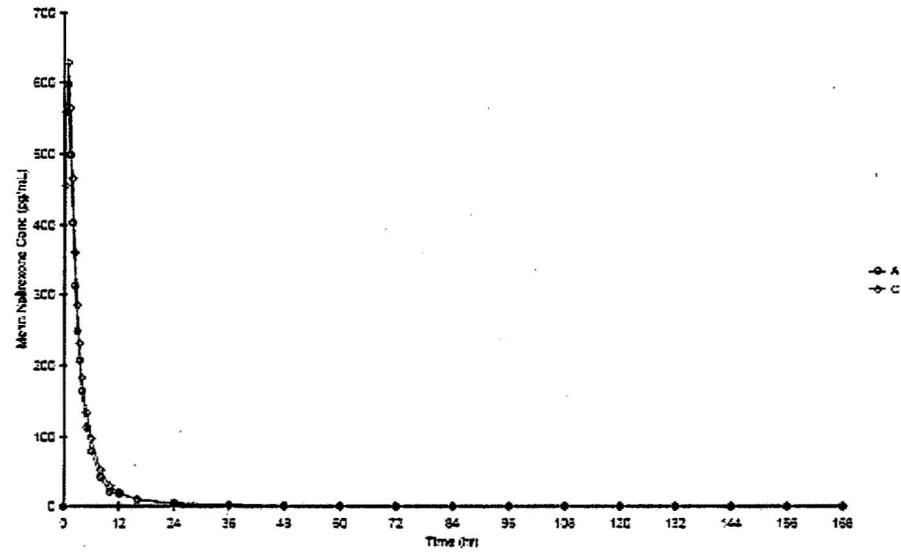
Synopsis Figure 1: Mean Morphine Concentration-Time Profiles after Administration of Crushed ALO-01 (Treatment A) and Whole, Intact ALO-01 (Treatment B)



Source data: Tables 14.2.1-14.2.2

Name of Sponsor/Company: Alpha Pharma Pharmaceuticals LLC	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(For National Authority Use Only)
Name of Finished Product: ALO-01		
Name of Active Ingredients: morphine sulfate and naltrexone hydrochloride		

Synopsis Figure 2: Mean Naltrexone Concentration-Time Profiles after Administration of Crushed ALO-01 (Treatment A) and Naltrexone HCl Solution (Treatment C)

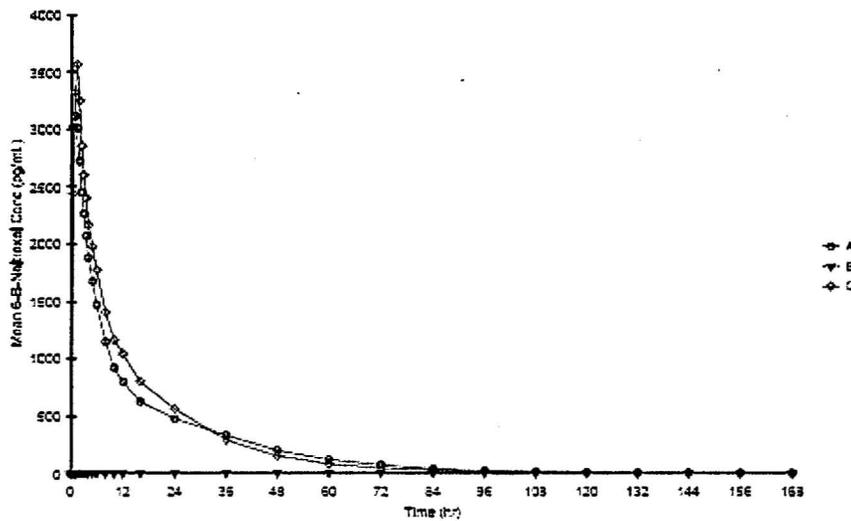


Source data: Tables 14.2.3 - 14.2.4

Synopsis ALO-01-104

Name of Sponsor/Company: Alpharma Pharmaceuticals LLC	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(For National Authority Use Only)
Name of Finished Product: ALO-01		
Name of Active Ingredients: morphine sulfate and naltrexone hydrochloride		

Synopsis Figure 3: Mean 6-β-Naltrexol Concentration-Time Profiles after Administration of Crushed ALO-01 (Treatment A), Whole, Intact ALO-01 (Treatment B), and Naltrexone HCl Solution (Treatment C)



Source: Data Tables 14.2.5 - 14.2.7

Synopsis Table 1: Pharmacokinetic Parameters of Morphine after Administration of Crushed ALO-01 (Treatment A) and Whole, Intact ALO-01 (Treatment B)

Parameter	Treatment A: ALO-01 - Crushed			Treatment B: ALO-01 - Whole, Intact		
	n	Mean	CV%	n	Mean	CV%
T _{max} (hr)*	23	2.00 [2.00-2.10]		23	7.03 [6.00-12.00]	
C _{max} (ng/mL)†	23	24.5	34.99	23	7.73	42.36
AUC _{last} (hr*ng/mL) †	23	162.6	33.10	23	173.7	31.40
AUC _{inf} (hr*ng/mL) †	23	177.4	29.30	23	201.8	37.53
T _{1/2} (hr)	23	16.75	51.11	23	23.96	76.54
CL/F (L/hr)	23	351.0	27.20	23	316.0	35.11
V _z /F (L)	23	8641	62.03	23	9885	55.69

Note: Full precision data used in pharmacokinetic analysis

*Reported as Median [Range]

† Reported as Geometric Mean

Source data: Tables 14.2.8 and 14.2.10

Synopsis ALO-01-104

Name of Sponsor/Company: Alpharma Pharmaceuticals LLC	Individual Study Table Referring to Part of the Dossier: Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: ALO-01		
Name of Active Ingredients: morphine sulfate and naltrexone hydrochloride		

Synopsis Table 2: Pharmacokinetic Parameters of Naltrexone after Administration of Crushed ALO-01 (Treatment A) and Naltrexone HCl Solution (Treatment C)

Parameter	Treatment A: ALO-01 - Crushed			Treatment C: Naltrexone HCl Solution		
	n	Mean	CV%	n	Mean	CV%
T _{max} (hr)*	23	1.00 [0.50-2.00]		23	1.00 [0.50-2.00]	
C _{max} (pg/mL)†	23	579	62.81	23	584	62.27
AUC _{0-∞} (hr*pg/mL) †	23	1811	61.19	23	1954	57.60
AUC _{inf} (hr*pg/mL) †	23	1870	61.29	23	2000	56.92
T _{1/2} (hr)	23	7.45	71.37	23	4.04	42.64
CL/F (L/hr)	23	1433	43.87	23	1317	42.34
V _Z /F (L)	23	13410	81.91	23	7475	61.76

Note: Full precision data used in pharmacokinetic analysis

*Reported as Median [Range]

† Reported as Geometric Mean

Source data: Tables 14.2.12 and 14.2.14

Synopsis Table 3: Pharmacokinetic Parameters of 6-β-Naltrexol after Administration of Crushed ALO-01 (Treatment A), Whole, Intact ALO-01 (Treatment B), and Naltrexone HCl Solution (Treatment C)

Parameter	Treatment A: ALO-01 - Crushed			Treatment B: ALO-01 - Whole, Intact			Treatment C: Naltrexone HCl Solution		
	n	Mean	CV%	n	Mean	CV%	n	Mean	CV%
T _{max} (hr)*	23	1.00 [0.50-2.00]		11	60.00 [1.50-84.03]		11	1.00 [0.50-2.53]	
C _{max} (pg/mL)†	23	3530	35.43	11	8.91	95.54	11	3710	34.39
AUC _{0-∞} (hr*pg/mL) †	23	38130	30.48	11	304.3	118.56	11	41330	29.64
AUC _{inf} (hr*pg/mL) †	23	38210	30.47	10	367.7	110.01	10	41440	29.65
T _{1/2} (hr)	23	19.03	15.35	10	16.86	20.89	10	26.32	39.22

Note: Full precision data used in pharmacokinetic analysis

*Reported as Median [Range]

† Reported as Geometric Mean

Source data: Tables 14.2.16, 14.2.18, and 14.2.20

Synopsis ALO-01-104

Name of Sponsor/Company: Alpha Pharma Pharmaceuticals LLC	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(For National Authority Use Only)
Name of Finished Product: ALO-01		
Name of Active Ingredients: morphine sulfate and naltrexone hydrochloride		

Synopsis Table 4: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Morphine after Administration of Crushed ALO-01 (Treatment A) and Whole, Intact ALO-01 (Treatment B) n=23

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C _{max})	24.3842	7.7622	314.14	288.93	341.54	0.9953	16.52
ln(AUC _{last})	162.9555	174.5450	93.36	87.49	99.63	0.9998	12.81
ln(AUC _{inf})	177.6866	202.8975	87.57	78.04	98.28	0.9389	22.92

Excluding Subjects Due to Adverse Events n=17

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C _{max})	23.1336	6.9532	332.70	304.46	363.56	0.9909	14.35
ln(AUC _{last})	159.4948	161.5546	98.73	94.55	103.08	1.0000	6.96
ln(AUC _{inf})	171.2891	174.5067	98.16	94.20	102.28	1.0000	6.64

^a Geometric Mean for Treatment A - ALO-01 Crushed (Test) and Treatment B - ALO-01 Whole, Intact (Ref) based on Least Squares Mean of log-transformed parameter values

^b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

^c 90% Confidence Interval

Source data: Listing 16.4.3.1, 16.4.3.2, 16.4.3.7, and 16.4.3.8

Name of Sponsor/Company: Alpharma Pharmaceuticals LLC	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(For National Authority Use Only)
Name of Finished Product: ALO-01		
Name of Active Ingredients: morphine sulfate and naltrexone hydrochloride		

Synopsis Table 5: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Naltrexone after Administration of Crushed ALO-01 (Treatment A) and Naltrexone HCl Solution (Treatment C) n=23

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C _{max})	571.2954	579.8535	98.52	83.79	115.85	0.7390	32.61
ln(AUC _{last})	1798.1676	1949.0311	92.26	83.34	102.14	0.9736	20.16
ln(AUC _{inf})	1857.1264	1994.4908	93.11	84.43	102.69	0.9804	19.39

Excluding Subjects Due to Adverse Events n=18

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C _{max})	523.9604	534.6031	98.01	82.61	116.28	0.7005	29.59
ln(AUC _{last})	1734.1037	1855.0268	93.48	85.37	102.36	0.9891	15.47
ln(AUC _{inf})	1801.7316	1903.0223	94.68	86.94	103.11	0.9937	14.53

^a Geometric Mean for Treatment A - ALO-01 Crushed (Test) and Treatment C - Naltrexone HCl Solution (Ref) based on Least Squares Mean of log-transformed parameter values

^b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

^c 90% Confidence Interval

Source data: Listing 16.4.3.3, 16.4.3.4, 16.4.3.9, and 16.4.3.10

Synopsis ALO-01-104

Name of Sponsor/Company: Alpharma Pharmaceuticals LLC	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(For National Authority Use Only)
Name of Finished Product: ALO-01		
Name of Active Ingredients: morphine sulfate and naltrexone hydrochloride		

Synopsis Table 6: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of 6-β-Naltrexol after Administration of Crushed ALO-01 (Treatment A) and Naltrexone HCl Solution (Treatment C) n=23

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C _{max})	3500.9945	3696.3222	94.72	86.30	103.95	0.9872	18.42
ln(AUC _{last})	38132.8195	41339.3744	92.24	85.52	99.50	0.9984	14.94
ln(AUC _{inf})	38211.4698	41451.1518	92.18	85.45	99.45	0.9984	14.98

Excluding Subjects Due to Adverse Events n=18

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C _{max})	3191.9529	3335.4647	95.70	85.14	107.56	0.9342	20.01
ln(AUC _{last})	35434.4178	37566.8909	94.32	86.70	102.62	0.9944	14.36
ln(AUC _{inf})	35502.9269	37651.4878	94.29	86.66	102.60	0.9943	14.38

^a Geometric Mean for Treatment A - ALO-01 Crushed (Test) and Treatment C - Naltrexone HCl Solution (Ref) based on Least Squares Mean of log-transformed parameter values

^b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

^c 90% Confidence Interval

Source data: Listing 16.4.3.5, 16.4.3.6, 16.4.3.11, and 16.4.3.12

Synopsis ALO-01-104

Name of Sponsor/Company: Alharma Pharmaceuticals LLC	Individual Study Table Referring to Part of the Dossier:	<i>(For National Authority Use Only)</i>
Name of Finished Product: ALO-01	Volume: Page:	
Name of Active Ingredients: morphine sulfate and naltrexone hydrochloride		
<p>SAFETY RESULTS:</p> <p>Subjects were monitored for any adverse events from the time of consent until study discharge. Two adverse events were reported pre-dose period 1. A total of 89 treatment-emergent AEs were reported by 15 of the 24 subjects over the course of the study. Eighty-seven of the AEs were mild and two were moderate. Forty-six of the AEs were definitely related, 10 were probably related, 9 were possibly related, and 24 were not related to the study treatment. No clinically significant abnormalities in vital signs, ECGs, or physical exams were observed. Please refer to Section 14, Table 3.1 for more detailed data regarding AE/study treatment relationship.</p> <p>CONCLUSIONS:</p> <p>The relative bioavailability of plasma naltrexone and 6-β-naltrexol from crushed ALO-01 was bioequivalent to the naltrexone oral solution for rate, extent and total absorption.</p> <p>The relative bioavailability of plasma morphine from crushed ALO-01 was similar to the whole, intact product for total exposure only. The rate and extent of exposure of plasma morphine from crushed ALO-01 was similar to a morphine IR product.</p> <p>Naltrexone and 6-β-naltrexol were successfully sequestered in ALO-01 whole, with only sparse measurable concentrations close to the limit of quantitation in a few subjects.</p> <ul style="list-style-type: none"> • There were no unusual or unexpected adverse events related to the study medication. Subjects tolerated all study treatments. 		
<p>Date of Report: 11 October 2007</p>		

4.2.5 Synopsis of Study ALO-01-07-103

Title: A Phase 1, Single-Center, Open-label, Drug Interaction Study to Evaluate the Effect of Alcohol Ingestion on the Pharmacokinetics of Alpharma Branded Products Division Inc. Abuse Deterrent KADIAN NT 60 mg Morphine Sulfate-Naltrexone Core Capsules in Healthy Adult Volunteers under Fasting Conditions

Objective: The objective of this study was to compare the single-dose relative bioavailability of Abuse Deterrent ALO-01 60 mg morphine sulfate-naltrexone core capsules (hereafter referred to as ALO-01) when dosed with 4%, 20% and 40% alcohol under fasting conditions compared to water.

Study Design: This was an open-label, randomized, single-dose, 4-way crossover, 4-sequence, pharmacokinetic drug interaction study between 60 mg morphine sulfate-naltrexone core extended-release capsules and alcohol, following their administrations under fasting conditions. The study was performed on 32 healthy adult volunteers (29 males and 3 females) who were divided into three groups for dosing: Group 1 (Subject Nos. 1 - 10), Group 2 (Subject Nos. 11 - 20) and Group 3 (Subject Nos. 21 - 32). Thirty-one (31) subjects completed the study. Subjects were housed from at least 10 hours before dosing until after the 36-hour blood draw and following the alcohol breath test, as judged by the Principal Investigator or his designate. Subjects returned for the remaining blood samples up to 168 hours post-dose. Each period (morphine administration) was separated by a washout of 14 days.

All subjects received a single oral dose of one 60 mg ALO-01 capsule under fasting conditions, and were randomized to the following regimens:

Regimen A: ALO-01 with 4% alcohol
Regimen B: ALO-01 with 20% alcohol
Regimen C: ALO-01 with 40% alcohol
Regimen D: ALO-01 with water

Methods: The AUC 0-t, AUCinf, AUC 0-t/AUCinf, Cmax, tmax, half-life and kel pharmacokinetic (PK) parameters were calculated for morphine in plasma. For information purposes only, these parameters were also calculated for 6-beta-naltrexol. No pharmacokinetic analysis was performed for naltrexone in plasma, because most concentration values in most subjects were below the limit of quantitation (BLQ). Analyses of variance (ANOVA) were performed on the ln-transformed AUC 0-t, AUCinf, and Cmax PK parameters for morphine in plasma.

Ninety-percent confidence intervals for the ratios of least-squares means (LSM) were derived by exponentiation of the confidence intervals obtained for the difference between regimen LSM resulting from the analyses on the ln-transformed AUC 0-t, AUCinf and Cmax PK parameters for morphine in plasma. The comparisons of interest were: A vs. D, B vs. D, and C vs. D.

Safety and tolerability were assessed by monitoring adverse events (AEs), clinical laboratory results, vital signs, ECGs and physical examinations. In addition, alcohol blood tests and an alcohol breath test were performed.

Results: The ANOVA was performed on the following datasets for morphine in plasma: 1) including all subjects who had completed at least two periods of the study corresponding to a comparison of interest, 2) including those subjects who did not vomit during the labeled dosing interval (12 hours). Results of the ANOVA are presented below.

ANOVA Results for Morphine in Plasma

Parameter	Trt	Ratio of Least Square Means (%)	CI: Lower Limit (%)	CI: Upper Limit (%)	CV (%)
Including subjects with at least one comparison of interest					
AUC 0-t (ng-h/mL)	A/D	100.0	91.3	109.5	21.8
	B/D	96.7	88.3	105.8	
	C/D	97.3	88.9	106.5	
Cmax (ng/mL)	A/D	102.1	90.6	115.0	28.6
	B/D	107.2	95.3	120.8	
	C/D	199.5	177.5	224.4	
Including subjects with at least one comparison of interest who did not vomit within the labeled dosing interval (12 h)					
AUC 0-t (ng-h/mL)	A/D	98.9	94.3	103.8	11.3
	B/D	96.8	92.3	101.6	
	C/D	102.7	97.3	108.5	
Cmax (ng/mL)	A/D	101.5	92.0	111.9	23.3
	B/D	107.1	97.1	118.2	
	C/D	204.4	183.0	228.4	

A = ALO-01 + 4% alcohol; B = ALO-01 + 20% alcohol; C = ALO-01 + 40% alcohol; D = ALO-01

The median (minimum and maximum) tmax values for regimens A, B, C and D were 8.00 (2.50 – 18.00) hours, 8.00 (4.00 – 12.00) hours, 4.00 (2.00 – 6.00) hours and 9.00 (2.50 – 12.00) hours, respectively.

ANOVA results are not presented for AUCinf, since most of the subjects' terminal phase parameters could not be estimated (there were only up to 12 subjects per treatment).

The ratios of LSM and the 90% CI derived from the analyses of the ln-transformed pharmacokinetic parameters AUC 0-t and Cmax for morphine in plasma (ALO-01 administered with 4% or 20% alcohol as compared to ALO-01 alone) were within the 80-125% acceptance range.

The ratio of LSM and the 90% CI derived from the analyses of the ln-transformed pharmacokinetic parameter AUC 0-t for morphine in plasma (ALO-01 + 40% alcohol as compared to ALO-01 alone) were within the 80-125% acceptance range. The ratio of LSM and the 90% CI derived from the analyses of the ln-transformed pharmacokinetic parameter Cmax for morphine in plasma (ALO-01 + 40% alcohol as compared to ALO-01 alone) were approximately 200% and consequently, the tmax was earlier by 5 hours.

The sequestration of naltrexone in ALO-01 was successful when administered with 4%, 20% and 40% alcohol as evidenced by only a few naltrexone concentrations, which were low and similar to ALO-01 with water. Overall, 8 of the 32 subjects (25%) had measurable plasma naltrexone concentrations during the study. Plasma naltrexone concentrations ranged from 4.41 to 14.6 pg/mL. Concentrations of 6-beta-naltrexol following dosing with ALO-01 with 4%, 20% and 40% alcohol were also low and similar to ALO-01 with water. Plasma 6-beta-naltrexol concentrations ranged from 0.501 – 221 pg/mL.

Single oral doses of 60 mg ALO-01 Morphine Sulfate (naltrexone core) capsules administered with 4% alcohol, 20% alcohol, 40% alcohol or water were tolerated by healthy adult subjects under fasting conditions.

Conclusions: The rate and extent of bioavailability and total exposure to ALO-01 (AUC, Cmax) were not affected when the drug was administered concomitantly with either 4% or 20% alcohol, in comparison to administration without alcohol.

When ALO-01 was administered with 40% alcohol, the rate and extent of bioavailability (C_{max}) doubled and the t_{max} was earlier by 5 hours, when compared to administration of ALO-01 without alcohol. The total systemic exposure to the drug (AUC) was not affected.

Co-administration of alcohol had no effect on the sequestration of naltrexone.

Single oral doses of 60 mg ALO-01 capsules administered with 4% alcohol, 20% alcohol, 40% alcohol or water under fasting conditions were tolerated by all subjects during the study.

The safety profile of 60 mg ALO-01 capsules after administration with water was comparable to administration with 4% alcohol under fasting conditions. AEs were most frequent when ALO-01 capsules were administered with 40% alcohol, followed by administration with 20% alcohol, in comparison to administration with water.

Software: The following software were used to generate the report, tables and figures for this study: Microsoft[®] Word 2003, Microsoft[®] Excel 2003, PhAST 2.3-001, SAS[®] System for Windows[™] releases 6.12 and 8.2, and SAS[®] 8.2 for Open VMS.

4.2.6 Synopsis of Study ALO-KNT-201

Name of Sponsor/Company: Alharma Branded Products Division Inc.	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use only)</i>
Name of Finished Product:	Volume:	
Name of Active Ingredient: Morphine and naltrexone	Page:	
Title of Study: Restricted-randomized, double-blind, cross-over, placebo-controlled trial evaluating the effect of dose ranging of naltrexone on the morphine-induced euphoria in non-dependent, opioid- experienced subjects under fasting conditions.		
Investigators: The clinical trial was conducted under the direction of Dr. Myroslava Romach. The analytical phase was conducted under the direction of (b) (4) .		
Study center(s): Ventana Clinical Research Corporation 720 King St. W., Suite 700 Toronto, ON M5V 2T3 Canada		
Publication (reference): Not applicable.		
Studied Period: First subject enrolled: 9 October 05 Last subject completed: 12 December 2005	Phase of Development: Phase I	
Objectives: The primary objective of this study was to assess the appropriate naltrexone to morphine ratio required to abate the euphoric effects of morphine in opiate experienced non-dependent drug users. A secondary objective was to assess the safety and tolerability of the combination of morphine with naltrexone. Lastly, an exploratory objective was to assess morphine and naltrexone pharmacokinetics when the drugs were administered together.		
Methodology: This was a single center, restricted-randomized, double blind, crossover, placebo controlled study in healthy subjects with a history of recreational opiate use. A qualifying visit was conducted to determine if subjects could distinguish a single dose of morphine from placebo. Subsequently, a treatment period was conducted to assess the appropriate naltrexone to morphine ratio required to abate the euphoric effects of morphine.		
Pre-Randomization Period The qualification session lasted approximately 60 hours. The subjects were admitted to the		

Name of Sponsor/Company: Alpharma Branded Products Division Inc.	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
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<p>research unit the evening prior to the first dosing. During the session the subjects were administered two treatments, morphine 120 mg and morphine placebo, according to a double blind randomized crossover design and the treatments were separated by 24 hours. The subjects were required to fast from approximately 10:00 pm prior to each dosing until approximately four hours after dosing. All treatments were administered between 8:00 am and 10:00 am. A range of pharmacodynamic, safety and pharmacokinetic measures were repeatedly collected to assess subjects' tolerability of the two treatments and their ability to distinguish between them. Only subjects who tolerated the morphine sulfate 120 mg treatment (without clinically significant adverse events related to the drug such as excessive sedation, respiratory depression rate [eight or less breaths per minute] and vomiting [two or more episodes]) and who were able to discriminate the effect of morphine from placebo (peak change score from placebo on Visual Analog Scale Drug Effect Questionnaire (VAS DEQ) for Drug Liking > 30 mm on a 100 mm VAS) were included in the Treatment Period.</p>		
<p>Since the VAS Drug Liking scale is a bipolar scale, it evaluates drug liking and disliking. Therefore the liking component of the scale is only 50 mm and 15 mm peak change score on 50 mm VAS scale is equivalent to 30 mm peak change score on 100 mm VAS scale.</p>		
<p>Treatment Period</p>		
<p>During the Treatment Period, subjects received seven different treatments in a seven visit, double blind, restricted-randomized, and crossover design.</p>		
<p>In Stage 1 Dosing, five treatments were administered: morphine (120 mg as oral solution) in combination with three different doses of naltrexone (2.4, 4.8, or 9.6 mg as oral solution) or naltrexone placebo as well as morphine placebo in combination with naltrexone placebo.</p>		
<p>Following Stage 1 Dosing an interim analysis was conducted based on which it was decided to administer the Stage 2 Dosing. Stage 2 Dosing treatments consisted of the administration of morphine (120 mg as oral solution) with one of two doses of naltrexone (19.2 and 38.4 mg as oral solution).</p>		
<p>For each Treatment Visit, subjects were admitted to the research unit for approximately 36 hours, from the evening before dosing until approximately 24 hours post dosing. The subjects were required to fast from approximately 10:00 pm the day before dosing until approximately 12:00 pm the next day (four hours after dosing).</p>		
<p>For the Treatment Stage pharmacodynamic, pharmacokinetic, and safety measures were determined at different time points. Treatment periods were separated by at least 6 to 14 days between dose administrations.</p>		
<p>Number of patients (planned and analysed): Planned: 20 Analysed: 19 (Per Protocol Population); 16 (Responder Population)</p>		

Name of Sponsor/Company: Alpharma Branded Products Division Inc.	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use only)</i>
Name of Finished Product:	Volume:	
Name of Active Ingredient: Morphine and naltrexone	Page:	
<p>Diagnosis and main criteria for inclusion:</p> <p>27 healthy male and female subjects, aged 18 to 55 years, inclusive, who had previous experience with opiates, but who were not physically dependent on opiates as confirmed by medical history and DSM IV criteria entered the study. Opiate use was defined as non-therapeutic use at least 10 times in the last 12 months and at least once in the 12 weeks prior to screening.</p>		
<p>Test product, dose and mode of administration, batch number:</p> <p>Stage 1 Subjects received each of the following treatments orally:</p> <ul style="list-style-type: none"> ○ morphine sulfate 120 mg + naltrexone HCl placebo ○ morphine sulfate placebo + naltrexone HCl placebo ○ morphine sulfate 120 mg + naltrexone HCl 2.4 mg (naltrexone/morphine ratio - 1:50) ○ morphine sulfate 120 mg + naltrexone HCl 4.8 mg (1:25) ○ morphine sulfate 120 mg + naltrexone HCl 9.6 mg (1:12.5) <p>Stage 2 Subjects received the following treatments orally:</p> <ul style="list-style-type: none"> ○ morphine sulfate 120 mg + naltrexone HCl 19.2 mg (1:6.25) ○ morphine sulfate 120 mg + naltrexone HCl 38.4 mg (1:3.125) <p>Statex® oral drops (lot numbers 403854, 402721) was administered as morphine sulfate and Revia® (lot numbers 201774002, 201775002) was administered as naltrexone hydrochloride. Mott's™ was administered as morphine and naltrexone placebo.</p>		
<p>Duration of treatment:</p> <p>Duration of the study from the Screening Visit to the Follow-Up Visit was up to 22 weeks. The duration of the Treatment Period (including Stage 1 and 2 Dosing) was up to 10 weeks.</p>		
<p>Reference therapy, dose and mode of administration, batch number:</p> <p>N/A</p>		

Name of Sponsor/Company: Alpharma Branded Products Division Inc.	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use only)</i>
Name of Finished Product:	Volume:	
Name of Active Ingredient: Morphine and naltrexone	Page:	
Criteria for Evaluation: Efficacy: <ul style="list-style-type: none"> ○ The primary variables assessed in this study were changes in the following scales as summarized by peaks, mean and the AUC: <ul style="list-style-type: none"> ○ VAS DEQ for Drug Liking. ○ Subjective Drug Value. ○ Addiction Research Centre Inventory (ARCI) – Morphine Benzadrine Group (MBG). ○ Cole/ARCI Abuse Potential ○ Cole/ARCI Stimulation-Euphoria ○ The secondary variables assessed in this study were changes in the following scales as summarized by peaks, mean and the AUC: <ul style="list-style-type: none"> ○ VAS DEQ for Any Drug Effects, ○ VAS DEQ High. ○ VAS DEQ Good Effects. ○ VAS DEQ Bad Effects. ○ VAS DEQ Sick. ○ VAS DEQ Nausea. ○ VAS DEQ Sleepy. ○ VAS DEQ Dizzy. ○ ARCI scales (except MBG scale) ○ Cole/ARCI (except Abuse Potential and Stimulation-Euphoria scale) ○ Pupillometry ○ Plasma levels of morphine and naltrexone and its metabolite (6-beta-naltrexol) were assessed as an exploratory variable. Safety: <ul style="list-style-type: none"> ○ Type, incidence and severity of adverse events ○ Vital signs (sitting blood pressure, respiration rate, heart rate and temperature) ○ 12-lead electrocardiogram (ECG) ○ Cardiac telemetry (pulse rate, 3-lead ECG, oxygen saturation) ○ Clinical laboratory (at screening and follow-up). 		
Statistical Methods:		

Name of Sponsor/Company: Alpharma Branded Products Division Inc.	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use only)</i>
Name of Finished Product:	Volume:	
Name of Active Ingredient: Morphine and naltrexone	Page:	
<p>Post-dose pharmacodynamic data for each naltrexone to morphine ratio was summarized as: means, peaks, and areas under the curve for responses on each measure and over the eight hours since dosing for all measures, and at 24 hours for Subjective Drug Value. The means, peaks and AUCs, separately, were entered into a statistical model with treatment and period as fixed effects, baseline (pre-dose) measurement as a covariate, and subject as a random effect. From this model, analyzed via PROC MIXED of SAS 8.2, means and confidence intervals for treatments and treatment differences were computed, along with the statistical significances of all treatment differences. The Benjamini and Hochberg procedure (Benjamini & Hochberg, 1995) was used to control for Type I errors arising from the multiple comparisons to be undertaken. The detailed description of study population, statistical model applied, pharmacodynamic measures and safety analysis was provided in the statistical analysis plan (SAP). The SAP was finalized prior to the database lock. An informal and pre-planned interim analysis was performed. Supplemental analysis requested by the sponsor was also conducted.</p>		
<p>SUMMARY – CONCLUSIONS</p>		
<p>EFFICACY RESULTS:</p>		
<p>Pharmacodynamic results:</p>		
<p>The objective of this study was to assess the appropriate naltrexone to morphine ratio required to abate the euphoric effects of morphine. Thus the pharmacodynamic results have been organized primarily by pharmacologic effect with the emphasis on the measures of the positive effects (as assessed by:</p>		
<ul style="list-style-type: none"> o VAS Liking, o VAS High, o VAS Good Effects, o Subjective Drug Value, o ARCI Morphine Benzedrine Group, o Cole\ARCI Stimulation Euphoria, o Cole\ARCI Abuse Potential. 		
<p>Administration of oral solutions of morphine 120 mg and co-administration of naltrexone 2.4 mg, 4.8 mg, 9.6 mg, 19.2 mg and 38.4 mg with morphine 120 mg resulted in distinct response patterns for the positive measures confirmed by the significant treatment effects that were observed on all variables per planned analysis [maximum effect (E_{MAX}) and area under the response curve 0-24 h post dose (AUE_{0-24h})]. Additionally the morphine induced positive effects were significantly elevated in comparison to the placebo induced</p>		

Name of Sponsor/Company: Alpharma Branded Products Division Inc.	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product:	Volume:	
Name of Active Ingredient: Morphine and naltrexone	Page:	
<p>positive effect thus confirming validity of this study. For instance, on VAS Drug Liking the difference between the mean peak value for morphine and placebo was 29.7 mm on a 100 mm bipolar scale. A summary of the maximum effect (Emax) for each measure is displayed in Error! Reference source not found.</p> <p>Morphine administration resulted in a characteristic and expected increase for the positive effects scales. The mean positive effects for the morphine alone treatment peaked sharply at approximately 1.5 hours post dose. Co-administration of naltrexone with morphine reduced morphine-induced positive effects in a dose dependent fashion though the reduction induced by the two highest naltrexone doses (19.2 mg and 38.4 mg) was similar. That is, naltrexone flattened the morphine induced positive peak and lowered the magnitude of the peak values. As an example naltrexone 4.8 mg reduced the morphine induced mean peak value (VAS Drug Liking) by 33% while naltrexone 34.8 mg reduced the value by 61%.</p> <p>Naltrexone 4.8 mg was the lowest naltrexone dose that reliably (statistically or marginally significant) attenuated morphine induced euphoria and did not produce a sharp increase in positive effects characteristic for drugs of abuse. Furthermore administration of this treatment resulted in reduction of the morphine-induced EMAX positive measures (as assessed by VAS Drug Liking) by at least 30% in 56% of subjects who completed this study.</p> <p>Examination of the negative drug effect measures as assessed by:</p> <ul style="list-style-type: none"> o VAS Bad Effects, o VAS Feeling Sick, o VAS Nausea, o ARCI LSD, o Cole/ARCI Unpleasantness Dysphoria o Cole/ARCI Unpleasantness Physical <p>indicated that administration of morphine was associated with a strong negative response that peaked at approximately 6 to 8 hours post dose.</p> <p>Administration of naltrexone with morphine reduced the morphine-induced negative effects and shifted the time to reach the peak effect. That is, the time to reach peak effect after administration of naltrexone with morphine was shorter than after administration of morphine alone. This shift in the peak time appeared to be naltrexone dose dependent.</p>		

Name of Sponsor/Company: Alpharma Branded Products Division Inc.	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product:	Volume:	
Name of Active Ingredient: Morphine and naltrexone	Page:	
<p>Co-administration of naltrexone 19.2 mg and 38.4 mg with morphine blocked the later expression of morphine induced negative effects as the peak emerged at about 1-2 hours post dose. In general, greatest abatement of the negative effects was observed after administration of naltrexone 4.8 mg, while the smallest abatement was recorded after administration of the two highest naltrexone doses (19.2 mg and 38.4 mg). Generally, the differences among the naltrexone treatments were not significant with respect to the negative effects of morphine.</p> <p>The patterns of responses on the measures of other drug effects were similar to the positive and negative measures. Examination of pupillometry, a measure of opiate physiologic effect, demonstrated characteristic morphine induced miosis (42% reduction of the pupil of the eye after administration of morphine in comparison to placebo). This effect was dose proportionally reversed by co-administration of naltrexone with morphine (4% reduction of the pupil size after co-administration of naltrexone 38.4 with morphine in comparison to placebo).</p> <p>In general, the pattern of responses observed for the planned analysis was consistent with the pattern of responses observed for the supplemental analysis (1.5 hours post dose time point and AUE_{0.5-8h}). Furthermore, analysis of the responder population did not differ from the analysis of the Per Protocol Population (PPP), thus confirming results of the PPP.</p> <p>Pharmacokinetic results:</p> <p>Examination of the summary statistics suggests that co-administration of naltrexone and morphine dose dependently increases morphine plasma concentration in comparison to administration of morphine alone.</p> <p>As expected administration of higher naltrexone doses resulted in higher plasma concentrations of naltrexone and 6-β-naltrexol, a naltrexone metabolite.</p> <p>The high level of variability among subjects in metabolism of morphine, naltrexone and 6-β-naltrexol might provide a possible explanation of the variability observed in the pharmacodynamic measures.</p> <p>Safety results:</p> <p>The adverse events recorded during this study were largely consistent with the expected effects of the study medications. One Serious Adverse Events (SAE) was recorded for this study and was assessed as probably not related to study drug (a clavicle fracture resulting from a cycling accident). The subject was discontinued from the study. One</p>		

Name of Sponsor/Company: Alpharma Branded Products Division Inc.	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product:	Volume:	
Name of Active Ingredient: Morphine and naltrexone	Page:	
<p>other subject was discontinued because of an AE (unsustained ventricular tachycardia).</p> <p>Of subjects who experienced an AE within each treatment group, the majority were of a maximum intensity of mild and a maximum relationship of possibly/probably related to study drug. No AEs were assessed with a definite relationship to study drug.</p> <p>No clinically significant laboratory abnormalities were recorded. In addition, there were no clinically significant findings for vital signs or ECG assessments (at screening and follow-up).</p> <p>CONCLUSION:</p> <ul style="list-style-type: none"> • Administration of an oral solution of morphine 120 mg induced significantly higher positive effects (as measured by VAS Drug Liking, VAS High, VAS Good Effects, Subjective Drug Value, ARCI MBG, Cole/ARCI Abuse Potential and Cole/ARCI Stimulation Euphoria) than administration of placebo thus confirming validity of this study. On VAS Drug Liking the difference between the mean peak value for morphine and placebo was 29.7 mm on a 100 mm bipolar scale • Administration of an oral solution of morphine 120 mg also induced significantly higher negative effects (as assessed by VAS Bad Effects, VAS Feeling Sick, VAS Nausea, ARCI LSD, Cole/ARCI Unpleasantness Dysphoria and Cole/ARCI Unpleasantness Physical) than administration of placebo. The negative effects are typically observed after the peak positive effects. • 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 was the lowest naltrexone dose that reliably reduced the morphine induced positive effects. The degree in reduction might be sufficient to decrease diversion of morphine and abuse since one does not have to abate all positive effects to change risk of abuse among abusers as long as they have access to other drugs of abuse. 		
Date of the report: 10-OCT-2006		

4.2.7 Synopsis of Study ALO-01-07-205

Name of Sponsor/Company: Alpharma Pharmaceuticals LLC	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: EMBEDA (ALO-01; Kadian NT)		
Name of Active Ingredients: Morphine Sulfate Naltrexone Hydrochloride		
Title of Study: A Randomized, Double-Blind, Triple-Dummy, Single-Dose, Four-Way Crossover Study to Determine the Relative Bioavailability, Pharmacodynamic Effects and Safety of Equivalent Oral Doses of whole and Crushed ALO-01 Versus Morphine IR In Opioid Experienced, Non-Dependent Subjects		
Principal Investigator: Myroslava K. Romach, MSc, MD, FRCPC VP of Medical and Scientific Affairs, DecisionLine Clinical Research Corporation Investigators: (b) (6) <div style="background-color: gray; width: 100%; height: 150px; margin-top: 5px;"></div>		
Study center(s): DecisionLine Clinical Research Corporation 720 King St. W., Suite 700 Toronto, ON, Canada M5V 2T3		
Publications (reference):		

Studied period (years): 3 months Date first patient enrolled: 02 March 2007 Date last patient completed: 28 May 2007	Phase of development: Phase I
Objectives: Primary: <ul style="list-style-type: none">• To determine the relative pharmacodynamic effects and safety of crushed and whole ALO-01 compared to MSIR and to Placebo and of crushed ALO-01 to whole ALO-01. Secondary: <ul style="list-style-type: none">• To determine the relative bioavailability of plasma morphine from crushed and whole ALO-01 compared to MSIR and from crushed ALO-01 to whole ALO-01.• To determine the relative bioavailability of plasma naltrexone and 6-β-naltrexol from crushed ALO-01 to whole ALO-01.	

Methodology:

This study was a randomized, double-blind, triple-dummy, single-dose, four-way crossover study in opioid experienced, non-dependent subjects. Study visits included a Screening Session, Qualifying Period, Treatment Period and Follow-Up Period.

SCREENING/QUALIFYING PERIOD**Screening Session**

The following procedures were performed to determine subject eligibility:

- Informed consent
- Alcohol breath test
- Medical history
- Review inclusion and exclusion criteria
- Subject demographics
- Alcohol and drug use screen (including drug use history and assessment of drug dependence)
- Review concomitant medication
- Physical examination (including height and weight)
- 12-lead ECG
- Vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation and oral temperature)
- Rapid urine drug screen using 5-panel MedTox kits
- Serum pregnancy test for women
- Symptom Checklist-90 (SCL-90)
- Serology [Human Immunodeficiency Virus (HIV)-1/-2, hepatitis B surface antigen and hepatitis C antibodies]
- Laboratory tests (hematology, clinical chemistry and urinalysis)

Qualifying Session***Purpose:***

To identify subjects' ability to perceive a single dose of morphine sulfate immediate release (IR) 120 mg as being active and distinct from placebo.

Procedures (admission):

Subjects were admitted to the clinical unit the evening prior to the first dosing. The following procedures were performed at admission:

- Review of inclusion and exclusion criteria for continued eligibility
- Vital signs (sitting blood pressure, respiration rate, heart rate, oxygen saturation and temperature)
- Urine pregnancy test for women
- Rapid urine drug screen using 5-panel MedTox kits
- Alcohol breath test
- Pharmacodynamic measures training and practice session

The subjects fasted for approximately 8 hours prior to dosing until approximately four hours post dosing (approximately 12 hours). Between 08:00 and 10:00 am, a single oral dose of morphine (IR) 120 mg solution in 247.5 mL of apple juice or placebo (250 mL of apple juice) was administered according to a double-blind randomized crossover design. Subjects were asked to swallow the drugs immediately. An additional 50 mL of apple juice was provided as a rinse to ensure complete ingestion of study drug.

Procedures (Dosing Days 1 and 2):

The following assessments were conducted:

Pharmacodynamic measures:

- Randomization (prior to dosing on Day 1 only)
- VASs (Drug Liking (at this moment), Good Effects and High) and ARCI (MBG scale only) at 0.5, 1, 1.5, 2, 3, 4, 6 and 8 hours post dose. Pre-dose assessments were conducted for 'High' and ARCI only.
- SDV and VAS for Overall Drug Liking at approximately 8 hours post-dose

Safety measures:

- Vital signs (sitting blood pressure, respiration rate, heart rate, oxygen saturation and temperature) at approximately 1 hour pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6 and 8 hours post dose. Temperature was measured at pre-dose only.
- Concomitant medications and adverse events were collected and recorded throughout
- Continuous cardiac monitoring-continuously from pre-dose until approximately 8 hours post dose, or longer if clinically required and indicated by investigator or designee

Each subject remained in the clinic unit overnight. Subjects fasted for approximately 8 hours prior to dosing until approximately four hours post dosing (approximately 12 hours). On the second dosing day, the same procedures were repeated as in the first dosing day. Between 08:00 and 10:00 am, a single oral dose of either morphine sulphate (IR) 120 mg or placebo (beverage), whichever the subject did not receive the previous day, was administered according to the blinded randomization schedule.

Subjects were discharged from the clinic following the 24 hour post-dose (second dosing) procedures, at the discretion of the investigator or designee.

Following the qualifying session, each subject's eligibility for the study was determined. The tests administered ensured appropriate placebo and baseline responses, and screen out subjects who did not demonstrate a consistent discrimination between active drug and placebo or who could not tolerate 120 mg of oral morphine IR. In addition, the tests demonstrated that subjects were able to complete and feel comfortable with the pharmacodynamic measures, that that they could follow directions, and were cooperative. The following six measures contributed to the decision about eligibility into the treatment period:

- VAS for Drug Liking ('at this moment')
- VAS for Overall Drug Liking
- ARCI MBG
- SDV
- VAS for High
- VAS for Good Effects

For a subject to be eligible for the treatment period, they had to show:

- A peak score in response to oral IR morphine greater than that of placebo on at least four of the six measures described above; the four measures had to include Drug Liking ('at this moment').
- Responses from 0 to 8 hours consistent with the known pharmacologic effects of morphine IR and placebo (including appropriate baseline and placebo responses), as judged by the investigator or designated research scientist.
- The ability to tolerate 120 mg morphine IR as judged by the Investigator or designated sub-investigator based on available safety data.
- General behaviour suggestive that they could successfully complete the study, as judged by the clinic staff.

TREATMENT PERIOD (PERIODS 1-4)

Procedures (Day -1)

Subjects were admitted to the unit the evening prior to dosing. The following procedures were performed at admission:

- Ongoing eligibility criteria (inclusion/exclusion) assessment
- Updated medical history (review of any changes)
- Brief physical examination if a change in medical status has occurred
- Rapid urine drug screen using 5-panel MedTox kits
- Alcohol breath test
- Urine pregnancy test for women
- Vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation and temperature)
- Review of adverse events and concomitant medications
- PD training and practice session (Period 1 only). PD practice session (abbreviated) for Periods 2-4.
- Randomization

Procedures (Days 1 and 2):

The following procedures were performed on Days 1 to 2:

- Treatment administration between 8:00 and 10:00 am (subjects fasted for approximately 8 hours prior to receiving treatment)
- Pupillometry, VAS (Drug Liking, Good Effects, Bad Effects, Any Effects, High, Sick, Nausea, Sleepy, and Dizziness), ARCI and Cole/ARCI at pre-dose and at approximately 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours post-dose. VAS (Drug Liking, Good Effects, Bad Effects and Any Effects) were not measured at pre-dose.
- SDV and Overall Drug Liking at 12 and 24 hours post dose.
- PK sampling at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours post-dose
- Continuous telemetry collected continuously from pre-dose until approximately 8 hours post dose, or longer if clinically required and indicated by investigator or designee
- Vital Signs (blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature) at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours post-dose. Temperature was measured at pre-dose only.

- Adverse Events were monitored continuously. AEs were solicited using a non-leading question and recorded at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours post-dose.

A brief physical examination was conducted prior to discharge. Each treatment period was be separated by a 14 to 21 day washout period, in-between dosing.

FOLLOW-UP PERIOD

The following procedures were performed:

- Physical examination (including weight measurement)
- Updated medical history
- Clinical laboratory tests (hematology, clinical chemistry and urinalysis)
- Serum pregnancy test for women
- Vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation and oral temperature)
- 12-lead ECG
- Update use of concomitant medications
- Assessment of adverse events

Number of patients (planned and analyzed):

A total of a 132 subjects were screened for inclusion in this study. Of the 132 subjects screened, 73 were eligible for inclusion, and 58 of those subjects were randomized and dosed in the qualifying session. As planned, thirty two eligible subjects were entered into the double-blind treatment period. It was intended to have 24 subjects complete the study. All 32 (100.0%) subjects were included in the safety and per protocol (i.e., completers) populations.

Diagnosis and main criteria for inclusion:

Thirty two healthy male and female subjects aged 18 to 55 years, inclusive, were entered into the double-blind treatment period. The subject population consisted of opiate experienced, non-dependent volunteers. The specific inclusion and exclusion criteria for enrolling subjects were as follows:

Subjects were eligible for inclusion in this study only if all of the following criteria were met:

1. Male or female subjects 18 to 55 years of age, inclusive.
2. Subjects had to be opioid users who were not currently physically dependent on opioids (based on DSM-IV criteria) but had experience in the use of opioids for non-therapeutic purposes (i.e., for psychoactive effects) on at least 10 occasions within last year and at least once in the 12 weeks prior to the screening session.
3. Subjects had to be healthy, as indicated by medical history, physical examination, vital signs, oxygen saturation, clinical laboratory tests, and 12-lead ECG performed at the screening session.
4. Subjects had to consent to use two medically acceptable methods of contraception throughout the entire study period, including washout periods, and for females until 1 week after the study was complete. The medically acceptable methods of contraception that could be used by the subject and/or their partner included birth control pills or patches, diaphragm, spermicide, intrauterine device (IUD), condom, progestin implant or injection, vasectomy (by history), and bilateral tubal ligation (by history). Abstinence and total abdominal hysterectomy with bilateral salpingoophorectomy (by history) were sufficient and medically acceptable methods of birth control to be used individually. Post-menopausal women had to be at least 2 years post-menses.
5. Female subjects had to have a negative serum pregnancy test at screening and a negative urine pregnancy test prior to the qualifying session and each treatment session, and not be lactating.
6. Subject was willing and able to remain in the study unit for the entire duration of each confinement period and return to the study site for any outpatient visits.
7. Subjects with a positive urine drug screen for opiates, amphetamines, cocaine, and benzodiazepines at screening could enroll, provided they tested negative for the substances at the qualifying and each treatment session and had no clinically observed signs or symptoms of drug withdrawal.
8. Subjects with a positive urine screen of tetrahydrocannabinol (THC) at screening could be enrolled, provided the THC levels were stable or decreasing on subsequent drug screens (prior to the qualifying and each treatment session).
9. Subjects with body mass index (BMI) within the range 21-31 kg/m² and weight greater than 55 kg, inclusive.
10. Subjects had to voluntarily consent to participate in this study, provide their written informed consent prior to commencement of any study-specific procedures, and understand that they were free to withdraw from the study at any time.

Subjects who were excluded from the study were those:

1. With a history or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease or any other condition, which, in the opinion of the investigator, would jeopardize the safety of the subject or the validity of the study results.
2. With a history of clinically significant brain conditions (e.g., neoplasms, cerebrovascular disease, history of stroke, syncope, infectious disease, or significant head trauma) or currently were being treated with medications or treatment regimens that lower seizure threshold.
3. With a history or presence of drug or alcohol dependence, excluding nicotine and caffeine. This included subjects who had ever been in a drug rehabilitation program.
4. Who had a current psychiatric illness, except nicotine dependence. Subjects with a past history of psychiatric illness could be excluded at the discretion of the Investigator or designee.
5. Who had a history of chronic obstructive pulmonary disease or any other lung disease (e.g., asthma) that could cause CO₂ retention.
6. Who had a clinically significant abnormal finding on the physical exam, medical history or clinical laboratory results at screening.
7. Who had a history of allergic or adverse response to the study drugs or related drugs.
8. Who had started a significantly restrictive diet during the 4 weeks preceding the first dose of study medication (qualifying session).
9. Who had donated blood or plasma within 30 days prior to the first dose of study medication.
10. Who had hemoglobin less than 125 g/L for male subjects or hemoglobin less than 115 g/L for female subjects.
11. Who had participated in another clinical trial within 30 days prior to the first dose of study medication (qualifying session).
12. Who had used any over-the-counter (OTC) medication, including vitamins and natural health products, within 7 days prior to the first dose of study medication (qualifying session) without evaluation and approval by the study investigator.
13. Who had used any prescription medication, except hormonal contraceptives or hormonal replacement therapy, within 7 days prior to the first dose of study medication (qualifying session) without evaluation and approval by the study investigator.
14. Who had a history of glaucoma or any other pupil abnormalities that in the opinion of the qualified investigator or designee could interfere with the ability to perform pupillometry.
15. Who were not able to abstain from nicotine smoking while being in the clinical unit.
16. Who had had a positive test for or had been treated for hepatitis B, hepatitis C or HIV.

17. Who had current or pending legal charges.

18. Who, in the opinion of the investigator, were not considered to be suitable and were unlikely to comply with the study protocol for any reason.

Test product, dose and mode of administration, batch number:

The treatment period study drugs included ALO-01 (otherwise known as EMBEDA; formerly Kadian NT, batch number PI-1594), consisting of a 60 mg morphine sulfate (ER) pellet and a naltrexone core inner pellet (Alpharma Pharmaceuticals LLC, Piscataway, NJ, U.S.A).

Matching placebo capsules (matched to ALO-01) were administered throughout the treatment period (placebo capsules, batch number PL-2008, Alpharma Pharmaceuticals LLC,

Piscataway, NJ, U.S.A). Subjects were administered two capsules (total 120 mg Morphine sulfate) orally. For crushed drug administration, ALO-01 or placebo capsules were opened to release the inner pellets. The pellets were completely crushed (b) (4)

and were then dissolved in 150 mL of sugar-free apple juice at room temperature, (b) (4)

Placebo capsules were administered whole and/or crushed, in order to maintain blinding and to mask for texture (crushed capsule administration).

Treatment Randomization and Duration:

The study was approximately 19 weeks in duration. The qualifying session was conducted within 28 days prior to the first dosing (treatment session), with a minimum of three days between the second drug administration (qualifying session) and admission to Treatment Period 1. Treatment periods were separated by a minimum of 14 days and a maximum of 21 days, between dosing.

During the qualifying session, all eligible subjects randomly received single doses of MSIR 120 mg containing beverage and placebo beverage, administered once over 2 days.

During each treatment session, all eligible subjects received two whole capsules (with active drug or placebo) and two beverages (with active drug and/or placebo) orally. All eligible subjects received each of the four following treatments, one per treatment session:

- **Treatment A:** 2 x Placebo capsules (whole) + ALO-01 2 x 60 mg capsules (crushed) in apple juice (Beverage 1) + apple juice (MSIR Placebo) (Beverage 2)
- **Treatment B:** 2 x 60 mg ALO-01 (whole) + 2 x Placebo capsules (crushed) in apple juice (Beverage 1) + apple juice (MSIR Placebo) (Beverage 2)
- **Treatment C:** 2 x Placebo capsules (whole) + 2 x Placebo capsules (crushed) in apple juice (Beverage 1) + 120 mg Morphine Sulfate IR in apple juice (Beverage 2)
- **Treatment D:** 2 x Placebo capsules (whole) + 2 x Placebo capsules (crushed) in apple juice (Beverage 1) + apple juice (MSIR Placebo) (Beverage 2)

During each treatment period, subjects ingested two capsules, containing either ALO-01 or placebo and two separate 150 mL apple juice beverages: Beverage 1 contained either dissolved ALO-01 or placebo, and Beverage 2 contained either MSIR solution or placebo. MSIR was available as a liquid solution formulation (Statex Oral Drops), which was administered in apple juice.

Reference therapy, dose and mode of administration, batch number:

Morphine Sulfate (immediate release) solution (Statex Oral Drops, 50 mg/mL, batch number 416449, (b) (4)) was used for both the Qualifying Session and Treatment Period. The morphine sulfate (120 mg) was prepared for oral administration by diluting 2.4 mL of Statex Oral Drops 50 mg/mL in 148 mL of room temperature sugar-free apple juice shortly before administration. The placebo beverage was comprised of 150 mL of sugar-free apple juice.

Criteria for evaluation:

Pharmacodynamic/Pharmacokinetic:

Primary Endpoints:

- Pupillometry
- Drug Liking, Overall Drug Liking, Subjective Drug Value (SDV), Addiction Research Center Inventory (ARCI) - Morphine-Benzedrine Group (MBG) scale, and the Cole Modification of the ARCI (Cole/ARCI) - Abuse Potential and Stimulation-Euphoria scales

Secondary Endpoints:

- VAS (for Any Drug Effects, High, Good Effects, Bad Effects, Sick, Nausea, Sleepy and Dizziness), ARCI (except for MBG scale), and Cole/ARCI (except for Abuse Potential and Stimulation-Euphoria scales)
- Plasma levels of morphine, naltrexone and 6- β -naltrexol.

Safety:

- Type, incidence and severity of adverse events
- Vital signs (sitting blood pressure, respiration rate, heart rate, oxygen saturation and temperature)
- 12-lead electrocardiogram (ECG)
- Continuous cardiac monitoring (heart rate, cardiac rhythm, and oxygen saturation)
- Clinical laboratory (at screening and follow-up)

Statistical methods:

Pharmacodynamics

The following summary parameters were calculated for Pharmacodynamic measures:

- The peak effect (E_{max} or E_{min})
- The time of peak effect (t_{Emax})
- The area under the effect curve to 2 hours (AUE_{0-2h})
- The area under the effect curve to 8 hours (AUE_{0-8h})
- The area under the effect curve to 24 hours (AUE_{0-24h})

For Subjective Drug Value and VAS for Overall Drug Liking, the mean and peak response was calculated.

The comparisons of interest were as follows:

- ALO-01 whole – Morphine IR
- ALO-01 crushed – Morphine IR
- ALO-01 whole – ALO-01 crushed
- ALO-01 whole – Placebo
- ALO-01 crushed – Placebo
- Morphine IR – Placebo

The within-subject differences were calculated for each subject for each endpoint and the data was summarized using standard summary statistics, including the 95% prediction interval. A Morphine IR-Placebo comparison was made to confirm study validity.

A linear mixed model was fit to each endpoint. This model contained a random subject effect, and fixed effect terms for period, drug, crushing and the drug-by-crushing interaction. The cell means for this model were presented with their associated 95% confidence intervals. The contrasts of interests were extracted from this model and their point estimates and associated 95% confidence intervals were presented.

Pharmacokinetics

Pharmacokinetic parameters were calculated for the plasma morphine, naltrexone and 6- β -naltrexol concentration data using non-compartmental methods. Relative bioavailability was calculated for ALO-01 (crushed versus whole) using the ratio (and 90% confidence interval) of geometric mean AUC_{NF} and AUC_{0-8h} , and the ratio (and 90% confidence interval) of geometric mean C_{max} . As per the protocol, the comparisons of the pharmacokinetic and pharmacodynamic endpoints between treatments were to be made using a mixed linear model having random subject effect and fixed effect terms for period, drug, crushing, and drug-by-crushing interaction. However, the pharmacodynamic and pharmacokinetic endpoints were analyzed using the linear mixed effect model with subjects within the sequence as a random effect and the treatment, period, and sequence as fixed effects.

In addition, the within-subject relative bioavailabilities were calculated from the AUC_{NF} , AUC_{0-8h} and C_{max} and presented using standard summary statistics, including the 95% prediction interval. The same comparisons were made for plasma morphine relative bioavailability calculated for crushed and whole ALO-01 to morphine sulphate IR.

SUMMARY – CONCLUSIONS

PHARMACODYNAMIC RESULTS:

The objective of this study was to determine the relative pharmacodynamic effects of crushed and whole ALO-01 (120 mg) compared to Morphine Sulfate IR (120 mg) and Placebo and of crushed ALO-01 to whole ALO-01. Therefore, the pharmacodynamic results have been organized primarily by pharmacologic effects, with the emphasis on the positive effects (as assessed by VAS-Liking, VAS-High, VAS-Good Effects, Subjective Drug Value, ARCI-Morphine Benzedrine Group, Cole/ARCI-Stimulation-Euphoria, and Cole/ARCI-Abuse Potential). Administration of MSIR resulted in a characteristic and expected increase for the positive effects scales. The mean positive effects for the MSIR treatment peaked sharply at approximately 1.5 hours post-dose and were significantly elevated in comparison to the placebo induced positive effect, thus, confirming validity of this study. Administration of ALO-01 whole and crushed resulted in lower level of response and flatter profile on measures of the positive effects than administration of MSIR. That is, the release of naltrexone in the crushing process resulted in E_{max} lower than E_{max} for MSIR; however, the TE_{max} for both treatments was similar. Such a response pattern is indicative of ALO-01 whole and crushed having a lower abuse potential than MSIR. Generally, the distinct response patterns were confirmed by the significant treatment effects and treatment contrasts between MSIR vs. ALO-01 whole and crushed on all measures and all variables (maximum effect [E_{max}], area under the response curve 0-2 h post-dose [$AUE_{(0-2h)}$], 0-8 h post-dose [$AUE_{(0-8h)}$], 0-24 h post-dose [$AUE_{(0-24h)}$], and at the 1.5 hours post-dose time point [HR1.5]). Overall, treatment differences between ALO-01 crushed vs. whole were not significant suggesting similar abuse potential.

Examination of the negative drug effect measures (as assessed by VAS-Bad Effects, VAS-Feel Sick, VAS-Nausea, ARCI-LSD, Cole/ARCI-Unpleasantness Physical and Cole/ARCI-Unpleasantness-Dysphoria) indicated that administration of MSIR was associated with a strong negative response that peaked at approximately 6.0 hours post-dose. Administration of ALO-01 whole and crushed induced similar levels of negative response; the response levels were lower than those seen after administration of MSIR but higher than after administration of Placebo.

The patterns of responses on the measures of other drug effects were similar to the positive and negative measures. Examination of pupillometry, a measure of opiate physiologic effect, demonstrated characteristic morphine induced miosis following administration of MSIR. Administration of ALO-01 whole and crushed resulted in less pupillary constriction, presumably because of the slow morphine release due to the extended release formulation (ALO-01 whole condition) and the release of naltrexone (ALO-01 crushed condition). No significant differences between the ALO-01 whole and crushed treatments were observed.

PHARMACOKINETIC RESULTS:

Administration of ALO-01 crushed resulted in similar morphine pharmacokinetics as administration of MSIR and different than administration of ALO-01 whole. Specifically, for the ALO-01 crushed and the MSIR treatments $AUC_{(0-8h)}$ and AUC_{INF} were statistically different from the ALO-01 whole treatment but not statistically different from each other. Although C_{max} for all the treatments were significantly different from each other, in

comparison to MSIR (C_{max}) relative bioavailability of ALO-01 crushed was 94.3, while relative bioavailability of ALO-01 whole was 23.4. Median T_{max} was approximately 1 hour for ALO-01 crushed and MSIR and 8 hours for ALO-01 whole.

Examination of naltrexone and 6- β -naltrexol pharmacokinetic profile revealed that only trace amounts of the substance was detected after administration of the ALO-01 whole treatment, and the pattern of results observed for the ALO-01 crushed treatment were within expected levels.

SAFETY RESULTS:

There were no deaths or SAEs recorded in this study, and no subjects discontinued from the study because of an AE. No subjects, in either the qualifying session or the treatment period, experienced an AE that was severe in intensity. All AEs experienced in this study were mild or moderate in severity; no subjects experienced an AE that was severe in intensity. For all treatments, the majority of AEs were related to the study drugs (31 [96.9%] subjects with AEs probably related and 1 [3.1%] subject with an AE possibly related). All 32 (100.0%) subjects in the qualifying session receiving MSIR experienced an AE related to the study drug. There were no deaths or SAEs recorded in this study, and no subjects discontinued from the study because of an AE.

AEs that occurred during this study were consistent with the expected effects of morphine sulfate. The most common AEs across all active treatments (MSIR, ALO-01 whole, and ALO-01 crushed) were expected side effects: euphoric mood, pruritus, somnolence, vomiting, and nausea. Incidences of subjects reporting euphoric mood, pruritus, and vomiting during ALO-01 whole treatment were almost half of those reported for MSIR treatment. Subjects reported lower incidences and frequencies of all AEs while receiving ALO-01 crushed, in comparison to both ALO-01 whole and MSIR administration. When compared to whole capsule administration, subjects administered ALO-01 crushed reported fewer gastrointestinal and nervous system AEs, but no notable difference was seen in the number of subjects reporting psychiatric or skin disorder AEs.

CONCLUSIONS:

- Administration of ALO-01 intact and ALO-01 crushed resulted in lower subjective effects on the positive, as well as negative and other measures, of response than administration of MSIR but higher than administration of Placebo. Therefore, the abuse potential for ALO-01 whole and crushed is lower than the abuse potential of MSIR, however, higher than Placebo.
- The adverse events observed during this study were mild to moderate in intensity and were consistent with the expected profile of MSIR side effects. Subjects reported lower incidences and frequencies of all AEs while receiving ALO-01 crushed, in comparison to both ALO-01 whole and MSIR administration.
- Administration of ALO-01 whole and crushed resulted in similar subjective effects; thus, tampering with the ALO-01 (crushing) did not increase the abuse potential of ALO-01.
- Administration of ALO-01 crushed resulted in similar morphine pharmacokinetics

as administration of MSIR but different than administration of ALO-01 whole. Specifically, for the ALO-01 crushed and the MSIR treatments, $AUC_{(0-8h)}$ and AUC_{inf} were statistically different (higher) from the ALO-01 whole treatment but not statistically different from each other. In comparison to MSIR C_{max} , relative bioavailability of ALO-01 crushed was 94.3, while relative bioavailability of ALO-01 whole was 23.4. Median T_{max} was approximately 1 hour for MSIR and ALO-01 crushed and 8 hours for ALO-01 whole.

Date of the report: 17 September 2007

4.2.8 Synopsis of Study ALO-01-07-106

Name of Sponsor/Company: Alpha Pharma Pharmaceuticals, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product:	Volume: Page:	
Name of Active Ingredient: Morphine, Naltrexone HCl		
Title of Study: A Randomized, Placebo-Controlled, Double-Blind, Single-Dose, Three-Way Crossover Study to Determine the Relative Drug-Liking/Euphoria Effects of Intravenous Morphine Alone or in Combination with Naltrexone in Opioid Experienced, Non-Dependent Male Subjects		
Principal Investigator: Lynn R. Webster, MD Sub Investigator: (b) (4)		
Study center(s): Lifetree Clinical Research, LLC		
Publications (reference):		
Studied period (years): Date first subject screened: September 20, 2007 Date last subject completed: November 21, 2007		Phase of development: Phase I
Objectives: Primary: <ul style="list-style-type: none"> • To determine the relative drug-liking and euphoric effects of intravenous (IV) morphine alone to IV morphine combined with IV naltrexone as reflected in pharmacodynamic (PD) measures following single IV bolus doses. Secondary: <ul style="list-style-type: none"> • To determine the relative drug-liking and euphoric effects as reflected in PD measures following single IV bolus doses for IV morphine alone to placebo and IV morphine combined with IV naltrexone to placebo. • To determine the relative effect of IV morphine alone compared to IV morphine plus IV naltrexone on end-tidal carbon dioxide (EtCO₂) as measured by capnography. • To determine the relative effect of IV morphine alone compared to IV morphine plus IV naltrexone on pupillometry. • To evaluate the safety of single doses of IV morphine alone and IV morphine combined with IV naltrexone. • To assess the pharmacokinetics (PK) of IV morphine and IV morphine with IV naltrexone. • Possibly to explore plasma naltrexone concentrations associated with 25%, 50%, 75%, and 100% (i.e., no different from placebo) decreases in drug-liking and euphoria from maximum effects of IV morphine alone over time. [Note: Analyses not done.] • Possibly to explore plasma naltrexone concentrations associated with changes in other PD measurements (EtCO₂ and pupillometry). [Note: Analyses not done.] 		

Name of Sponsor/Company: Alpharma Pharmaceuticals, LLC	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
Name of Finished Product:	Volume: Page:	
Name of Active Ingredient: Morphine, Naltrexone HCl		
Methodology: This was a single-center, randomized, double-blind crossover trial in non-dependent opioid-preferring male subjects to characterize the effect of naltrexone on the euphorogenic effects of morphine as reflected in the subjective responses to the Drug Effects Questionnaire (DEQ) and Cole/ Addiction Research Center Inventory (ARCI) Stimulation Euphoria Scale.		
Number of subjects (planned and analyzed): In total, 29 subjects signed the consent form and were screened for the study. All 29 subjects participated in the Naloxone Challenge, 29 subjects enrolled and 28 subjects completed the Drug Discrimination Phase of the study, and 26 subjects completed the study.		
Diagnosis and main criteria for inclusion: Healthy adult male subjects who had abused prescription opioids on at least 5 occasions within the previous 12 months but who were not physically dependent on opioids were included in the study. Subjects must have been able to distinguish morphine from placebo during the Drug Discrimination Phase of the study.		
Test product, dose and mode of administration, lot number: Morphine 30 milligrams (mg) IV, Lot number 52-232-DK; Naltrexone 1.2 mg IV, Lot number H05870		
Duration of treatment: Approximately 3 weeks: a 4-day in-patient phase and a two-week out-patient phase		
Reference therapy, dose and mode of administration, batch number: Sodium Chloride 0.9% sterile diluent, Lot number P199190		
Criteria for evaluation:		
Pharmacodynamic: The DEQ, the COLE/ARCI Stimulation Euphoria Scale were used to assess pharmacodynamics. The results of the DEQ question #5, "How high are you now?" constituted the primary efficacy as well as the primary pharmacodynamic endpoint of this trial.		
Safety: Adverse events (AEs), physical examination, electrocardiogram (ECG), clinical laboratory evaluations (including hematology, serum chemistry, and urinalysis), urine drug screen, and ethanol breath test were performed at the initial screening visit and at check in prior to each period of the Treatment Phase. Serology for hepatitis B and C antigens and human immunodeficiency virus (HIV) antibody were also performed at the initial screening visit. Vital signs and pulse oximetry measurements were taken prior to all doses and at 1, 2, 4, 8, and 12 hours post-dose.		
Pharmacokinetic and Pharmacodynamic Analyses: The PK analyses were based on all available post-dosing PK data. For each subject, the PK parameters		

Name of Sponsor/Company: Alpharma Pharmaceuticals, LLC	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product:		
Name of Active Ingredient: Morphine, Naltrexone HCl		

were determined using a non-compartmental approach.

Summary statistics for plasma concentrations of morphine, naltrexone, and 6 β -naltrexol were calculated by time and dose as well as for PK and PD parameters. For the purpose of plotting the data, plasma concentration values that were below the limit of quantification (BLQ) imbedded between two measurable concentrations were set to missing; however, BLQ values occurring after the last measurable plasma concentration were set to zero. For the purpose of the non-compartmental PK analysis, all BLQ values occurring after the first measurable plasma concentration were set to missing.

PK parameters including initial plasma concentration [C_0] back extrapolated from the elimination rate constant [k_{el}] to time 0; area under the concentration-time curve [including partial areas AUC_{0-2} , AUC_{0-8} , AUC_{0-24} , and AUC_{inf}]; terminal half life [$t_{1/2}$]; total plasma clearance [CL_t]; and steady-state volume of distribution [V_{ss}], and PD parameters (E_{max} , TE_{max} , and area under the effect curve [AUE, which includes AUE_{0-2} , AUE_{0-8} , and AUE_{0-24}]) were summarized by dose using descriptive statistics (n , arithmetic mean, median, standard deviation [SD], minimum, maximum, coefficient of variation, geometric mean (E_{max} , AUC, AUE and C_0 only)).

The E_{max} and AUEs for each PD assessment within a period were used for analyses. Each PD assessment was analyzed using a linear mixed model with fixed effects for sequence, period, and treatment arm, and a random effect for subject nested in sequence was used. Least squares means along with 95% confidence intervals were provided for each treatment arm and for all pair-wise contrasts between treatment arms.

Statistical methods:

Safety analyses were based on the double-blind safety population that included all randomized subjects who received at least one dose of study medication (IV morphine, IV naltrexone, or IV placebo) in the Treatment Phase. (In the event a subject received a treatment other than what they were randomized to receive, subjects were analyzed based on the treatment actually received.) Clinical laboratory data, AEs, vital signs, and ECG data were listed and summarized by treatment arm within a period and overall.

AEs reported on case report forms (CRFs) were coded into system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). A treatment-emergent AE (TEAE) was defined as an AE with an onset date on or after the start of dosing in the Treatment Phase. Each TEAE was assigned to a single treatment period according to the date and time of onset. TEAEs that continued over multiple treatment periods were counted only once in the period during which the event started unless the TEAE worsened in intensity. The incidence of TEAEs was summarized by system organ class, preferred term, and treatment arm. Intensity of TEAEs and relationship to study drugs were also summarized in a similar manner.

Name of Sponsor/Company: Alpharma Pharmaceuticals, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product:	Volume: Page:	
Name of Active Ingredient: Morphine, Naltrexone HCl		

SUMMARY – CONCLUSIONS

PHARMACODYNAMIC RESULTS:

In this study, groups treated with morphine + naltrexone and with morphine alone reached maximum effect approximately 6 minutes post infusion (median TE_{max} , 0.1 hr), and the euphoric effect of morphine alone was approximately 11-fold greater than for morphine + naltrexone (geometric mean: 84.2 vs. 7.6 nm) according to the DEQ #5. The abuse liability implication of this analysis suggests dissolution of ALO-01 pellets will provide not only immediate bioavailability of morphine, but sufficient dosage of naltrexone to significantly abate the morphine high. Both treatments were significantly different from placebo for E_{max} . Not surprisingly, the geometric LS mean of the DEQ #5 for placebo was 0, indicating an absence of any reported high. As such, the order of treatment administration for the morphine + naltrexone treatment becomes important in comparison to placebo. Administration of IV naltrexone after morphine administration allowed a temporary high for several minutes as the delayed effect of displacement of morphine from the μ -opioid receptors by the secondarily administered naltrexone took place. In an abusive scenario, both morphine and naltrexone would be simultaneously injected, which may not provide any experience of a high.

For the secondary endpoint using the Cole/ARCI Stimulation Euphoria Scale, the 95% CIs and p-values for the LS means for E_{max} showed a statistically significant, though less dramatic, difference between treatment with morphine + naltrexone and morphine alone. The morphine + naltrexone group reached maximum effect approximately 6 minutes post infusion (median TE_{max} , 0.1 hr) compared with a maximum effect after approximately 18 minutes for the morphine alone group (median TE_{max} , 0.3 hr). The euphoric effect of morphine alone was approximately twice that of morphine + naltrexone (LS mean: 27.8 vs. 13.7), further reinforcing the findings from DEQ #5 that ALO-01 pellets will provide immediate bioavailability of morphine with a sufficient dosage of naltrexone to significantly abate the morphine high. Both treatments were significantly superior to placebo for E_{max} . The LS mean of the Cole/ARCI Stimulation Euphoria Scale for placebo was 1.1. Because this level of high is so much lower than that reported for morphine + naltrexone and morphine alone, the order of administration for the morphine + naltrexone treatment remains important compared with placebo.

DEQ items #1, #2 and #4 can be considered subjectively "desirable" outcomes in that they indicate feeling effects, and in particular feeling good effects, and liking the drug. The remaining DEQ items of bad effect (#3), feeling sick (#6), having nausea (#7), feeling sleepy (#8), and feeling dizzy (#9) are subjectively indicative of "undesirable" outcomes. For these DEQ items, median TE_{max} values for the desirable outcomes were equal or slightly shorter for the combination of morphine + naltrexone group compared with the morphine alone group while the median TE_{max} for "undesirable" outcomes were shorter for the morphine + naltrexone group compared with the morphine alone group for all but one item. Thus, while combination treatment does not curtail immediate bioavailability of morphine, concomitant administration of naltrexone and morphine allows the undesirable effects to become evident more quickly and reduces the euphoric effect by half.

Exploratory PD analyses (E_{max} , AUE_{0-2} , AUE_{0-3} , and AUE_{0-24}) of the other 8 DEQ questions revealed statistically significant differences across all 3 treatments ($p < 0.0001$ using a linear mixed model with

Name of Sponsor/Company: Alpharma Pharmaceuticals, LLC	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
Name of Finished Product:	Volume: Page:	
Name of Active Ingredient: Morphine, Naltrexone HCl		

fixed effects for sequence, period, and treatment, and a random effect for subject nested in sequence). In addition, significant geometric mean differences between treatments were detected in all but one pair-wise comparison ($p \leq 0.05$) for all assessments. In most instances, the mean E_{max} , AUE_{0-2} , AUE_{0-3} , and AUE_{0-24} values for morphine alone were significantly greater than the corresponding mean values for the morphine + naltrexone and placebo groups. The exception was for AUC_{0-2} for DEQ #6 "Does the drug make you feel sick?", where there was no geometric mean difference between morphine + naltrexone and morphine alone ($p=0.1014$), though both the mean and median values were numerically higher for the morphine alone group.

Analyses of $EtCO_2$ detected statistically significant differences in LS means across all treatment groups for E_{max} , AUE_{0-2} , AUE_{0-3} , ($p < 0.0001$ for all) and AUE_{0-24} ($p=0.0011$). Median TE_{max} was 5.0 hours for morphine + naltrexone compared with 1.0 hour for morphine alone and 2.0 hours for placebo. No difference was detected between the combination morphine + naltrexone and placebo groups in $EtCO_2$ levels ($p=0.3064$), which emphasizes the PD effect of morphine displacement on the μ -opioid receptor by naltrexone. This finding is consistent with the PD effects of naltrexone previously described. Pupillometry analyses revealed statistically significant differences in LS means across all treatment groups for E_{max} ($p=0.0008$) and for AUE_{0-2} , AUE_{0-3} , and AUE_{0-24} assessments ($p \leq 0.0001$). Pair-wise comparisons showed significant differences in LS means between treatment groups for most PD assessments ($p \leq 0.0045$), though the median E_{max} of 5.0 mm for morphine alone was not different than 5.5 mm for morphine + naltrexone treatment ($p=0.4646$). The median change from pre-dose to E_{max} in pupil diameter was 0.0 mm for both morphine and combination treatment.

Results of this single-dose, three-way crossover study comparing morphine alone, morphine + naltrexone, and placebo in this population of opioid experienced, non-dependent males subjects suggest that the combination of morphine + naltrexone diminishes the drug-liking/euphoric effects associated with morphine when it is administered alone.

PHARMACOKINETIC RESULTS

Plasma morphine and naltrexone following single IV bolus doses demonstrated multi-exponential decline. The pharmacokinetics of plasma morphine PKs were not affected by co-administration with naltrexone. Based on partial AUCs, approximately 55% of the exposure to plasma morphine was achieved by 2 hours post dose and approximately 83% was achieved by 8 hours post dose. The elimination half-life was approximately 9 hours and 3 hours for plasma morphine and plasma naltrexone, respectively. The steady state volume of distribution for plasma morphine and plasma naltrexone was much greater than the volume of total body water ^{(b) (4)}. This suggests low plasma protein binding, with extensive distribution and binding to tissue compartments. As expected, clearance was high for both plasma morphine and plasma naltrexone, which is consistent with high first pass effect for both drugs.

SAFETY RESULTS:

In this study, 21 of 28 (75%) subjects experienced a total of 69 TEAEs. Nineteen (67.9%) subjects experienced 50 of these TEAEs during treatment with morphine alone compared with 9 (33.3%) subjects who experienced 17 TEAEs during treatment with morphine + naltrexone and 2 placebo

Name of Sponsor/Company: Alpharma Pharmaceuticals, LLC	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
Name of Finished Product:	Volume: Page:	
Name of Active Ingredient: Morphine, Naltrexone HCl		
<p>(7.4%) subjects who reported 2 TEAEs. Four subjects had severe events: 3 while being treated with morphine and the fourth subject had a severe event while being treated with morphine + naltrexone. One subject discontinued prematurely because of an AE of a tooth infection and another subject was discontinued for non-compliance. No subjects died or experienced an SAE, and no clinically significant abnormal laboratory values were reported.</p> <p>Based on results of this study, combination treatment with morphine + naltrexone appears to be well tolerated in this population of opioid experienced, non-dependent male subjects.</p> <p>CONCLUSION:</p> <p>Results of this single-dose, three-way crossover study comparing morphine alone, morphine + naltrexone, and placebo in this population of opioid experienced, non-dependent males subjects suggest that the combination of morphine + naltrexone administered in intravenous doses in the same ratio as the solid dosage investigational product, ALO-01, diminishes the drug-liking/euphoric effects evident when morphine is administered alone. The implications of the results of this study suggest that abuse of ALO-01 by dissolution and injection will abate drug-liking and euphoria. All treatments were well-tolerated in this population.</p> <p>Date of the report: 30 January 2008</p>		

Detailed analysis of this study can be found in the Controlled substance staff review.

4.2.9 Synopsis of Study # ALO-01-07-107

Name of Sponsor/Company: Alpharma Pharmaceuticals, LLC	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: KADIAN®		
Name of Active Ingredient: Morphine Sulfate Extended Release		
Title of study: An Open-label Study to Assess the Pharmacokinetic and Pharmacodynamic Effects of Increasing Doses of Naltrexone in Precipitation of a Moderate Withdrawal Syndrome in Subjects with Chronic, Non-Malignant Pain on Extended Release Morphine		
Principal investigator: Lynn R. Webster, MD Sub Investigator: (b) (4)		
Study center: Lifetree Clinical Research		
Publications (reference): There was no publication based on this trial.		
Studied period (years): Date first subject enrolled: 17 October 2007 Date last subject completed: 02 January 2008		Phase of development: 1
Objectives: Primary: <ul style="list-style-type: none"> To determine the plasma concentration of naltrexone resulting in the production of predefined withdrawal symptoms in 50% of subjects with chronic pain on a stable dose of extended release morphine. Secondary: <ul style="list-style-type: none"> To determine the plasma concentration of naltrexone resulting in the production of predefined withdrawal symptoms in at least 90% of subjects with chronic pain on a stable dose of extended release morphine. 		
Methodology: This was a single-center, open-label study of male and female subjects to assess the effects of increasing doses of naltrexone in precipitation of a moderate withdrawal syndrome in subjects with chronic, non-malignant pain on a stable dose of extended release morphine as determined using the Clinical Opiate Withdrawal Scale (COWS) assessment.		
Number of subjects (planned and analyzed): Up to 18 subjects with chronic moderate to severe nonmalignant pain who met all inclusion/exclusion criteria and were currently on opioid therapy were to be enrolled into this study to have a minimum of 12 completed subjects (experience withdrawal). Sixteen subjects were enrolled and included in safety analyses and 13 subjects were included in the pharmacodynamic analyses.		

Name of Sponsor/Company: Alpharma Pharmaceuticals, LLC	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
Name of Finished Product: KADIAN [®]	Volume:	
Name of Active Ingredient: Morphine Sulfate Extended Release	Page:	
Diagnosis and main criteria for inclusion: Subjects currently on opioid analgesics for chronic moderate to severe nonmalignant pain		
Test product, dose and mode of administration, batch number: KADIAN [®] 20 mg (lot # 586B71), 30 mg (lot # 579B71), 50 mg (lot # 539B71), 60 mg (lot # 363E71), 80 mg (lot # 144L61), and 100 mg (lot # 551B71) capsules for oral administration and naltrexone, ≤ 3 mg for intravenous (IV) administration (powder provided by Alpharma as lot H05870)		
Duration of treatment: up to 8 weeks		
Reference therapy, dose and mode of administration, batch number: None		
Criteria for evaluation: Efficacy: Efficacy was not assessed in this study. Safety: Vital signs, urine drug screen, ethanol breath test, and urine pregnancy tests were performed at Screening and prior to the Treatment Visit. Electrocardiograms (ECGs), physical examinations, and clinical laboratory tests were performed at Screening and at Discharge. Serology for hepatitis B and C antigens and human immunodeficiency (HIV) antibody were also performed at the initial screening. COWS and vital signs were assessed during the Dose Titration Period. Adverse events (AEs), continuous monitoring for vital signs and pulse oximetry measurements, and COWS were assessed throughout the Treatment Visit. Pharmacokinetic and Pharmacodynamic Analyses: Plasma concentrations of morphine, naltrexone, and 6β-naltrexol were to be summarized and plotted by time and descriptive statistics were to be calculated for the naltrexone plasma concentrations where 50% and 90% of subjects experiencing moderate withdrawal symptoms as determined by a COWS score ≥ 13. For reasons described in the Results section below, however, these analyses were not performed and plasma concentrations were listed by subject and plotted by subject on both a linear and a log scale.		
Statistical methods: Safety analyses were based on the safety population that included all subjects who received at least one dose of study medication (KADIAN [®] or naltrexone). Adverse events reported on case report forms (CRFs) were coded into system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). A treatment-emergent AE (TEAE) was defined as an AE with an onset date on or after the start of dosing during the Treatment Visit. The incidence of TEAEs was summarized by system organ class and preferred term. Intensity of TEAEs and relationship to study drugs were also summarized in a similar manner. Vital signs and changes from pre-dose were descriptively summarized by time.		

Name of Sponsor/Company: Alpharma Pharmaceuticals, LLC	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
Name of Finished Product: KADIAN®	Volume: Page:	
Name of Active Ingredient: Morphine Sulfate Extended Release		

SUMMARY – CONCLUSIONS

Sixteen subjects were enrolled, 10 females (62.5%) and 6 (37.5%) males from 23 to 66 years old (mean 44.1 years), and comprised the safety population. The intent-to-treat (ITT) population included 13 subjects, excluding 2 for whom the dose could not be titrated during the Dose Titration and Stabilization Period and 1 who did not receive naltrexone at the Treatment Visit.

PHARMACOKINETIC/PHARMACODYNAMIC RESULTS:

The study was inconclusive regarding the primary and secondary objectives of identifying plasma naltrexone concentrations resulting in the production of predefined withdrawal symptoms in 50% and 90% of subjects with chronic pain on a stable dose of extended release morphine. For subjects who did not demonstrate complete withdrawal symptoms (COWS \geq 13) following the first dose, plasma naltrexone concentrations were inconsistent, i.e., remained the same or decreased, in all but one subject when they went into complete withdrawal. It is speculated that the primary reason for the inconsistent plasma naltrexone concentrations was the unknown temporal relationship for naltrexone equilibrium between the plasma and central nervous system (CNS) compartments leading to subsequent withdrawal symptoms. The study was designed based upon an assumed plasma-CNS compartment equilibrium attained within the first 10 minutes post IV bolus dosing. However, rapid early phase elimination from the plasma compartment resulted in plasma naltrexone concentrations that were not cumulative even after 10 minutes for subjects who received non-escalating doses. Additionally, it is suggested that absorption of naltrexone into the CNS compartment following the first dose may have initiated early withdrawal symptoms (COWS < 13) as assessed by the investigator. Subsequent IV naltrexone doses resulted in sufficient displacement of morphine from the μ -opioid receptor by naltrexone and precipitated complete withdrawal even though plasma naltrexone concentrations were similar or less than those following previous doses.

Additionally, the safety of the subject was the primary concern of the investigator and COWS assessments following the first dose prohibited an escalation of dosing in all but one subject. Therefore, repeat dosing with IV naltrexone was in a non-escalating manner for most subjects. The inconsistent plasma naltrexone concentrations observed at complete withdrawal may have been a result of non-escalating dosing.

The study design therefore did not adequately address the objectives of the study. A study design allowing for adequate washout of naltrexone for subjects who did not reach a COWS of \geq 13 after the first dose followed by escalated dose(s) of IV naltrexone might have provided plasma naltrexone concentrations that could have been directly correlated with complete withdrawal.

The mean COWS scores among the ITT population were 0.4 at baseline, 6.9 (n = 13) after the first dose of naltrexone, 12.0 (n = 10) after the second dose, 8.0 (n = 5) after the third dose, and 10.5 (n = 2) after the fourth dose. Only 1 subject received more than 4 doses of naltrexone.

Name of Sponsor/Company: Alpharma Pharmaceuticals, LLC	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: KADIAN®		
Name of Active Ingredient: Morphine Sulfate Extended Release		
SAFETY RESULTS: Two subjects (12.5%) experienced 8 TEAEs related to naltrexone: chest discomfort, fatigue, feeling hot and cold, abdominal pain, nausea, arthralgia, headache, and dyspnea. One of these subjects also experienced constipation related to morphine. There were no deaths, no other SAEs, and no discontinuations due to AEs. There were no clinically significant findings for laboratory evaluations, vital signs, physical examination findings, and ECGs.		
CONCLUSION: In conclusion, the plasma naltrexone concentrations obtained following IV doses of naltrexone in a non-escalating manner for most subjects, and without a sufficient washout interval between doses for all subjects who received multiple doses, could not be correlated and were inconclusive in satisfying the study objectives. Since this was an exploratory study designed to provide a scientific understanding of the relationship between naltrexone plasma concentrations and patient withdrawal symptoms, the impact of these results on the clinical development program for ALO-01 is minor. Further investigations are required.		
Date of the report: 30 January 2008		

4.2.10 Synopsis of Study # ALO-KNT-202

Name of Company: Alpharma Branded Products Division	Individual Study Table Referring to part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Kadian NT	Volume:	
Name of Active Ingredients: Morphine sulfate, sequestered naltrexone hydrochloride	Page:	
Title of Study: 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		
Investigators: (b) (4)		
Study Centers: (b) (4)		
Publication (Reference): None.		
Study Period (months): 5 First subject enrolled: 20 March 2006 Last subject clinic visit: 18 August 2006	Phase of Development: Phase II	
Objectives: The <u>primary</u> objective of the study was to characterize and assess the pharmacokinetics (PK) of Kadian NT (morphine sulfate and naltrexone) following multiple doses in subjects with chronic pain due to OA of the hip or knee. The <u>secondary</u> objective of this study was to assess the safety and efficacy of Kadian NT following multiple doses in subjects with chronic pain due to osteoarthritis (OA) of the hip or knee.		
Methodology: This was a Phase II, multi-center, randomized, double-blind study in subjects with chronic pain due to OA of the hip or knee to characterize and assess the PK of multiple doses of Kadian NT. The study had a crossover design with open-label Kadian treatment in Periods 1, 3, and 5, and double-blind Kadian NT or Kadian treatment in Periods 2 and 4. Subjects who received Kadian in Period 2 were treated with Kadian NT in Period 4, and subjects who received Kadian NT in Period 2 were treated with Kadian in Period 4. Prior to starting study treatment, subjects washed out of their previous pain medications in order to induce flare. Once flare had been achieved, (defined as a pain intensity score ≥ 5 on an 11-point numerical rating scale [NRS]), the subject completed his/her baseline visit and enrolled into Period 1. If the subject did not experience flare, then the subject was considered a screen failure and was withdrawn from the study. During Period 1, all subjects were initially dispensed 20 mg Kadian twice daily (BID). Their doses were titrated to manage their pain; the maximum allowable dose was 160 mg BID (320 mg/day). A subject was considered "stabilized" on a Kadian dose when the subject's pain was adequately controlled (pain		

intensity score ≤ 3 on an 11-point NRS scale), and the subject had been on the same BID dose of Kadian for four consecutive days with no unacceptable adverse effects.

Once subjects stabilized on Kadian, they entered Period 2 where they were randomized to continue receiving Kadian or to receive Kadian NT at the BID morphine dose on which the subject was stabilized. On Day 7, subjects returned to the clinic and underwent safety and efficacy assessments and had trough blood samples collected. On Day 14, subjects underwent pre-dose assessments and trough sample collection, received the morning dose of blinded study medication, and then remained in the clinic for blood sampling for 12 hours after dosing.

During Period 3, subjects received open-label Kadian at the BID morphine dose on which the subject was stabilized in Period 1. After 7 days of open-label Kadian treatment, subjects returned to the clinic to enter Period 4.

On Day 1 of Period 4, subjects switched from Kadian to the alternate (crossover) blinded study medication from Period 2. On Day 7 of Period 4, subjects returned to the clinic for safety and efficacy assessments and to have trough samples collected. On Day 14, subjects underwent pre-dose assessments and trough sample collection, received the morning dose of blinded study medication, and then remained in the clinic for blood sampling for 12 hours after dosing.

During Period 5, subjects received open-label Kadian. On Day 7 of Period 5 (or at early termination from the study) subjects returned to the clinic for end-of-study procedures and assessments. Seven days after the end of Period 5, subjects were telephoned by study personnel to determine if adverse events (AEs) had occurred in the previous week.

Efficacy of Kadian and Kadian NT was assessed by pain intensity ratings throughout the study. The Western Ontario and MacMaster Universities (WOMAC) Osteoarthritis Index, the subject's global assessment of study medication, and the use of rescue medications for breakthrough pain were also evaluated. Safety and tolerability were assessed by AEs and by changes in physical examinations, vital signs, clinical laboratory testing and electrocardiogram (ECG) results.

PK was assessed by sample analyses for morphine, naltraxone, and 6- β -naltraxol concentrations. The following PK parameters were determined (using noncompartmental methods) for Kadian and Kadian NT at the time points specified: maximum (peak) plasma concentration (C_{max}), area under the concentration-time curve from time zero to 12 hours (AUC_{0-12}), and time to maximum (peak) plasma drug concentration (t_{max}). Other PK parameters included apparent terminal phase elimination rate constant (K_d), terminal-phase elimination half-life ($t_{1/2, \alpha}$) and apparent clearance of drug from plasma after extravascular administration (CL/F). After the clinical database was locked and the study unblinded, the following PK parameters were added to the analyses: minimum plasma concentration (C_{min}), average plasma concentration (C_{avg}), time to minimum plasma drug concentration (t_{min}), and fluctuation index (FI%) (Section Error! Reference source not found.).

Number of subjects (planned and analyzed):

Planned: Approximately 60 subjects were to have been randomized into Period 2 to achieve a total of at least 50 completed subjects.

Actual: Overall, 113 subjects were enrolled into Period 1 of which 72 subjects were randomized into Period 2. A total of 69 randomized subjects completed the study.

Diagnosis and main criteria for inclusion:

Male or female subjects 21 years of age or older with a primary diagnosis of Functional Class I-III OA of the hip or knee and met American College of Rheumatology clinical classification for OA of the hip and knee. The subject must have required treatment of target joint pain within 90 days of entering the study and was either unable to consistently control pain using non-opioid analgesics or received chronic opioid treatment with the equivalent of ≤ 40 mg/day of oral morphine sulfate. In addition, the subject must have had a pain intensity of ≥ 5 on an 11-point NRS after the washout period. Subjects were excluded

from the study if they had any of the following: a document history of allergic reaction or clinically significant intolerance to morphine or other opioids, an allergy to acetaminophan, a documented history of drug or alcohol abuse, a positive result for alcohol and/or drugs of abuse at screening, or a primary diagnosis of Functional Class IV OA. Subjects were also excluded if they were unable to discontinue all formulations of prior analgesics during the washout period of the study or were pregnant or breast-feeding.

Test product, dose and mode of administration, batch number:

Kadian NT: 20 mg/0.8 mg morphine/naltrexone (Lot number PI-1505), 30 mg/1.2 mg morphine/naltrexone (Lot number PI-1506), 50 mg/2.0 mg morphine/naltrexone (Lot number PI-1507), and 80 mg/3.2 mg morphine/naltrexone (Lot number PI-1509) were administered orally to a maximum dose of 160 mg BID (320 mg daily).

Duration of treatment: Subjects received treatment with study medication for up to 70 days.

Reference therapy, dose and mode of administration, batch number:

Open-label Kadian: 20, 30, 50, or 80 mg capsules (Lot numbers 122K51, 383M51, 039K51, and PI-1499, respectively) were administered orally to a maximum dose of 160 mg BID (320 mg daily).

Double-blind Kadian: 20, 30, 50, or 80 mg capsules (Lot numbers PI-1500, PI-1501, PI-1502, and PI-1503) were administered orally to a maximum dose of 160 mg BID (320 mg daily).

Criteria for evaluation:

Efficacy: The efficacy variables in this study were in-clinic pain; worst, least, average, and current pain (from daily diary); WOMAC Osteoarthritis Index Pain Subscale, Stiffness Subscale, Physical Function Subscale, and Composite Index at each assessment visit; subject's global assessment of study medication; and the proportion of subjects who rescued (i.e., who reported taking any medications other than study medication for pain).

Safety: The safety variables in this study were study drug administration, AEs, and changes in clinical laboratory results, vital signs, and ECG results.

Pharmacokinetics: The PK parameters for this study were C_{max} , C_{min} , C_{trv} , AUC_{0-12} , t_{max} , t_{min} , $FI\%$, K_{el} , $t_{1/2, z}$, and CL/F .

Statistical methods: Four analysis populations were defined for this study: the

Pharmacokinetic-bioequivalence (PK-BE) population included all subjects who completed both Periods 2 and 4 and had sufficient PK samples assayed during those periods to properly characterize the 12-hour profiles; the Intent-to-treat (ITT) population included 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 was obtained after Period 2, Day 1; the Completer population included all randomized subjects who completed both Period 2 and Period 4; and the Safety population included all subjects who received at least one dose or portion of a dose of Kadian or Kadian NT.

Subject Characteristics: Subject characteristics analyses were conducted on all analysis populations. Demographic variables and subject characteristic were summarized by treatment sequence. P-values for difference between the two treatment sequences were provided. P-values for continuous variables were generated from a one-way analysis of variance (ANOVA) with a term for sequence. P-values for categorical variables were generated from Fisher's Exact test.

Prior and concomitant medications were summarized separately.

Pharmacokinetics: PK analyses were conducted for the PK-BE population. Morphine, naltrexone, and 6- β -naltrexol concentrations were summarized at each time point using descriptive statistics, including the mean, standard deviation (SD), minimum, maximum, and quartiles, by treatment. The numbers of concentrations below the limit of quantification (BLQ) were tabulated.

Standard non-compartmental PK parameters were calculated for the 12-hour PK profiles for morphine, naltrexone, and 6- β -naltrexol, including C_{max} , C_{min} , C_{TPO} , AUC₀₋₁₂, t_{max} , t_{min} , and FI%. Other PK parameters included K_{el} , $t_{1/2}$, and CL/F. These parameters were summarized by treatment using descriptive statistics. The log (natural logarithm) of AUC of morphine concentration was modeled using a mixed linear model for a two-period crossover and was used to produce a 95% confidence interval (CI) for the difference between the treatments.

Efficacy: Efficacy analyses conducted on the ITT and Completers populations. All efficacy variables were summarized descriptively by treatment, period, and time point, as appropriate. Efficacy analyses were presented for Periods 2 and 4 only. Period 3 and 5 data is present in the listings, but was not analyzed in the tables.

Change from baseline (Period 2, Day 1) to Day 14 of Periods 2 and 4 for in-clinic pain was modeled using a mixed linear model for a two-period crossover. Within each period, missing in-clinic pain data was imputed using the last observation carried forward (LOCF) approach.

The subject's global assessment of study medication on Day 14 of period 2 and 4 was summarized for Kadian and Kadian NT.

The proportion of subjects who used rescue medication at any time during Periods 2 and 4 was summarized for the ITT population and compared between Kadian and Kadian NT using McNemar's test for the Completer population.

The Completer population analysis did not use LOCF methodology for missing data, but was done using Observed Cases (OC).

Safety: Safety analyses were conducted for the Safety population. Safety was assessed based on study drug administration, AEs, and changes in laboratory results, vital signs, and ECG results.

Study drug administration was summarized in terms of each subject's duration of exposure. The denominators for percentages of subjects in analyses by study period were the number of subjects who received at least one dose or portion of a dose of Kadian or Kadian NT in the period in question.

AEs were assigned to study periods based on the start date of the event. The number and percentage of subjects with AEs were displayed for each period and treatment by system organ class and preferred term. Summaries in terms of intensity and relationship to study drug were also provided. McNemar's test was performed for AE rates for the Completer population. Serious adverse events (SAEs) were summarized separately in a similar fashion.

For vital signs variables and for quantitative laboratory tests, descriptive statistics including the mean, SD, minimum, maximum, and quartiles were given for the values themselves as well as for change from baseline (CFB). Vital signs variables were summarized by treatment at each time point and quantitative laboratory tests were summarized by sequence at each time point.

For qualitative laboratory tests, the number and percentage of subjects in each category were produced for each sequence at each time point. For all laboratory tests, a shift table was produced summarizing changes from normal (at baseline) to abnormal and vice versa.

The number and percentage of subjects with normal and abnormal ECG findings were displayed for each treatment sequence at each time point.

SUMMARY – CONCLUSIONS

PHARMACOLOGY RESULTS:

The 95% CI for the AUC_{0-12} of Kadian NT/ AUC_{0-12} of Kadian was 0.824 to 1.069, and thus demonstrated bioequivalence, limited to extent of exposure at steady state, for morphine in the Kadian NT and Kadian formulations. The mean steady state C_{max} of morphine was approximately 12% greater for Kadian NT treatment compared with Kadian treatment. The median t_{max} of morphine was shorter for Kadian NT treatment (4.0 hours) compared with Kadian treatment (5.0 hours). Therefore, the rate of exposure to plasma morphine in Kadian NT was slightly greater than that in Kadian.

Mean trough morphine concentrations on double-blind Days 1, 7, and 14 were similar during Kadian NT treatment and Kadian treatment. Mean morphine concentrations from serial blood sampling post-dose on Day 14 of Periods 2 and 4 were slightly higher for Kadian NT treatment compared with Kadian treatment at all time points through 10 hours, and mean concentrations were similar between treatments at the 12-hour time point.

Trough naltrexone concentrations were BLQ for the majority of subjects for both study treatments. All detectable plasma naltrexone concentrations were ≤ 25.5 pg/mL and were considered negligible since no clinically-relevant difference in pain scores was noted between subjects with measurable naltrexone concentrations and those with no measurable naltrexone concentrations.

Naltrexone concentrations from serial blood sampling post-dose on Day 14 of Periods 2 and 4 were BLQ for the majority of subjects during Kadian NT treatment (80.6% to 83.6% of subjects) and Kadian treatment (88.1% to 91.0% of subjects). Nine subjects had detectable naltrexone concentrations after dosing with Kadian NT (range, 4.11 pg/mL to 21 pg/mL). Two subjects had detectable naltrexone concentrations (range, 4.4 pg/mL to 13 pg/mL) after dosing with Kadian, and one of these occurred before the subject received any Kadian NT treatment.

Trough 6- β -naltrexol concentrations on double-blind Days 1, 7, and 14 were BLQ for the majority of subjects during Kadian treatment. All detectable concentrations of 6- β -naltrexol were ≤ 520 pg/mL following Kadian NT treatment and were not considered clinically significant.

The 6- β -naltrexol concentrations from serial blood sampling post-dose on Day 14 of Periods 2 and 4 were BLQ for the majority of subjects during Kadian treatment (83.6% to 86.6% of subjects); however, 6- β -naltrexol concentrations after dosing were detectable in the majority of subjects during Kadian NT treatment at all time points after dosing. Mean 6- β -naltrexol concentrations on Day 14 during Kadian NT treatment were low, ranging from 20.129 pg/mL to 22.792 pg/mL, during the 1- to 12-hour time points after dosing. Detectable mean 6- β -naltrexol concentrations during Kadian treatment were lower and closer to the limit of quantitation (0.25 pg/mL) during the 1- to 12-hour time points after dosing (0.321 pg/mL to 0.823 pg/mL) compared with Kadian NT treatment.

EFFICACY RESULTS: No treatment difference was noted between Kadian NT and Kadian in the in-clinic pain assessment mean scores at double-blind Days 7 and 14. The mean changes from baseline (Period 2, Day 1) for the in-clinic pain scores were small for each treatment, and no statistically significant difference was noted between the treatments.

The summed Brief Pain Inventory (BPI) mean scores for worst, least, average, and current pain were similar between study treatments. The mean changes from baseline for summed BPI scores were small for each treatment, and no statistically significant differences were noted between the treatments. BPI mean scores by day were also similar between study treatments.

WOMAC Osteoarthritis Index Subscale and Composite Index mean scores were numerically lower for Kadian NT treatment compared with Kadian treatment. Mean changes from baseline scores were also lower for Kadian NT treatment compared with Kadian treatment. The mean CFB for the Stiffness Subscale was statistically, significantly lower for Kadian NT treatment compared with Kadian treatment.

A higher proportion of subjects rated their study medication as good, very good, or excellent during

Kadian NT treatment than during Kadian treatment.

The majority of subjects used rescue medication during the double-blind treatment periods for both study treatments, and a higher proportion of subjects used rescue medication during Kadian treatment than during Kadian NT treatment.

Results for the Completer population were similar to those for the ITT population for all efficacy evaluations.

SAFETY RESULTS: No deaths occurred during the study, and one subject experienced an SAE (chest pain) in Period 1 during treatment with open-label Kadian. A total of 29 subjects withdrew from the study due to non-serious AEs: 27 subjects during treatment with open-label Kadian in Period 1, one subject during treatment with double-blind Kadian in Period 2, and one subject during treatment with double-blind Kadian NT in Period 2.

Safety population: Overall, 83.8% of subjects experienced 493 AEs during treatment with open-label Kadian. A total of 45.1% of subjects experienced 113 AEs during treatment with double-blind Kadian, and 46.5% of subjects experienced 94 AEs during treatment with double-blind Kadian NT. AEs experienced by $\geq 10\%$ of subjects during treatment with open-label Kadian (in decreasing order of incidence) were constipation, nausea, somnolence, vomiting, dizziness, headache, dry mouth, and pruritus. Constipation was the only AE experienced by $\geq 10\%$ of subjects during treatment with double-blind Kadian or Kadian NT. These AEs are well-known and documented side effects of morphine and other potent opioid analgesics.

For each study treatment, most AEs were of mild or moderate intensity. During treatment with open-label Kadian, 13/111 (11.7%) subjects experienced AEs that were considered to be severe compared with 1/71 (1.4%) subjects who experienced severe AEs during treatment with double-blind Kadian. No subjects experienced severe AEs during treatment with double-blind Kadian NT.

Treatment-related AEs experienced by $\geq 10\%$ of subjects during treatment with open-label Kadian (in decreasing order of incidence) were constipation, nausea, somnolence, vomiting, dizziness, dry mouth, pruritus, and headache. Constipation was the only treatment-related AE experienced by $\geq 10\%$ of subjects during treatment with double-blind Kadian or double-blind Kadian NT. Per the protocol, investigators were to initiate a stool-softener regimen (e.g., Senokot[®] titrated to effect) for the treatment of opioid-related constipation.

No evidence of an adverse effect on laboratory parameters, vital signs, or ECGs was noted for either of the study treatments.

Completer population: Results for the Completer population were similar to those for the Safety population, and no statistically significant difference was noted in the incidence of AEs in the Safety population compared with the Completer population ($p = 0.8083$).

CONCLUSIONS: Based on the results of this well-controlled study in subjects with chronic OA pain:

- Plasma morphine from Kadian NT and Kadian formulations are bioequivalent limited to extent of exposure at steady state (AUC_{0-12h}).
- The minimal release of naltrexone and its metabolite, 6- β -naltrexol, from Kadian NT after chronic dosing with time-released morphine did not increase pain scores.
- Kadian NT appears to be safe and effective in treating chronic pain of osteoarthritis of the knee and hip.

Date of report: 06 March 2007

4.2.11 Synopsis of Study # ALO-KNT-301

Name of Sponsor/Company: Alpharma Pharmaceuticals LLC	Individual Study Table Referring to Part of the Dossier Volume:	<i>(For National Authority Use Only)</i>
Name of Finished Product: ALO - 01 (formerly referred to as Kadian NT)	Page:	
Name of Active Ingredient: Morphine Sulfate Extended Release With Sequestered Naltrexone Hydrochloride		
Title of Study: 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		
Investigators: Multicenter, See Appendix 16.1.4.		
Study center(s): 74		
Publications (reference): There were no publications based on the trial.		
Studied period (years): Date first patient enrolled: 10 January 2007 Date last patient completed: 08 November 2007	Phase of development: 3	
Objectives: The primary objective of this study was to evaluate the efficacy of ALO - 01 (twice daily [BID]) compared with placebo for the treatment of chronic moderate to severe pain (focusing on osteoarthritis [OA] of the hip or knee) as measured by mean change in diary Brief Pain Inventory (BPI) score of average pain (daily scores of average pain averaged over 7 days) from randomization to 12 weeks following randomization. Secondary: <ul style="list-style-type: none"> • To evaluate the efficacy of ALO - 01 BID compared with placebo as measured by in-clinic BPI, daily diary BPI (worst, least, and current pain), the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index, Medical Outcomes Study (MOS) Sleep Scale, Beck Depression Inventory, and the Patient Global Impression of Change (PGIC) • To evaluate the safety and tolerability of ALO - 01 compared to placebo using adverse events (AEs), clinical laboratory data, vital signs, and two measures of opioid withdrawal: Subjective Opiate Withdrawal Scale (SOWS) and Clinical Opiate Withdrawal Scale (COWS). 		

Methodology:

This study was a randomized, double-blind, placebo-controlled study in subjects with moderate to severe chronic pain due to OA of the hip or knee. The study included a 14-day Screening Period, a Washout Period (a 1- to 7-day period during the Screening Period), a Baseline Visit, a Titration Phase lasting up to 6 weeks, a 12-week Maintenance Phase, and a Follow-Up Visit. Subjects completing 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.

The purpose of the Washout Period was to establish a minimum pain score of ≥ 5 on the BPI. During this period, subjects were dispensed an electronic diary and were instructed to stop taking all prohibited medications and pain medications. Once the required pain score was achieved (defined as an average 24-hour pain intensity of ≥ 5 on the 11-point BPI scale), the subject was instructed by the electronic diary to contact the site and return to the clinic for the Baseline Visit within 72 hours of having achieved the minimum pain score. If the subject had not achieved a pain score of ≥ 5 on the 11-point BPI by the end of the Washout Period, then the subject was to be discontinued.

Subjects who met all entrance criteria and achieved the minimum pain score were to complete the Baseline Visit, enter the Titration Phase, and begin titrating to an effective dose of open-label ALO - 01 (morphine sulfate extended release with sequestered naltrexone hydrochloride). Subjects who failed to achieve the minimum pain score at the Baseline Visit were not allowed to re-qualify for entry into the Titration Phase of the study.

Subjects who were unable to tolerate their pain with the maximum allowed rescue medication (≤ 2 g of acetaminophen/day) were to be discontinued from the study.

During the Titration Phase, all opioid-naïve subjects (defined as subjects who had not received any opioid in the last 30 days) were to start with 20 mg ALO - 01 at bedtime for the first 3 nights. If the subject was taking opioids prior to the washout, the starting dose was to be 20 mg BID (the first dose was to be taken at bedtime). The dose of study drug may have been titrated up or down to obtain a ALO - 01 BID dose sufficient to manage the subject's pain once subject had been on study drug for at least 3 days. The maximum allowed dose was 80 mg BID (160 mg/day). Two back-titrations (dose reductions) were allowed if necessary to establish the tolerated effective dose. Subjects were dispensed an electronic take-home diary to record daily pain assessments and rescue medication (acetaminophen up to 500 mg every 6 hours as needed) which was collected, reviewed, and re-dispensed at each visit. All subjects were given a daily prophylactic bowel regimen for constipation.

A subject was considered a treatment responder (reached effective dose) when the average score of the "pain on the average in the last 24 hours" was ≤ 4 on the BPI scale over the last 4-day period prior to the clinic visit as collected in the diary with a minimum 2-point decrease from baseline. All treatment responders were to be randomized into the study. Treatment responders may have continued dose titration for increased pain relief prior to randomization, not to exceed 160 mg/day.

Subjects who successfully completed the Titration Phase entered the Maintenance Phase and were randomized to receive either the same effective dose of ALO - 01 achieved in the Titration Phase or placebo. Subjects randomized to the placebo arm were force tapered gradually (in a blinded fashion using a double-dummy design) from ALO - 01 to placebo. Subjects completing the Maintenance Phase completed a tapering period and were scheduled for a Post-Treatment Follow-Up Visit at the end of the taper.

Number of patients (planned and analyzed):

A total of 728 subjects were to be recruited for the Titration Phase to achieve approximately 200 subjects in each of the 2 treatment groups (ALO - 01 or placebo). A total of 547 subjects were enrolled in the Titration Phase and received at least 1 dose of study drug. Of these 547, 344 completed the Titration Phase, were randomized to placebo (173 subjects) or ALO - 01 (171 subjects), and received at least 1 dose of study drug.

Diagnosis and main criteria for inclusion:

Males and postmenopausal, surgically sterile, or of childbearing potential and practiced protocol-specified method of birth control females ≥ 21 years of age with a primary diagnosis of Functional Class I-III OA of the hip or knee who met American College of Rheumatology clinical classification criteria for OA of the hip and knee, were judged to be in generally good health and required treatment of target joint pain within the last 90 days and met at least 1 of the following criteria: were unable to consistently control target joint pain with non-opioid analgesics or tramadol OR currently required opioid treatment (single or combination product) for target joint pain, with the equivalent of ≤ 40 mg/day of oral morphine sulfate, inclusive of breakthrough pain medication.

Test product, dose and mode of administration, batch number:

ALO - 01 (morphine sulfate extended release with sequestered naltrexone hydrochloride) formulated as extended release capsules of 20, 30, 40, 50, 60 or 80 mg/initiated at 20 mg QD or 20 mg BID and titrated to a maximum dose of 80 mg BID (160 mg daily).

Duration of treatment:

Up to 22 weeks

Reference therapy, dose and mode of administration, batch number:

Placebo to match ALO - 01

Criteria for evaluation:**Efficacy:**

The primary efficacy measure was the change from randomization baseline (Visit Y) to the Visit Y + 12 weeks diary BPI average pain score (daily scores of average pain were averaged for each subject over a 7-day interval to obtain a weekly score).

Continuous secondary efficacy variables included the following: Diary BPI average pain averaged over the entire Maintenance Phase; In-clinic BPI; Weekly diary BPI worst, least, and current pain (daily scores averaged over 7 day intervals to obtain weekly scores); WOMAC Osteoarthritis Index Pain Subscale, Stiffness Subscale, Physical Function Subscale, and Composite Index; MOS Sleep Scale subscale scores and 9-item overall sleep problems index; Beck Depression Inventory score; and amount of rescue medication (pill counts summed over 7-day intervals to obtain weekly counts).

Categorical secondary efficacy variables included the following: Patient Global Impression of Change (PGIC) and responders at Week 12 based on in-clinic BPI.

Safety:

The safety and tolerability of ALO - 01 was compared to placebo using adverse events, clinical laboratory data, vital signs, and two measures of opioid withdrawal: Subjective Opiate Withdrawal Scale (SOWS) and Clinical Opiate Withdrawal Scale (COWS).

Statistical methods:

The primary efficacy measure was the change from randomization baseline (Visit Y) to the Visit Y + 12 weeks diary BPI average pain score (daily scores of the BPI average pain evaluation were averaged for each subject over a 7-day interval to obtain a weekly score). For subjects who completed the study, the final 7-day interval on study was used.

The primary statistical analysis was the analysis of covariance (ANCOVA) with treatment as a categorical factor and the randomization baseline score as covariate. The primary efficacy analysis population was the ITT population.

Continuous secondary efficacy variables observed during the Titration Phase (in-clinic BPI and diary BPI worst, least, average, and current pain) were summarized at each visit in terms of descriptive statistics. Additionally, the proportion of subjects who were responders at Visit Y was summarized.

Continuous secondary efficacy variables observed during the Maintenance Phase were summarized at each scheduled visit in terms of descriptive statistics by treatment. Change from Visit Y was compared between treatments at each visit using an ANCOVA with treatment as a categorical factor and the Visit Y value as covariate. Change from Visit Y + 2 week was compared between treatments at each subsequent visit using an ANCOVA with treatment as a categorical factor and the Visit Y + 2 week value as covariate.

The Maintenance Phase continuous secondary efficacy variables were also analyzed using a mixed effects repeated measures model. The response variable was the efficacy variable in question at each visit in the Maintenance Phase. The model included fixed-effects model terms for days on study, treatment, and their interaction, and included the Visit Y value of the variable in question as a covariate. The covariance structure with the largest value for Schwarz's Bayesian Criterion from PROC MIXED was employed.

The cumulative proportion of subjects who were responders at Visit Y + 12 weeks of the Maintenance Phase was summarized. Subjects were defined as responders by the percent decrease from Visit X to Visit Y + 12 weeks on the in-clinic 24-hour pain assessment. Subjects who discontinued from the study before Visit Y + 12 weeks were considered non-responders. Treatment differences in the proportion of subjects who reported at least 20%, 30%, 40%, and 50% improvement were assessed with Fisher's exact test.

Categorical secondary efficacy variables (e.g., the PGIC) were summarized at each visit in terms of frequencies and percentages, by treatment. They were compared between treatments using a Cochran-Mantel-Haenszel (CMH) test with row mean scores.

Safety was assessed based on the incidence of treatment-emergent adverse events, vital signs, clinical laboratory tests, COWS and SOWS. These analyses were conducted on the safety population, composed of all subjects who received at least one dose of the study medication during the Maintenance Phase.

Quantitative laboratory results were summarized at Visit Y + 12 weeks in terms of descriptive statistics, by treatment. Actual values and change from Visit X were summarized. Change from Visit X was compared between treatments at each visit using an ANCOVA with treatment as the factor and Visit Y value as the covariate. In addition, laboratory results were also categorized according to potentially clinically significant (PCS) criteria. The frequency and percentage of subjects with at least 1 value during the Maintenance Phase that met the PCS criteria was summarized by treatment.

COWS were summarized in terms of descriptive statistics by treatment. Actual values and change from Visit Y to Visit Y + 1 were summarized for subjects whose dose of ALO - 01 was ≤ 80 mg at randomization. For subjects whose dose of ALO - 01 was > 80 mg at randomization, actual values and change from Visit Y to Visit Y + 2 were summarized.

Statistical methods (continued):

SOWS were summarized in terms of descriptive statistics by treatment. Actual values and change from Visit Y to the most severe score on Days 5-7 were summarized for subjects whose dose of ALO - 01 was ≤ 80 mg at randomization. For subjects whose dose of ALO - 01 was > 80 mg at randomization, actual values and change from Visit Y to the most severe score on Days 12-14 were summarized.

Vital signs were summarized in terms of descriptive statistics including the mean, standard deviation, minimum, maximum, and quartiles. Actual values and change from Baseline (Visit X) to each visit and to the final value prior to randomization or discontinuation were summarized.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

- ALO - 01 is efficacious for the treatment of subjects experiencing chronic non-malignant, moderate to severe pain from OA of the knee or hip.
- The superior efficacy of ALO - 01 BID compared with placebo was demonstrated with respect to the primary endpoint, mean change in diary BPI score of average pain (daily scores of average pain averaged over 7 days) from randomization to 12 weeks following randomization in subjects with moderate to severe pain from OA of the hip or knee.
- Primary endpoint results were directionally consistent when alternative methods of defining the last 7 days on study were examined. Further, all protocol-specified sensitivity analyses of the primary endpoint were directionally consistent with the primary analysis.
- For BPI diary average pain score, clinic BPI pain score, and weekly diary assessment of pain (worst, least, and current), statistically significant treatment differences favoring ALO - 01 were observed beginning at the first Maintenance Phase visit and continued throughout the Maintenance Phase.
- For each of the BPI measures, persistency of effect was noted across imputation methods, with both directionally consistent and statistically significant differences favoring ALO - 01 over 12 weeks.
- A statistically significantly greater proportion of subjects in the ALO - 01 treatment group compared to the placebo treatment group reported at least a 30% improvement based on in-clinic BPI.
- For the WOMAC Osteoarthritis Index pain and composite scores, statistically significant treatment differences favoring ALO - 01 were observed beginning at the first Maintenance Phase visit and continued throughout the majority of visits during the Maintenance Phase, including Y + 12 Weeks.
- The observed treatment group differences in efficacy were not a result of differences in usage of rescue medications (average of 5.3 vs. 6.2 tablets/week for ALO - 01 and placebo, respectively).
- Results for the Beck Depression Inventory score, MOS sleep scale, and Patient's Global Impression of Change favored ALO - 01 over placebo, although no statistically significant treatment differences were observed. However, the study was not powered to detect differences for these instruments.
- These findings are not restricted to subjects with recent opioid experience, as greater than 75% of subjects in both the Titration and Maintenance Phases had not received

opioids within the last 30 days (opioid naïve).

The superior efficacy of ALO - 01 compared to placebo in the treatment of pain from OA of the knee or hip was demonstrated consistently across a variety of validated pain measures, imputation methods, and analysis populations.

SAFETY RESULTS:

Based on the results of this study, it is concluded that:

- The overall safety profile of ALO - 01 was consistent with other opioid products. The most frequently reported ($\geq 5.0\%$ of all subjects) TEAEs during the Titration Phase included constipation, nausea, somnolence, vomiting, dizziness, pruritus, headache, and dry mouth. The most frequently reported ($\geq 5.0\%$ of subjects in either treatment group) TEAEs during the Maintenance Phase included diarrhoea, nausea, constipation, headache, vomiting, and rhinorrhoea.
- No deaths occurred during the study and few treatment-emergent SAEs were reported. A single treatment-related SAE (hypotension) was reported during the study (Titration Phase).
- The most common ($\geq 2\%$ of all subjects) TEAEs that led to premature discontinuation from the Titration Phase were nausea, constipation, somnolence, and vomiting. The most common (≥ 2 subjects in either treatment group) TEAEs that led to premature discontinuation from the Maintenance Phase were nausea, vomiting, hyperhidrosis, diarrhoea, constipation, and somnolence.
- A clinical review of the COWS, SOWS, and adverse event profile did not detect an increased risk of opioid withdrawal in ALO - 01 compared to placebo.
- Analysis of laboratory and vital signs data revealed no clinically concerning results compared with placebo.

ALO - 01 was observed to be safe and well tolerated in this study. The overall safety profile of ALO - 01 was consistent with other opioid products.

CONCLUSION:

In conclusion, treatment with ALO-01:

- Resulted in a statistically significantly superior efficacy for ALO - 01 compared to placebo as measured by change from baseline to Visit Y + 12 weeks in BPI average pain score.
- Resulted in statistically significantly superior efficacy for ALO - 01 compared to placebo as measured by change from baseline to each Maintenance Phase visit in BPI diary average pain, in-clinic BPI pain, and weekly diary pain assessments.
- Resulted in statistically significantly superior efficacy for ALO - 01 compared to placebo as measured by change from baseline to Visit Y + 12 weeks in WOMAC Osteoarthritis Index composite score.
- Resulted in lower average weekly number of rescue tablets used and lower average daily use of rescue medication compared to the placebo group.
- Was safe and well tolerated, with an adverse event profile typical of morphine administration.

Date of the report:

1 February 2008

4.2.12 Synopsis of Study # ALO-KNT-302

Name of Sponsor/Company: Alpharma Pharmaceuticals LLC	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: EMBEDA™ formerly known as Kadian NT or ALO-01		
Name of Active Ingredient: Morphine Sulfate Extended Release with Sequestered Naltrexone HCl		
Title of Study: 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		
Principal Investigator: Investigators: Multi-center, See Appendix 16.1.4.		
Study center(s): 58		
Publications (reference): None		
Studied period (years): Date first subject enrolled: 11 December 2006 Date last subject completed: The study is on-going	Phase of development: Phase 3	
<p>Objectives:</p> <p>Primary: The primary objective of this study was to evaluate the long-term safety of morphine sulfate with sequestered naltrexone hydrochloride extended-release capsules (ALO-01) administered for up to 12 months.</p> <p>The secondary objectives of this study were to:</p> <ul style="list-style-type: none"> • 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, and the Global Assessment of Study Drug, • 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), • evaluate plasma naltrexone, 6-β-naltrexol, and morphine concentrations at Visits 2 through 15 in selected male and female subjects for pharmacokinetic (PK) study. <p>In addition, efficacy was evaluated by assessing the use of acetaminophen for rescue for break-through pain.</p>		

Synopsis of ALO-KN1-302

<p>Methodology:</p> <p>This is an ongoing long-term, open-label study designed to evaluate the safety of ALO-01 administered once daily (QD) or twice daily (BID). The study consisted of a 12-month Treatment Phase (Baseline to Visit 15) and a follow-up visit (Visit 16) approximately 1 month after the end of the Treatment Phase. This report presents data for the first 6 months of treatment. The report includes data for all subjects who completed Visit 8/Month 6 with the exception of those who discontinued from the study after 24 July 2007. Data for subjects who discontinued after 24 July 2007 will be included in the amended report submitted with the 120-day safety update. The information presented in this synopsis refers to the methods and results for the presentation of data for the first 6 months.</p>
<p>Number of subjects (planned and analyzed):</p> <p>Allowing for an expected drop out rate of 75% by 6 months and 87.5% by 12 months, enrollment of approximately 400 subjects was required to achieve goals of 100 subjects retained for 6 months and 50 subjects retained for the entire 12 month study. There were 623 subjects screened and 467 subjects enrolled. There were 441 subjects included in the evaluation of results up to the 6-month cut off date. The remaining 26 subjects discontinued after 24 July 2007. Of the 441 subjects included in the data base for the evaluation of results at 6 months, 2 subjects were not treated with study drug and 439 subjects were treated with study drug. All treated subjects were included in the intent-to-treat (ITT) and safety Populations.</p>
<p>Diagnosis and main criteria for inclusion:</p> <p>This study enrolled subjects 18 to 70 years of age who had chronic moderate to severe nonmalignant pain for at least 3 months and who were otherwise healthy. Subjects with pain due to malignancy, fibromyalgia, migraine, recent trauma, infection, or those who had received recent surgical or parenteral treatment for their condition (e.g., intraspinal infusions, local corticosteroid injections) were excluded. Subjects were carefully screened by Investigators for evidence of past or potential drug abuse or dependence and excluded if these conditions were suspected</p>
<p>Test product, dose and mode of administration, batch number:</p> <p>ALO-01 is morphine sulfate and sequestered naltrexone hydrochloride formulated as extended-release capsules of 20, 30, 40, 50, 60, 80, or 100 mg, of morphine sulfate and a fixed 4% weight ratio of naltrexone hydrochloride which were packaged in bottles of 30 capsules each. The batch numbers used in this study to date are: PI-1568, PI-1569, PI-1570, PI-1571, PI-1572, PI-1573, PI-1574, PI-1590, PI-1591, PI-1592, PI-1593, PI-1594, PI-1595, and PI-1596.</p>
<p>Duration of treatment:</p> <p>The total duration of treatment is up to 12 months. This report presents data for the first 6 months of treatment.</p>
<p>Reference therapy, dose and mode of administration, batch number:</p> <p>None</p>

Criteria for evaluation:

Efficacy: The evaluation of efficacy was based on the subject's pain intensity, using the BPI Short Form questionnaire. Additional evaluations of efficacy included the results of the Global Assessment of Study Drug, and the use of rescue medication (acetaminophen).

Safety: Safety was evaluated by assessing the incidence of treatment-emergent adverse events (TEAEs), by vital signs (heart rate, respiratory rate, blood pressure after sitting for 3 minutes, and oral temperature), electrocardiograms (ECGs), clinical laboratory tests, and the occurrence of withdrawal symptoms as assessed by the COWS. In addition, qualitative urine drug screens were performed monthly and included reflex testing to identify all opioids that subjects had taken during study participation. Urine pregnancy tests were performed monthly for female subjects of childbearing potential.

Pharmacokinetics: Sparse PK sampling was performed on a randomly pre-determined sub-set of subjects in this study monthly after the Baseline Visit. Plasma naltrexone, 6- β -naltrexol and morphine determinations were performed from PK samples. The results of the PK study are presented in a separate report that will be included in the 120-day safety update.

Statistical methods:

General: Summary statistics consisted of frequencies and percentages of responses in each category for discrete measures and of means, medians, standard deviations, quartiles, minimum and maximum values for continuous measures. Data were summarized for all subjects in the ITT or Safety population, for subjects by average daily dose range (<80 mg, 80-120 mg, >120 mg) and by opioid status at baseline (opioid-naïve and opioid-experienced).

Efficacy: Each of the 4 components of the BPI was summarized descriptively at each visit by average daily dose and for all subjects. One-sided t-tests were conducted on the change and percent change from Baseline, with p-values presented to summarize the difference between each post-baseline time point and the baseline measurement at each average daily dose range and overall (all subjects treated). The Global Assessment of Study Drug, assessed as "Excellent", "Very Good", "Good", "Fair", or "Poor" was listed by subject and visit. The number and percent of subjects with each response was summarized at each visit by average daily dose range and for all subjects. In addition, the number and percent of subjects assessed as at least "Good" were summarized. The use of rescue medication (acetaminophen) was summarized in tabular presentations of the average daily dose and average daily dose range. The evaluation of efficacy was a secondary objective of this study.

Safety: Adverse Events (AEs) were summarized by System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities[®] (MedDRA[®]) v 9.1. Treatment-emergent AEs were defined as AEs occurring on or after the date of first administration of ALO-01. For each type of TEAE, the number and percent of subjects with the TEAE of interest were summarized overall and by System Organ Class and Preferred Term, by average daily dose range and for all subjects. Changes in laboratory values from baseline were summarized at each time point by average daily dose and for subjects overall. A shift table was produced for each laboratory test, summarizing changes from baseline to subsequent visits. Shift tables were used to summarize changes in electrocardiogram results. Other safety variables were summarized using descriptive statistics.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS: All efficacy measurements were evaluated in the ITT population (N = 439). There were statistically significant improvements in each pain category as early as Visit 2/Week 1 and at each assessment up to Visit 8/Month 6. For most measures, the magnitude of the improvement increased over time. As evaluated by dose group, there were statistically significant improvements for each type of pain in each dose group. The magnitude of the decrease in pain scores was highest in the <80 mg dose group, intermediate in the 80-120 mg group and lowest in the >120 mg dose group. It appeared that the magnitude of the improvement was greater in subjects whose pain was controlled at the lowest doses than in those whose pain was controlled at higher doses. In addition, subjects in the <80 mg dose group had improvements in BPI scores sooner than subjects in the higher dose groups. In the <80 mg dose group, statistically significant improvements for most measures were seen as soon as Visit 2/Week 1, but generally not until Visit 3/Week 4 in the 80-120 mg dose group or Visit 6/Month 4 in the >120 mg dose group. As evaluated by the Subjects Global Assessment, the percentage of subjects in the good/very good/excellent category was over 75% at each assessment after Week 2 in each dose group. By Visit 2/Week 1, over half the subjects rated their response to treatment as good, very good, or excellent. At Visit 3/Week 4, 76.5% of subjects rated their response as good, very good, or excellent and at subsequent visits, 89.0% to 93.1% of subjects were in this category. In addition, mean daily dose of rescue medication decreased over time in each dose group. Finally, it should be noted that only 34 subjects (7.7%) discontinued for lack of efficacy.

SAFETY RESULTS:

The primary objective of this study was to evaluate safety. There were no deaths reported. There were 19 subjects with serious adverse events (SAEs). Only 1 subject had any SAEs categorized as related to study drug. In this subject, all of these were gastrointestinal disorders and were categorized as "possibly" related to study drug.

Treatment-emergent AEs leading to discontinuation of study drug were reported by 105 subjects (23.9%). The most frequent TEAEs leading to discontinuation were well-known morphine side effects, such as nausea, constipation, vomiting, somnolence, headache, and pruritus.

There were 340 subjects (77.4%) who had 1 or more TEAEs. The most common TEAEs were those known to be associated with the administration of morphine, such as constipation, nausea, vomiting, somnolence, diarrhoea, pruritus, and fatigue. Treatment-emergent AEs known to be associated with morphine were among the most frequent TEAEs related to study drug, and the most frequent severe TEAEs.

Treatment-emergent AEs were also evaluated by average daily dose and opioid status at Baseline. As evaluated by dose group, there were no notable trends in the frequency or type of treatment-emergent SAEs (TESAEs) reported. Discontinuations due to TEAEs, and related TEAEs were more common in the <80 mg dose group than in the higher dose groups. This was not unexpected, as subjects who had TEAEs related to treatment were less likely to be up titrated, and more likely to be withdrawn for these TEAEs.

As evaluated by opioid status at Baseline, the percentage of subjects discontinued due to TEAEs was slightly higher in opioid-experienced subjects than in opioid-naïve subjects. The overall frequency of TEAEs was also slightly higher in opioid-experienced subjects than opioid-naïve subjects. However, in regard to the overall incidence of TEAEs, there were no notable differences between the groups as evaluated by preferred terms.

There were no clinically relevant changes observed in response to treatment as evaluated by assessments of clinical chemistry, urinalysis, hematology, vital signs, ECG results, or physical examination findings. A small percentage of subjects had mild withdrawal symptoms at Baseline, but the percentage with any withdrawal symptom decreased over time and was <5% at all post-baseline assessments.

Synopsis of ALO-KNT-302

CONCLUSION:

In conclusion, treatment with ALO-01

- Resulted in statistically significant decreases in pain for all subjects and for subjects in each dose group.
- Was rated as good, very good or excellent by over 50% of subjects after as little as 1 week of treatment and over 75% of subjects after Visit 3/Week 4.
- Resulted in decreases in the mean daily dose of rescue medication
- Was safe and well tolerated

4.2.13 OCP NDA Filing Memo

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	22-321	Brand Name	EMBEDA Capsules	
OCP Division (I, II, III, IV, V)		Generic Name	Morphine Sulfate extended release sequestered Naltrexone HCl Capsules	
Medical Division	Anesthesia, Analgesia and Rheumatology Products	Drug Class	Opioid	
OCP Reviewer	Srikanth C. Nallani, Ph.D.	Indication(s)	Management of moderate to severe chronic pain	
OCP Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Capsules	
Pharmacometrics Reviewer		Dosing Regimen		
Date of Submission	2/28/2008	Route of Administration	Oral	
Estimated Due Date of OCPB Review	7/28/2008	Sponsor	Alpharma Pharmaceuticals LLC	
Medical Division Due Date	7/28/2008	Priority Classification	Priority	
PDUFA Due Date	8/28/08			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling				
Reference Bioanalytical and Analytical Methods		██████	██████	
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	9	9	
multiple dose:				
Patients-				
single dose:				

multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	X	1	1	
Phase 3:	X	2	2	
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1	1	
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:	X	1	1	Oral solution of naltrexone was used
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X			
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	1	
Dissolution:	X	1	1	
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		13	13	

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/s/

Srikanth Nallani
11/24/2008 10:41:32 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
11/25/2008 05:31:16 AM
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