CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-897

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

2nd Cycle

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 870)** **Tracking/Action Sheet for Formal/Informal Consults**
From: Srikanth C. Nallani, Ph.D.	**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**

DATE: 4/7/2006	IND No.:	NDA No. **21-897**	DATE OF DOCUMENT	2/13/2006
NAME OF DRUG [**Vivitrol**]	PRIORITY CONSIDERATION **Standard**		Date of informal/Formal Consult:	2/13/2006

NAME OF THE SPONSOR: [**Alkermes, 88 Sidney St, Cambridge, MA 02139**]

TYPE OF SUBMISSION
CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☒ OTHER *(SPECIFY BELOW)*: [Complete Response for Action (12/28/2005) to Original NDA submitted on 3/31/2005]
☐ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated) ☐ E-mail comments to: ☐Medical ☐Chemist ☐Pharm-Tox ☐Micro ☐Pharmacometrics ☐Others (Check as appropriate and attach e-mail)	☐ Oral communication with Name: [ ] ☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☐ Formal Review/Memo (attached) ☒ See comments below ☐ See submission cover letter ☐ OTHER *(SPECIFY BELOW)*: [ ]

REVIEW COMMENT(S)
☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:
[Current submission consists of Alkermes' response to approvable letter issued on 12/28/2005 for NDA 21-897 submitted on 3/31/2005. With regard to Clinical Pharmacology and Biopharmaceutics comments (# 4, 5 and 6) in the approvable letter, the sponsor agrees to address them in an appropriate post-approval submission. The following is the proposed timeline for the completion of post-marketing commitments (PMC) agreed to by the sponsor:

1. Revise the drug release specifications to include Day 14 and Day 28 drug release information.
The timeline for this PMC will be addressed by the Office of New Drug Quality Assurance.
2. Conduct *in vitro* CYP inhibition studies using conventional CYP substrates and validated analytical methodology.
Protocol Submission: July/2006
Study Start: August/2006
Final Report Submission: May/2007
3. Conduct *in vitro* studies in human hepatocytes to evaluate the potential of naltrexone to induce CYP3A4 and CYP1A2.
Protocol Submission: July/2006
Study Start: August/2006
Final Report Submission: May/2007

Please find the cover letter from sponsor attached to this review. The sponsor also submitted labeling changes, however, none were pertinent to Clinical Pharmcaology and Biopharmaceutics aspects and hence were not reviewed.]

SIGNATURE OF REVIEWER: Srikanth C. Nallani Ph.D.	Date 4/7/2006
SIGNATURE OF TEAM LEADER: Suresh Doddapaneni, Ph.D.	Date 4/7/2006
CC.: HFD # [ ]; TL: [ ]	**Project Manager: Lisa Basham-Cruz** **Date**

4.4 Consent of Supervisor for the proposed Phase IV commitments

Nallani, Srikanth

From: Doddapaneni, Suresh
Sent: Friday, November 18, 2005 8:34 AM
To: Nallani, Srikanth
Subject: FW: Srikanth's NDA-Naltrexone depot formulationl

Srikanth

Print out this e-mail and attach it to the review as Division Director's concurrence. This is in line with OCPB's procedure.

Thanks, Suresh

-----Original Message-----
From: Malinowski, Henry J
Sent: Friday, November 18, 2005 8:28 AM
To: Doddapaneni, Suresh
Subject: RE: Srikanth's NDA-Naltrexone depot formulationl

Suresh,
Looks fine...Hank

-----Original Message-----
From: Doddapaneni, Suresh
Sent: Thursday, November 17, 2005 12:44 PM
To: Malinowski, Henry J
Subject: Srikanth's NDA-Naltrexone depot formulationl

Hank

The review for depot naltrexone product is being finalized. We had the briefing on this on Tuesday. I have extracted from the review, the recommendation/phase IV commitment related language that Srikanth and I drafted. Please provide your feedback.

Thanks, Suresh

1.1 Recommendation

From a Clinical Pharmacology and Biopharmaceutics perspective, NDA 21-897 is acceptable provided that a mutually satisfactory agreement can be reached between the Agency and Alkermes regarding the (a) language in the package insert (b) *in vitro* drug release method, and (c) post marketing commitment to further investigate potential of this product to inhibit or induce CYP enzymes. Specifically,

a) The drug release specifications should be revised with addition of Day 14 and Day 28 drug release information.
b) Conduct *in vitro* CYP inhibition studies using conventional substrates as the submitted data used florescent substrate(s) which tends to introduce non-specificity in detection.
c) Conduct *in vitro* studies in human hepatocytes to evaluate potential of naltrexone to induce CYP3A4 and CYP1A2.

1.2 Phase IV Commitments

a) Conduct *in vitro* CYP inhibition studies using conventional CYP substrates and validated analytical methodology.
b) Conduct *in vitro* studies in human hepatocytes to evaluate potential of naltrexone to induce CYP3A4 and CYP1A2.

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

/s/

Srikanth Nallani
11/21/2005 11:09:54 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
11/21/2005 01:47:33 PM
BIOPHARMACEUTICS

1ST Cycle

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-897	Submission Date(s): 03/31/05
Brand Name	Vivitrol® (Naltrexone Long-Acting Injection)
Generic Name	Naltrexone
Reviewer	Srikanth C. Nallani, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
ORM Division	Division of Anesthesia, Analgesia, , and Rheumatology Products
Sponsor	Alkermes, 88 Sidney St, Cambridge, MA
Relevant IND(s)	61,138
Submission Type; Code	Original NDA; 3P
Formulation; Strength(s)	Extended release microsphere formulation of naltrexone for suspension to be administered by IM injection; 380 mg in 5 mL vials
Indication	Treatment of alcohol dependence
Dosing Regimen	380 mg IM every 4 weeks or once a month

Table of Contents

1 Executive Summary

1.1 Recommendation

From a Clinical Pharmacology and Biopharmaceutics perspective, NDA 21-897 is acceptable provided that a mutually satisfactory agreement can be reached between the Agency and Alkermes regarding the (a) language in the package insert (b) *in vitro* drug release method, and (c) post marketing commitment to further investigate potential of this product to inhibit or induce CYP enzymes. Specifically,

a) The drug release specifications should be revised with addition of Day 14 and Day 28 drug release information.
b) Conduct *in vitro* CYP inhibition studies using conventional substrates as the submitted data used florescent substrate(s) which tends to introduce non-specificity in detection.
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1.2 Phase IV Commitments

a) Conduct *in vitro* CYP inhibition studies using conventional CYP substrates and validated analytical methodology.

b) Conduct *in vitro* studies in human hepatocytes to evaluate potential of naltrexone to induce CYP3A4 and CYP1A2.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Naltrexone is a pure opioid antagonist with highest affinity for the μ-opioid receptor. The mechanism of action of naltrexone in alcoholism is not clearly understood. However, it is believed that naltrexone decreases alcohol consumption through the blockade of endogenous opioids at μ-opioid receptors, resulting in inhibition of the reward pathways and thus reducing the subjective euphoric and reinforcing properties of alcohol. In 1994, oral naltrexone (Revia™) was approved for the treatment of alcoholism. Current NDA is a 505(b)(2) submission by Alkermes Inc. for a once a month extended release microsphere formulation of naltrexone for intramuscular injection for the same indication (referred to as Vivitrol in this document). Based on the sponsor's argument that this product will improve compliance compared to once a day administration of oral naltrexone, the NDA was awarded priority review status.

Data from five completed Clinical Pharmacology and Biopharmaceutics studies (ALK21-001, -002, -004, -005 & -009), one Phase III Clinical efficacy (ALK21-003) and safety study (ALK21-006), and one long-term safety study (ALK21-003extension) was submitted. The Clinical Pharmacology studies investigated the relative bioavailability, single dose (ALk21-001, -002) and multiple dose pharmacokinetics (ALK21-005), pharmacokinetics in mild and moderate hepatic impairment (Study # ALK21-009), effect of covariates (such as age, sex, body weight, race, and polysubstance dependency and markers of renal and hepatic function) using population pharmacokinetic analysis

(Report# ALK21-011), and a dose-finding opiate challenge study in opiate users (ALK21-004).

Vivitrol is an extended release microsphere-based formulation of naltrexone incorporated into a biodegradable matrix of polylactide-co-glycolide for intramuscular use. Based on *in vitro* studies, the drug release from the microsphere formulation is hypothesized to occur in three phases as described below;

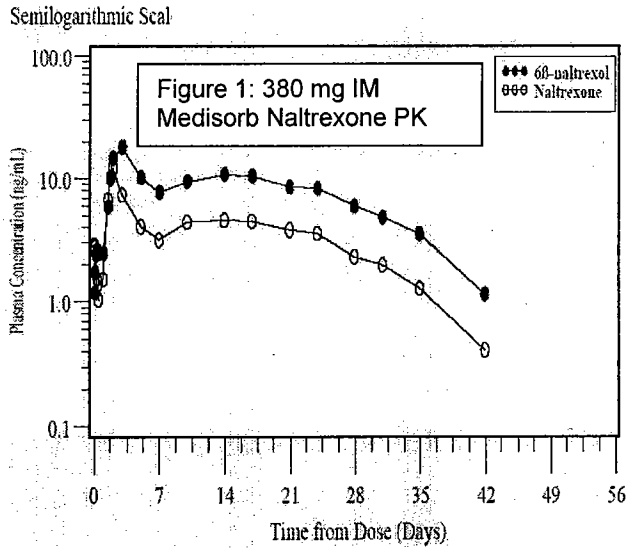
Phase 1 Initial Release	The Initial Release phase takes place during the first day following exposure of the microspheres to an aqueous environment. A small quantity of drug at or near the surface is released.
Phase 2 Hydration	The Hydration phase occurs during the first week. Physical erosion of the microspheres begins and some subsurface drug is released.
Phase 3 Sustained Release	The Sustained Release phase takes place from Week 2 until drug release is complete and is governed by polymer erosion. The Sustained Release phase constitutes the majority of the release profile both in terms of overall duration and quantity of drug released.

A real time release method was used to determine the *in vitro* profile [initial phase, secondary (hydration) phase and sustained release phase] of Vivitrol microspheres in the presence of buffered aqueous media (phosphate buffered saline with Tween 20 and sodium azide) at physiological pH (7.4) and temperature (37°C).

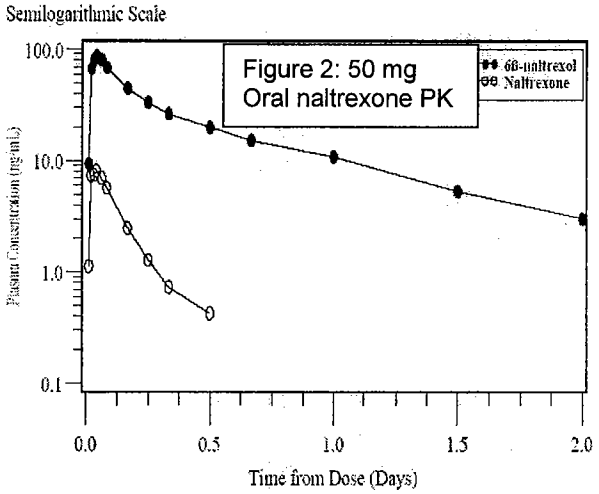
Based on the pharmacokinetic, pharmacodynamic, safety and efficacy profile of Vivitrol, the sponsor is proposing the use of 380 mg dose of Vivitrol for the treatment of alcoholism.

PK characteristics of Vivitrol

After IM administration of Vivitrol, peak plasma levels of naltrexone are observed in about 5 hours to 2 days. The increase in AUC of naltrexone was approximately dose-proportional in the range of 141 – 784 mg Vivitrol (study # ALK21-001, -002). Naltrexone elimination appears release rate-dependent as the elimination half life for the product is approximately 8 days; while oral naltrexone has a 5 hour half life (study # ALK21-005) (Figure 1).



Following IM administration of 380 mg IM Vivitrol, the plasma levels of 6β-naltrexol are ~ two-fold higher than naltrexone and the PK profile appears to be in parallel to naltrexone. This would indicate that 6β-naltrexol disposition is formation rate-dependent. Repeated administration of Vivitrol, once a month for four months, did not result in significant accumulation of naltrexone.



The proposed 380 mg dose of IM Vivitrol is approximately 1/3rd compared to oral naltrexone (50 mg QD for 28 days = 1400 mg over 28 days). However, the exposure to naltrexone (AUC_{0-28}) over 28 days is approximately four-fold higher than that observed with oral naltrexone. This appears to be a result of bypassing of first pass metabolism by the IM route. The C_{max} of naltrexone is highly variable following Revia and Vivitrol administration. Compared to oral naltrexone, 6β-naltrexol formation is only 36% following IM administration of Medisorb 380 mg Naltrexone dose. As shown in Figure 2, following oral administration, 6β-naltrexol plasma levels are ~ 15-fold higher and a $t_{1/2}$ of ~ 13 hours.

Plasma protein binding (21%) is not expected to change with this route of administration compared to oral route of naltrexone administration.

Dose-finding or PK-PD results

Evidence to support the dose, duration of action/dosing interval of Vivitrol suspension was derived from a pilot opioid blockade study (ALK21-004), where 75, 150 and 300 mg doses were studied. The presumed mechanism of action of naltrexone in the treatment of alcohol dependence is the blockade of endogenous rather than exogenous opioids. Nevertheless, results suggested that doses of Vivitrol ≥150 mg demonstrated blockade of opioid effects of hydromorphone challenge test over 28 days.

Pharmacokinetics in special populations

Population pharmacokinetic analysis (Study report # ALK21-011) was conducted to determine if demographic variables (such as age, sex, body weight, race, and polysubstance dependency) and laboratory markers of renal and hepatic function

contributed to differences in PK parameter estimates among individuals. The data from studies ALK21-004 (PK/PD study), -005 (PK study), -006 (Safety & efficacy study), -009 (PK study) were utilized in the population PK analysis. None of the covariate – parameter relationships determined by either the population PK analysis or the ANCOVA suggests that adjustments to the dosing regimen of Vivitrol are necessary.

The hepatic impairment study # ALK21-009 revealed that mild and moderate hepatic impairment did not affect pharmacokinetics of naltrexone following Vivitrol administration. Data was not acquired in severe hepatic impairment and the product is not recommended to be used due to the risk of coagulation.

Extra-hepatic sites play a major role in the clearance of naltrexone to 6β-naltrexol. Aldo-keto-reductases, the enzymes responsible for conversion of naltrexone to 6β-naltrexol, is expressed primarily in liver but also in brain, heart, kidney, lung, prostate, skeletal muscle, small intestine, spleen and testis. As such, it is unlikely that the CYP inhibitors affect the pharmacokinetics of Vivitrol.

In vitro CYP inhibition by naltrexone was evaluated by employing a high throughput fluorogenic substrate assay. While the results suggest remote possibility of CYP inhibition mediated drug-drug interactions by naltrexone; use of fluorogenic substrates is not acceptable per current Agency practices. These data would need to be required using conventional substrates.

Naltrexone and 6β-naltrexol C_{max} were about 30 to 40% lower while AUC_{0-28} were similar between females and males following a single dose of 380 mg Vivitrol. Dosage adjustment is not necessary based on gender of the subject as the pharmacokinetics were not significantly altered.

Based on naltrexone PK following Vivitrol microsphere administration, dose adjustment may not be necessary for subjects with renal impairment. If anything, 6β-naltrexol is likely to accumulate in renal impairment. However, the levels are substantially lower for Vivitrol compared to oral naltrexone and any accumulation in renal impairment is not likely to have clinically significant effect.

Data summarized from available sources did not show reports of QT prolongation or cardiac safety events.

Safety, effectiveness, and pharmacokinetics data was not acquired in pediatric patients less than 18 years of age.

The sponsor proposed the following *in vitro* drug release method and specifications for real time drug release testing:

Proposed drug release method and Specifications

A real time drug release method was used to determine the *in vitro* profile [initial phase, secondary (hydration) phase and sustained release phase] of Vivitrol microspheres in the presence of buffered aqueous media (release media) at physiological pH (7.4) and temperature (37°C).

While the Day 1 [redacted] and Day 7 [redacted], specifications are acceptable; the specifications should be tightened based on CMC reviewers assessment of the stability data for the pertinent lots. In addition, the sponsor's assumption that the Day 7 to Day 14 sampling will be representative of the remaining 14 days of drug release is not acceptable. About 26 – 75 % of drug from various lots of Vivitrol was released by day 14 from real time release method; hence additional sampling up to 30 days may be necessary depending on the stability of the drug in solution. Consistent product performance over 28 days is pivotal for the safety and efficacy of this drug. Hence, tentative specifications for Day 14 and Day 28 are proposed as [redacted] and [redacted] respectively. The specifications may be revised following CMC reviewers' assessment of the stability data provided for the pertinent lots.

Bridging of clinical trial and to-be-marketed formulation

The clinical studies were conducted employing lots from a [redacted] batch of Vivitrol. The to-be-marketed formulation lots are from a [redacted] batch of Vivitrol. The Agency indicated that bioequivalence study will not be necessary if the Sponsor provides stability data as well as comparative multi-point dissolution testing data using an acceptable dissolution testing method. Accordingly, employing a real time drug release method, drug release was evaluated from three lots of [redacted] batch and three lots of [redacted] batch. Comparison was done by means of the standard and a modified f_2 test which takes into consideration the multiphasic release characteristics of Vivitrol. Release of naltrexone on Day 1, Day 2-7 and Day 7-14 of the test and reference batches was in general comparable with the standard and modified f_2 test.

2 QBR

2.1 General Attributes

2.1.1. What is the rationale for the development of naltrexone long-acting injection?

Naltrexone long-acting injection is to be administered once a month and is supposed to improve compliance over the oral naltrexone.

Oral naltrexone (Revia Tablet, NDA# 18-932) was first approved in 1984 for the treatment of opioid addiction. In 1994, Revia was approved for alcohol addiction treatment. The recommended dose of oral naltrexone is 50 mg QD for up to 12 weeks. Since Naltrexone long acting injection is to be used once a month, compliance may be better by minimizing disruptions in therapy caused by missed medication due to impairment and fluctuation of motivation for treatment.

Alkermes, Inc., submitted this NDA under section 505(b)(2) of the Food Drug and Cosmetic Act for the treatment of alcohol dependence, using Revia as a Reference Listed Drug.

This product has not been approved anywhere else in the world at this time.

2.1.2. What are the highlights of the formulation of naltrexone long-acting injection?

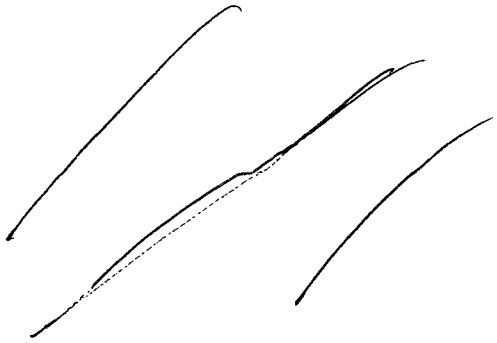
Vivitrol is an extended release microsphere-based formulation of naltrexone incorporated into a biodegradable matrix of polylactide-co-glycolide for intramuscular use.

Polylactide-co-glycolide is a common, biodegradable medical polymer with a history of safe human use in several medical products and is listed in the FDA Inactive Ingredient Guide (poly- -lactide-co-glycolide, Polyglactin, CAS # 026780507). The microspheres are comprised of approximately 34% (w/w) naltrexone within the polymer matrix. Following a single intramuscular (IM) injection, Vivitrol microspheres release naltrexone for greater than 1 month. The formulation and composition are described below:

Injection components: Vivitrol is provided as a kit containing a vial each of microspheres, diluent, one 5 mL syringe, one 1/2 inch 20 gauge preparation needle, two 1½ inch 20 gauge administration needles with safety device.

Active & Inactive Ingredients: Naltrexone is micro-encapsulated in 75:25 polylactide-co-glycolide (PLG) at a concentration of 337 mg of naltrexone per gram of microspheres. Inactive ingredients used and their function in the manufacture of the PLG microspheres are listed below:

COMPONENTS	FUNCTION



Diluent: The diluent for parenteral use is a sterile, clear, colorless solution. The composition of the diluent includes carboxymethylcellulose sodium salt, polysorbate 20, sodium chloride, and water for injection. The microspheres are suspended in the diluent prior to injection.

2.1.3. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Naltrexone is a pure opioid μ-receptor antagonist that reversibly blocks the effects of opiates by binding competitively at opioid receptors. It is believed that naltrexone decreases alcohol consumption through the blockade of endogenous opioids at μ-opioid receptors, resulting in inhibition of the reward pathways and thus reducing the subjective euphoric and reinforcing properties of alcohol. In patients with alcohol dependence, blockade of the endogenous opioid peptides leads to decreased craving for alcohol, decreased urge to drink, and reduction in the consumption of alcohol.

2.1.4. What are the proposed dosage(s) and route(s) of administration?

The recommended dose of Vivitrol is 380 mg by intramuscular injection every 4 weeks or once a month.

The proposed dosage and route of administration are as follows:

> The recommended dose of Vivitrol is 380 mg by intramuscular injection every 4 weeks or once a month. The injection should be administered by a health care professional as an IM gluteal injection, alternating buttocks using the kit components provided. Vivitrol should not be administered intravenously.
>
> If a patient misses a dose, he/she should be instructed to receive the next dose as soon as possible. Pretreatment with oral naltrexone is not required before using Vivitrol.

2.2 General Clinical Pharmacology

Clinical Pharmacology of oral naltrexone known from the approved oral product (Revia)

Following oral administration, naltrexone undergoes rapid and nearly complete absorption with approximately 96% of the dose absorbed from the gastrointestinal tract. Naltrexone undergoes extensive first pass metabolism to 6β-naltrexol and the peak plasma levels of both occur within one hour of dosing. The volume of distribution for naltrexone following intravenous administration is estimated to be 1350 liters. In vitro tests with human plasma show naltrexone to be 21% bound to plasma proteins over the therapeutic dose range. The renal clearance for naltrexone ranges from 30 – 127 mL/min and suggests that renal elimination is primarily by glomerular filtration. In comparison, the renal clearance for 6β-naltrexol ranges from 230-369 mL/min, suggesting an additional renal tubular secretory mechanism. The urinary excretion of unchanged naltrexone accounts for less than 2% of an oral dose; urinary excretion of unchanged and conjugated 6-β-naltrexol accounts for 43% of an oral dose. The pharmacokinetic profile of naltrexone suggests that naltrexone and its metabolites may undergo enterohepatic recycling. Naltrexone appears to have extra-hepatic sites of drug metabolism and its major metabolite undergoes active tubular secretion. Caution should be exercised when naltrexone hydrochloride is administered to patients with liver disease. In subject with compensated or decompensated hepatic impairment, there is an increase in naltrexone AUC of approximately 5- and 10-fold, respectively; while, 6β-naltrexol formation was delayed (longer T_{max}) .

Clinical Pharmacology of Vivitrol

In this NDA, Sponsor characterized the pharmacokinetic characteristics of the long acting formulation and obtained bridging information as applicable to this product while relying on the previously known Clinical Pharmacology aspects of naltrexone. As such, data

from five completed Clinical Pharmacology and Biopharmaceutics studies, one Phase III clinical efficacy and safety study, and one long-term safety study was submitted. The Clinical Pharmacology studies investigated the relative bioavailability, single dose and multiple dose pharmacokinetics, pharmacokinetics in mild and moderate hepatic impairment, effect of covariates (such as age, sex, body weight, race, and polysubstance dependency and markers of renal and hepatic function) using population pharmacokinetic analysis, and an opiate challenge study in opiate users. The Pivotal clinical study (ALK21-003) investigated the efficacy and safety of the product against placebo in 624 enrolled subjects. The ongoing clinical safety study (ALK-006) evaluated the safety aspects when Vivitrol was administered over a period of 24 weeks (6 doses, interim cutoff date 8/31/2004) in 436 subjects. The subjects participating in ALK21-003 and ALK21-006 could continue on extension studies for upto 5 years' total treatment with Vivitrol suspension.

2.2.1 What is the rationale for the proposed dose of naltrexone long acting injection?

The proposed dosing regimen is based on the pharmacokinetic, pharmacodynamic and efficacy evidence.

Pharmacokinetic basis: Based on initial PK study (# ALK21-001) with various doses of Vivitrol (141, 269, 530 and 784 mg) the sponsor estimated that the 190 mg dose would provide similar exposure compared to 50 mg oral naltrexone administered for 28 days. Based on PK study# ALK21-005, however, it appears that 190 mg and 380 mg doses of Vivitrol suspension may provide 2- and 4-fold higher AUC, respectively, compared to oral dosing of 50 mg per day for 28 days.

Pharmacodynamic basis: Evidence to support the dose, duration of action/dosing interval of Vivitrol suspension was derived from pilot opioid blockade study # ALK21-004; where 75, 150 and 300 mg doses were studied. The presumed mechanism of action of naltrexone in the treatment of alcohol dependence is the blockade of endogenous rather than exogenous opioids. Nevertheless, results suggested that doses of Vivitrol ≥150 mg demonstrated blockade of opioid effects of hydromorphone challenge test over 28 days.

Efficacy analysis: The sponsor evaluated the safety and efficacy of 190 and 380 mg of Vivitrol suspension in Phase III study # ALK21-003. The 380 mg dose of Vivitrol showed significant difference compared to subjects receiving placebo treatment employing the primary efficacy endpoint of "event rate of heavy drinking". The 190 mg dose showed evidence of a trend toward significance with this endpoint. Please refer to the Medical Officer's review for safety and efficacy assessments.

The single and multiple dose pharmacokinetics of Vivitrol suspension are discussed separately in the sections below (QBR question 3).

Study ALK21-004 is a randomized, single dose opiate challenge study of Vivitrol suspension in opioid using adult subjects. Subjects were randomized in a 1:1:1 ratio to receive a single gluteal IM injection of Vivitrol suspension 75, 150, or 300 mg. Subjects were administered hydromorphone challenge, naloxone challenge and oral naltrexone

tolerability assessment before study drug treatment. At Day 0, eligible subjects were administered the first dose of study drug. Experimental hydromorphone challenge sessions (to assess the level of opiate blockade) were conducted at Days 7, 14, 21, 28, 42, and 56, with 1 placebo hydromorphone challenge administered at a randomly selected visit. Blood samples for measurement of naltrexone and 6β-naltrexol were obtained at screening and before hydromorphone/placebo administration on Days 7, 14, 21, 28, 42, and 56.

Hydromorphone Challenge: IM hydromorphone injections were administered at 1-hour intervals at doses of 0 (placebo), 3, 4.5, and 6 mg. At a randomly selected evaluation visit, subjects received four 0 mg (placebo) doses at 1-hour intervals.

A variety of pharmacodynamic assessments were recorded upto 15 minutes before the first hydromorphone dose or placebo for hydromorphone dose and at 15, 30, 45 and 60 minutes after each dose. For the primary measure of pharmacodynamic effect, response to VAS question "Do you feel any drug effect?" and pupil measurements were utilized in the statistical analysis. Please see the attached study synopsis for information on details of the statistical plan other pharmacodynamic measures and their outcomes.

The sponsor indicated that they had difficulty in enrolling desired number of subjects for the complete study and hence, they amended the protocol to delete the placebo treatment arm. Accordingly, statistical comparisons were between different dose treatment groups and results are inconclusive based on the absolute analysis plan proposed. However, from an exploration stand point this study served the purpose of deriving qualitative information on duration of opiate blockade by Vivitrol.

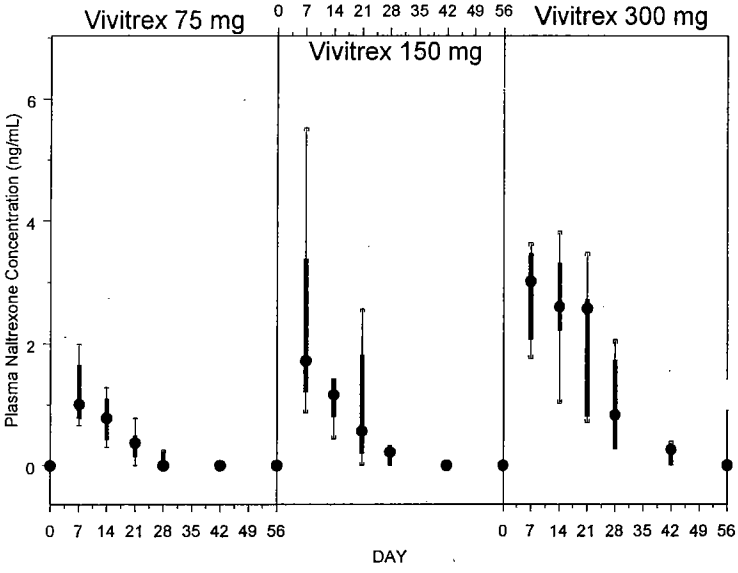
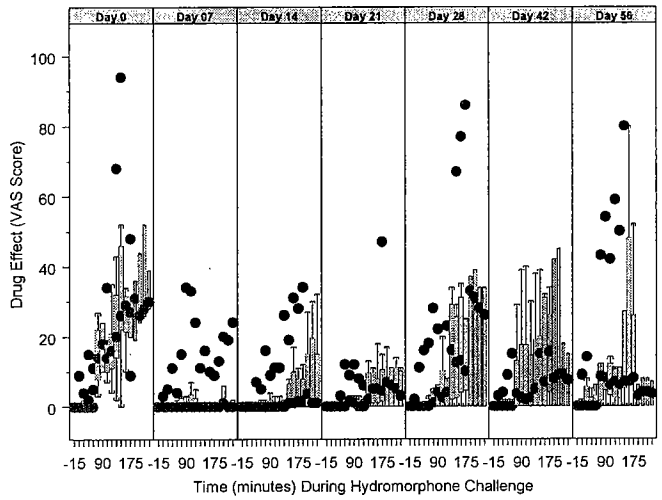


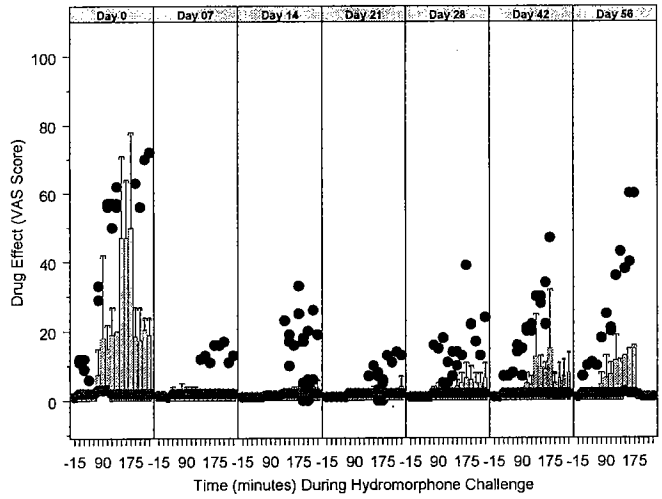
Figure Legend: Box-plot indicating plasma naltrexone concentrations at different days (0-56) in subjects receiving 75, 150 and 300 mg Vivitrol. The whiskers of the box plot include the data, the top of the box indicates 75th percentile, bottom of the box indicates 25th percentile, solid circles indicate median, solid squares indicate outliers.

The above figure is depicts the plasma levels of naltrexone in blood samples collected on Days 7, 12, 21, 28, 42 and 56. PK parameters, particularly C_{max} and complete AUC, may not be derived from this profile as plasma levels from a significant segment following dosing (Day 1-7) was not obtained. Nevertheless, the figure demonstrates that more number of subjects had plasma levels above 1 ng/mL at day following the 300 mg dose than any other dose group. The relevance of 1ng/mL plasma level is explained below.

Drug Effect During Hydromorphone Challenge In Subjects Receiving Vivitrex 75 mg



Drug Effect During Hydromorphone Challenge In Subjects Receiving Vivitrex 150 mg



Drug Effect During Hydromorphone Challenge In Subjects Receiving Vivitrex 300 mg

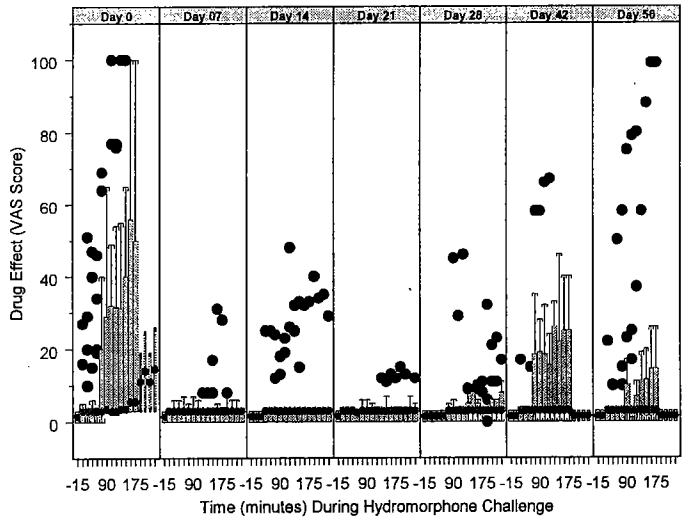


Figure Legend: Box-plot indicating VAS scores to the question "Do you feel any drug effect" administered during ~ 200 minutes of hydromorphone challenge test. Subjects received 75, 150 and 300 mg Vivitrol in parallel groups. The whiskers of the box plot include the data, the top of the box indicates 75th percentile, bottom of the box indicates 25th percentile, solid brown circles indicate median, solid black circles indicate outliers.

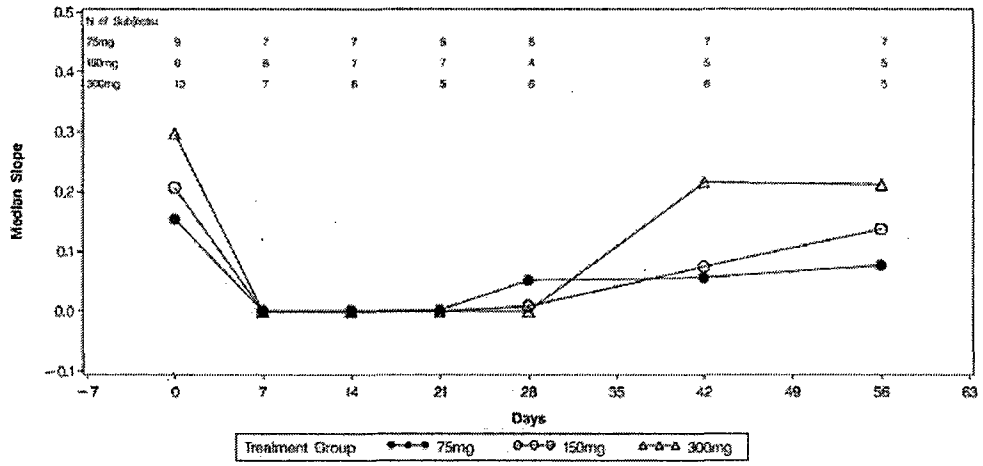
Assessed by the subjective responses to the question, "Do you feel any drug effect?" complete Vivitrol–mediated opiate blockade ranged from up to 42 days for the 75 mg group to up to 56 days for the 300 mg group. However, as shown in the adjacent figure more number of subjects had opioid-blockade beyond 28 days when receiving 150 mg and 300 mg dose of Vivitrol.

Assessed by the objective measure of pupil size, partial blockade of 3 mg of hydromorphone was demonstrated 14 days following the 75 mg dose of Vivitrol.

While this study demonstrates blockade of effects of an exogenously administered opioid, the presumed mechanism of action of naltrexone in the treatment of alcohol dependence is the blockade of endogenous.

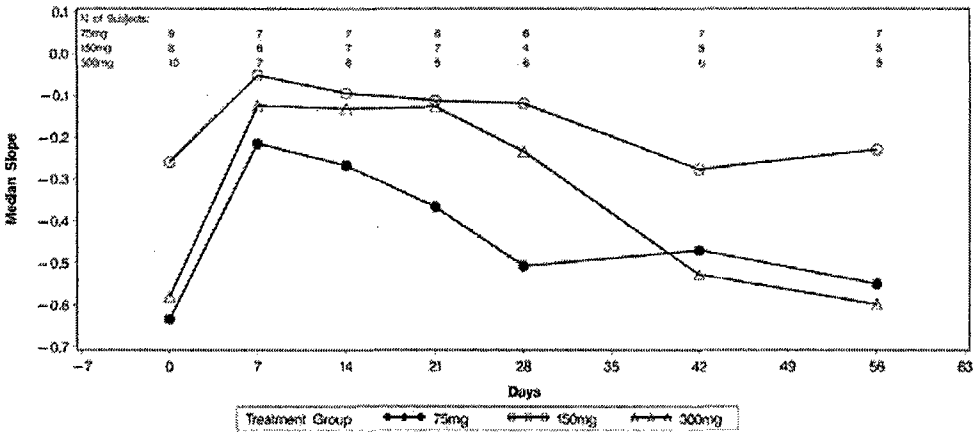
Based on this study's results, it is difficult to predict exactly how this product might affect endogenous opioid action.

The slope for the linear regression line was calculated for pharmacodynamic measures during the hydromorphone challenge test. The regression line extended over dose of 3 mg dose for VAS scores derived from question "Do you feel any drug effect?" and over 6 mg hydromorphone dose for pupil dilatation measurements. The statistical tests revealed that none of the Vivitrol dose groups were significantly different from another. However, as shown in the figures below, the median measures of PD indicate the Vivitrol treatment mediated opioid blockade appears more differentiated between doses with pupilometry compared to subjective question VAS measures.



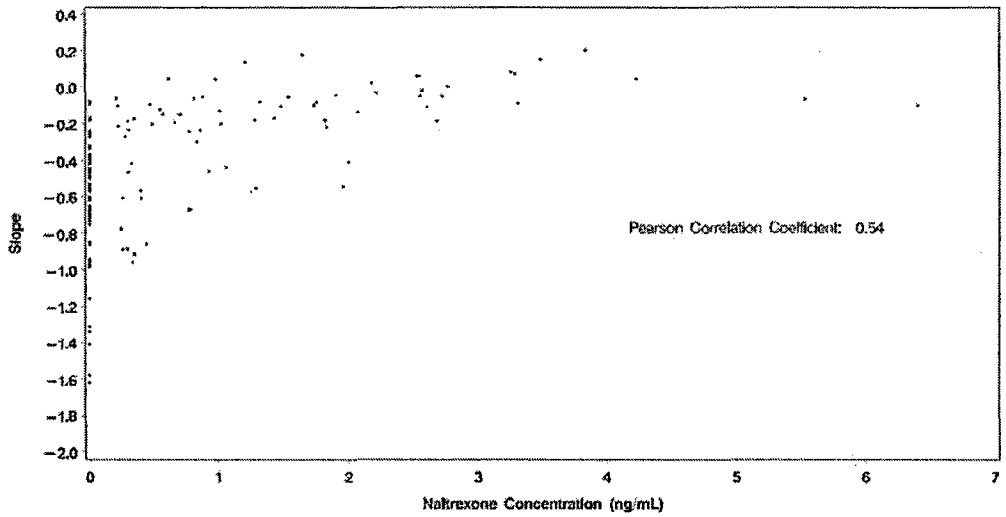
Slope was determined by the linear regression line over the 0mg and 6mg hydromorphone doses

Presence and Duration of Opiate Blockade: Median Slope for the Question "Do you feel any drug effect?"



Slope was determined by the linear regression line over the 0mg and 6mg hydromorphone doses

Degree of Surmountability: Median Slope for Pupil Size



Slope of Pupil Size versus Naltrexone Concentration

Association between naltrexone concentration and opiate blockade, during hydromorphone challenge test, is demonstrated in figure above by the slope of pupil size versus naltrexone concentration. It appears that naltrexone concentration of 1 ng/mL blocks exogenously administered opiate (hydromorphone) mediated pupil size changes.

2.2.2 Does naltrexone prolong QTc interval?

Adequate information was provided to show that naltrexone during its 20 years of marketing was not known to prolong QT interval or cause related cardiovascular adverse events.

Following information was provided to justify that naltrexone may not cause QT prolongation related cardiovascular adverse events.

QT measurements from ECG recordings were collected in Phase I clinical study # ALK21-005 following single and multiple dose administration of Vivitrol. Literature search was undertaken to identify any QT prolongation related information on naltrexone and other opioid antagonists and agonists (PubMed, 1969 – 2005). Additionally, a post-marketing safety database search for QT prolongation related adverse events for oral naltrexone was conducted (ADR and AERS). No preclinical studies were conducted or reported in literature evaluating effect of naltrexone or 6β-naltrexol on hERG channel, *in vitro*.

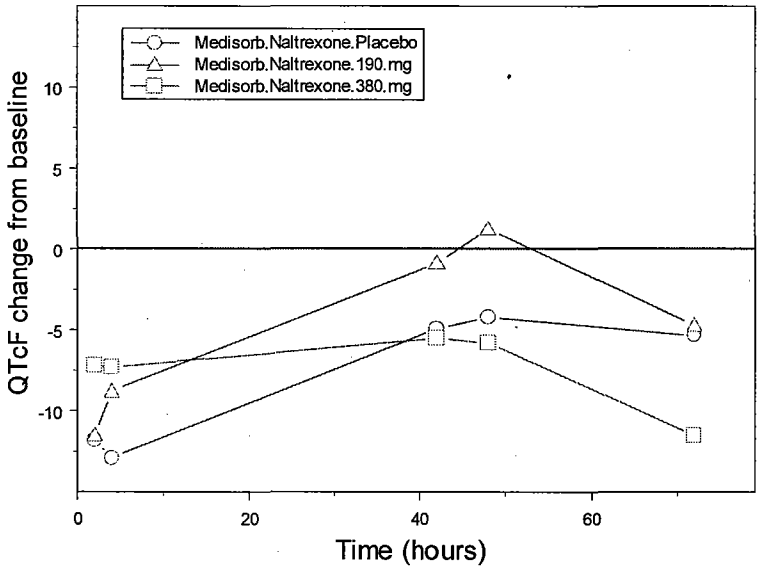
ECG recordings in study ALK21-005 were collected as per the scheme below. Study # ALK21-005 is PK, safety tolerability study and it is not a prospectively designed QT prolongation study. ECG recordings were not time matched; placebo treatment (was maintained for the assessment of tolerability of the drug.

COHORT	ROUTE OF ADMINISTRATION	DOSE NUMBER	TIME OF ECG RELATIVE TO DOSE
A*	Oral	1	Predose (3 recordings) and 0.5, 1, 1.5 and 2 hours postdose
B†	Oral	5	
A	IM	1	Predose (3 recordings) and 2, 4, 42, 48 and 72 hours postdose
B	IM	1	
B	IM	4	

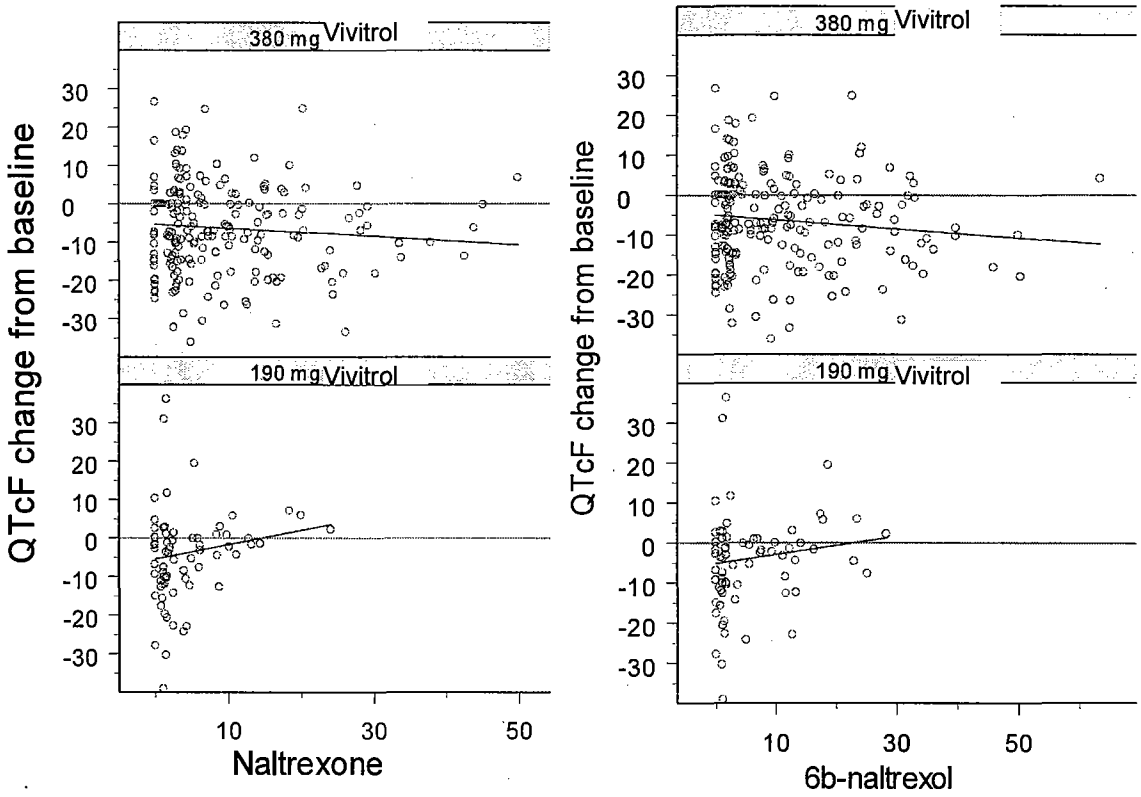
* Subjects in Cohort A (n=28) received a single dose of oral naltrexone and a single dose of Vivitrol suspension or placebo

† Subjects in Cohort B received 5 daily doses of oral naltrexone and 4 doses of Vivitrol suspension 380 mg or placebo every 28 days.

QT, QTcB (Bazette correction) and QTcF (Federicia Correction) intervals were evaluated using absolute and change from baseline values. Baseline was determined as the mean of 3 predose recordings. QT, QTcB and QTcF values >450 msec or change from baseline values >30 msec were flagged. Change from baseline data was summarized by treatment at each collection time-point. No subject had a QTcB or QTcF ≥480 msec during the study. One subject exhibited 47 msec increase in QTcF compared to predose observation following 190 mg Vivitrol treatment. The plasma concentration of naltrexone and 6β-naltrexol were not remarkable in this subject (# 026). Mean QTcF change over 72 hours of ECG collections in Vivitrol treated subjects is plotted below. All treatments including placebo were marked by high variability in QTcF values.



There was no correlation between naltrexone or 6β-naltrexol concentration and QTcF change.



There are no reports of QT prolongation or torsades de pointes (TdP) associated with the administration of oral naltrexone or structurally related compounds. Discussion on QT prolongation potential by Vivitrol is appended to this review.

2.2.3 What are the PK characteristics of naltrexone depot formulation?

Pharmacokinetics of naltrexone following Vivitrol administration appears release-dependent. After IM administration of Vivitrol peak plasma levels of naltrexone are observed in about 5 hours – 2 days. The increase in AUC of naltrexone was approximately dose-proportional in the dose range of 141 – 784 mg Vivitrol. Naltrexone elimination appears release-rate dependent and the elimination half life for the product is approximately 8 days. Compared to orally administered naltrexone, plasma 6β-naltrexol levels are very low with Vivitrol administration. Repeated administration of Vivitrol, once a month for four months, did not result in significant accumulation of naltrexone.

Single dose Pharmacokinetics

The pharmacokinetics of Vivitrol suspension following a single IM or SC injection were evaluated in healthy subjects (study ALK21-001). Subcutaneous administration provided a naltrexone concentration-time profile similar in shape to that observed for IM

administration, however; the bioavailability of SC administration relative to IM administration was 78 to 92% across the dose range 141 to 530 mg. Intramuscular administration was associated with improved tolerability and fewer injection-related adverse events compared with SC administration. Based on these results of, IM injection route of administration was chosen.

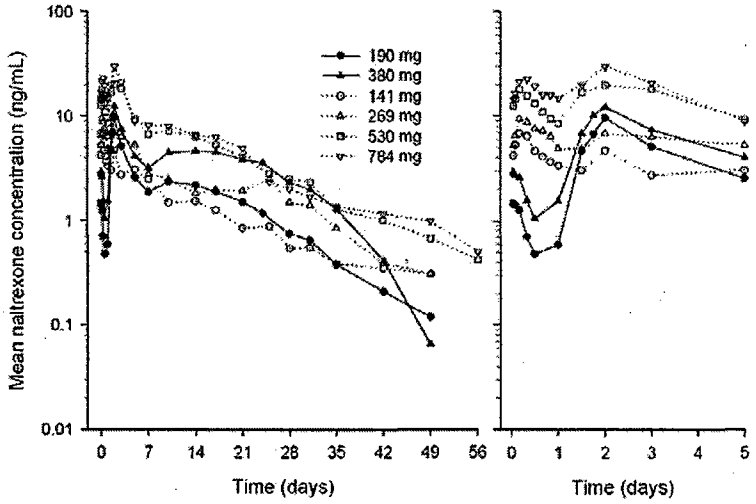


Figure Legend: Mean naltrexone plasma concentration-time profile following a single dose of Vivitrol suspension in ALK21-001 (dashed lines) and ALK21-005 (solid lines). *Left panel*: Days 0-56; *right panel*: Days 0-5

As Vivitrol suspension is intended for IM injection, results presented in this section will focus on this route of administration. In study ALK21-005, 190 mg and 380 mg doses of Vivitrol were studied in healthy volunteers. The naltrexone concentration-time profile following a single IM dose of Vivitrol suspension is depicted in the figure below.

The profile is characterized by a transient initial peak which occurs approximately 2 hours after injection, followed by a second peak observed approximately 2 days later. Beginning approximately 14 days post-dose, naltrexone concentrations slowly decline in a log-linear fashion. The dose-proportionality was investigated with information generated from healthy volunteers across three studies (ALK21-001, ALK21-005 and ALK21-009) and is depicted in the figure below.

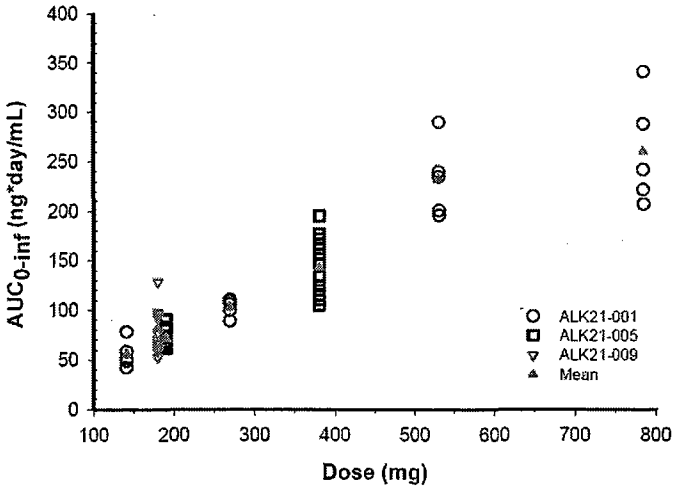


Figure Legend: Dose-proportionality (Dose Vs AUC) information collected from different PK studies

An approximate dose-proportional increase in $AUC_{0-\infty}$ was observed in doses up to 530 mg. Dose proportionality between 190 mg and 380 mg was confirmed in ALK21-005 ($AUC_{0-\infty}$ LS mean ratio 380:190 [90% CI]: 1.98 [1.76, 2.22]).

With respect to inter-subject variability, C_{max} on day 1and AUC_{0-1} exhibited % CV of ~ 50% with lower variability in AUC0-7 and AUC0-28 (CV% ~ 30%) observations in both the dose groups. Some individuals had a T_{max} beyond 14 days,

Study # ALK21-005

COHORT:A 190 mg Vivitrol							
	C_{max} (ng/mL)	AUC_{0-1} (ng.day/mL)	AUC_{0-7} (ng.day/mL)	AUC_{0-28} (ng.day/mL)	$AUC_{0-\infty}$ (ng.day/mL)	T_{max} (days)	$T_{1/2}$ (days)
Min:	[illegible]	0.54	8.1	43.3	62.1	0.02	0.08
Max:	[illegible]	2.25	43.9	87.9	90.7	24	11.7
Median:	9.4	0.87	26.9	61.4	67.7	0.92	3.8
Mean:	11.2	1.01	25.2	61.5	71.8	2.59	3.9
Stdev	6.6	0.55	12.6	14.8	9.1	5.70	4.2
COHORT:A 380 mg Vivitrol							
	C_{max} (ng/mL)	AUC_{0-1} (ng.day/mL)	AUC_{0-7} (ng.day/mL)	AUC_{0-28} (ng.day/mL)	$AUC_{0-\infty}$ (ng.day/mL)	T_{max} (days)	$T_{1/2}$ (days)
Min:	[illegible]	0.56	20.87	95.00	105.2	0.02	0.08
Max:	[illegible]	2.91	65.40	153.5	195.2	2	6.8
Median:	10.3	1.34	33.35	120.3	140.9	0.79	1.4
Mean:	11.6	1.42	37.40	120.6	143.5	0.96	2.5
Stdev	6.4	0.58	13.49	19.62	29.3	0.94	2.6
COHORT:B 380 mg Vivitrol (Data from Dose 1 and Dose 4)							
	C_{max} (ng/mL)	AUC_{0-1} (ng.day/mL)	AUC_{0-7} (ng.day/mL)	AUC_{0-28} (ng.day/mL)	$AUC_{0-\infty}$ (ng.day/mL)	T_{max} (days)	$T_{1/2}$ (days)
Min:	[illegible]	0.68	25.2	106.7	120.6	0.02	0.09
Max:	[illegible]	5.4	106.8	202.4	217.9	24	20.3
Median:	18.6	1.96	67.3	143.4	160.9	2	3.8
Mean:	22.3	2.2	68.0	147.8	168.1	2.1	4.46
Stdev	12.8	1.1	22.2	26.3	30.5	4.1	5.0

Multiple Dose Pharmacokinetics

The product is indicated for a repeat administration after approximately every four weeks (28 ± 3 days). Accordingly multiple dose pharmacokinetics were evaluated following four repeated doses of 190 and 380 mg strengths every four weeks. The AUC_{0-t} and C_{max} was dose-proportional between 190 mg and 380 mg dose.

Assessment of Dose Proportionality of Naltrexone & 6β-Naltrexol Pharmacokinetic Parameters Following Single Dose of Vivitrol 190 mg or 380 mg (Cohort A)

ANALYTE	PARAMETER	GEOMETRIC LS MEANS 190 MG	GEOMETRIC LS MEANS 380 MG	RATIO[a]	90% CI
Naltrexone	$AUC_{0-\infty}$ (ng*days/mL)	71.3	141	1.975	1.756, 2.222
	C_{max}(ng/mL)	8.34	12.1	1.455	0.991, 2.135
6ß-naltrexol	$AUC_{0-\infty}$ (ng*days/mL)	174	320	1.843	1.590, 2.137
	C_{max} (ng/mL)	11.8	18.4	1.565	1.075, 2.279

[a] Ratio of geometric LS means between the two doses.

Naltrexone and 6β-naltrexol increase by 13% and 11% following dose 4 compared to dose 1 of Vivitrol; however, 90% CI's of $AUC_{0-\tau}$ are with in 0.8-1.25 bounds and hence the observation is not statistically significant.

Assessment of Accumulation of Naltrexone and 6β-Naltrexol Following Multiple Doses of Vivitrol 380 mg (Cohort B)

ANALYTE	PARAMETER	GEOMETRIC LS MEANS		RATIO[a]	90% CI
		DOSE 1	DOSE 4		
Naltrexone	$AUC_{0-\tau}$ (ng*days/mL)	136	154	1.134	1.048, 1.226
6ß-naltrexol	$AUC_{0-\tau}$ (ng*days/mL)	255	284	1.114	1.043, 1.191

[a] Ratio of geometric LS means, calculated as $AUC_{0-\tau,\ Dose\ 4}/AUC_{0-\tau,\ Dose\ 1}$ (Cohort B).

Trough concentrations of both naltrexone and metabolite (day 28) following repeat dosing in alcohol and opiate dependent subjects (collected in ALK21-005 and ALK21-006) are indicated in the table below.

Pre-Dose Naltrexone and 6β-Naltrexol Concentrations Following Repeat Administration of Vivitrol Suspension at 28-day Intervals [Mean (SD)]

STUDY / DOSE	ANALYTE	PRE-DOSE 2	PRE-DOSE 3	PRE-DOSE 4	PRE-DOSE 5 *	PRE-DOSE 6	PRE-DOSE 7
ALK21-005 380 mg	naltrexone	1.93 (1.4) [n=12]	1.08 (0.84) [n=11]	1.08 (0.95) [n=10]	1.44 (1.2) [n=10]	-	-
	6β-naltrexol	4.32 (3.8) [n=12]	2.47 (1.6) [n=11]	2.46 (1.9) [n=10]	2.98 (2.3) [n=10]	-	-
ALK21-006 380 mg †	naltrexone	1.68 (2.3) [n=379]	1.66 (4.0) [n=352]	1.91 (6.8) [n=319]	1.48 (2.5) [n=292]	1.79 (3.6) [n=271]	2.31 (12) [n=238]
	6β-naltrexol	7.3 (19) *2.7*† [n=380]	6.5 (17) *2.4*† [n=352]	6.4 (16) *2.4*† [n=319]	6.1 (12) *2.4*† [n=292]	6.0 (13) *2.6*† [n=271]	6.1 (17) *2.4*† [n=238]

* A maximum of 4 doses were administered in ALK21-005 and ALK21-002. Values presented reflect concentrations 28-days post dose #4.
†median values for 6β-naltrexol are reported in italics.

Relative bioavailability:

The sponsor included a cohort of healthy subjects (Study ALK21-005) receiving oral naltrexone 50 mg QD for one day (Cohort A) or 5 days (Cohort B) to assess the relative bioavailability of naltrexone following single and multiple doses of 190 mg and 380 mg of Vivitrol.

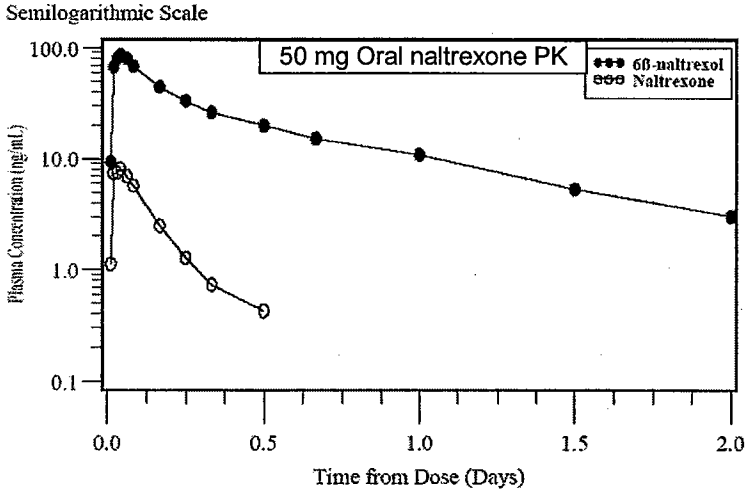
Relative dose of Revia and Vivitrol: The highest proposed of Vivitrol dose (380 mg) corresponds to approximately $1/3^{rd}$ of total dose of 1400 mg per month of oral naltrexone (Revia, 50 mg QD × 28 days = 1400 mg).

Relative exposure of naltrexone and 6β-naltrexol following Revia and Vivitrol administration: The AUC of naltrexone and 6β-naltrexol following Revia and Vivitrol administration are indicated in the table below.

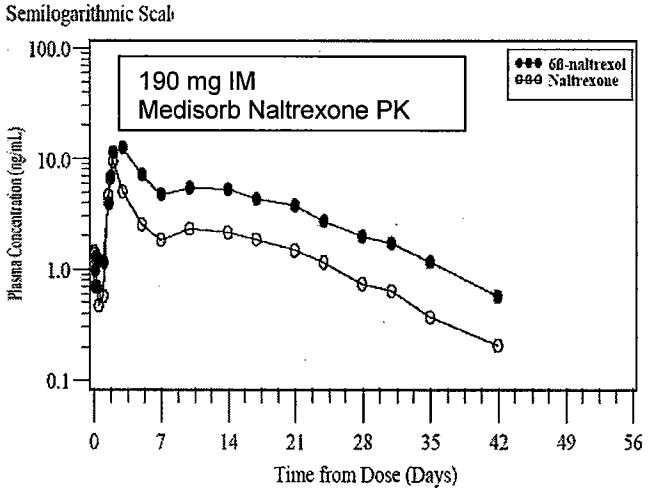
Parameter	Revia 50 MG		Medisorb Naltrexone 190 mg	Medisorb Naltrexone 380 mg
Naltrexone $AUC_{0-\tau}$ (ng*days/mL)	1 day 1.278 (0.589)	28 days ~ 35.78*	61.49 (14.78)	120.6 (19.6)
6β-naltrexone $AUC_{0-\tau}$ (ng*days/mL)	27.05 (5.92)	~ 757.4*	138.1 (40.7)	266.5 (48.0)

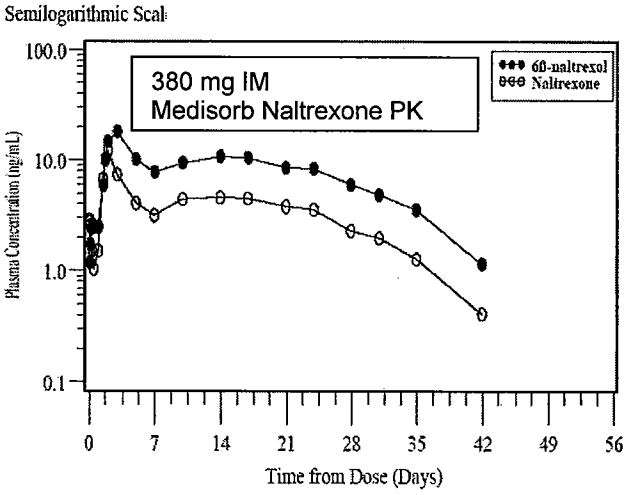
* Approximate drug or metabolite AUC over 28 days is calculated as exposure over day 1 × 28

As indicated above, the exposure to naltrexone is approximately 2- and 4-fold for 190 mg and 380 mg doses of Vivitrol, respectively. On the other hand, exposure to 6β-naltrexol is approximately 18% and 36% for 190 mg and 380 mg doses of Vivitrol, respectively compared to oral naltrexone.



Relative exposure of 6β-naltrexol to naltrexone following Revia and Vivitrol: As seen above there is difference in the extent of metabolism of naltrexone to 6β-naltrexone following oral and IM microsphere administration of naltrexone. The figures below depict the plasma levels of 6β-naltrexol to naltrexone following 50 mg oral naltrexone, 190 mg and 380 mg Vivitrol.





As shown in the table below, AUC ratio of 6β-naltrexol to naltrexone was approximately 30-fold higher following oral administration; while this ratio was ~ 2-fold in both 190 mg and 380 mg Vivitrol dose groups. In addition, the PK profile of 6β-naltrexol appears to be in parallel to naltrexone indicating that 6β-naltrexol disposition is formation rate-dependent.

Assessment of Metabolite: Parent Ratio and 90% CI of AUC Following Single (Cohort A) and Multiple (Cohort B) Doses of Oral Naltrexone and Vivitrol

COHORT	DOSE GROUP	AUC GEOMETRIC LS MEANS (ng*days/mL)		RATIO[a]	90% CI
		NALTREXONE	6β-NALTREXOL		
A	Oral Naltrexone 50 mg	1.16	35.0	30.253	25.969, 35.244
	Medisorb Naltrexone 190 mg	71.3	173	2.432	2.253, 2.626
	Medisorb Naltrexone 380 mg	141	320	2.274	2.117, 2.442
B	Oral Naltrexone 50 mg	1.24	34.7	28.074	20.752, 37.979
	Medisorb Naltrexone 380 mg	158	287	1.813	1.598, 2.056

Cohort A: Single dose; Cohort B: Multiple dose; [a] $AUC_{0-\infty}$ and $AUC_{0-\tau}$ were used to calculate the ratio and 90% CI following single and multiple doses, respectively.

2.3 Intrinsic Factors

Population pharmacokinetic analysis (Study report ALK21-011) was conducted looking at demographic variables (such as age, sex, body weight, race, and polysubstance dependency) and laboratory markers of renal and hepatic function to determine if they contributed to differences in PK parameter estimates among individuals. The data from studies ALK21-004, -005, -006, -009 were utilized in the population PK analysis. The demographics of subjects in these studies are tabulated below:

Study	SEX (M/F)	RACE (Caucasian/ Black/ Oriental/ Hispanic/ Other)	STAT (Healthy/ Alcohol dependent/ Polysubstance abuse)	HEP (Healthy/ Mild hepatic impairment/ Moderate hepatic impairment)
ALK21-004	22/3	9/ 16/0/ 0/ 0	0/ 0/ 25	25/ 0/ 0
ALK21-005	18/ 18	2/ 3/ 0/ 31/ 0	36/ 0/ 0	36/ 0/ 0
ALK21-006	230/ 137	308/ 30/ 2/ 21/ 6	0/ 268/ 99	367/ 0/ 0
ALK21-009	15/ 10	10/ 0/ 0/ 15/ 0	25/ 0/ 0	13/ 6/ 6
Overall	285/168	329/ 49/ 2/ 67/ 6	61/ 268/ 124	441/ 6/ 6

Study		AGE yr	WT, kg	HT, cm	CRT µM	CRCL, mL/min	ALT IU/L	AST IU/L	ALP IU/L	BILI, mg/dL	GGT, IU/L	PROT g/dL
ALK21-004	Min	23	45	152	0.6	75.1	4	13	50	0.2	9	6.7
	Median	37	74	175	1.0	103.1	17	19	73	0.5	25	7.8
	Max	50	100	188	1.3	131.9	100	70	100	1.6	88	8.8
ALK21-005	Min	20	54	150	0.6	87.4	9	13	51	0.2	7	5.8
	Median	40	72	168	0.8	117.0	17	19	76	0.4	17.5	7.6
	Max	49	90	191	1.0	150.0	41	32	109	1.2	56	8.4

ALK21 -006	Min	18	46	152	0.3	29.4	6	10	30	0.2	7	6.4
	Median	41	78	174	0.8	124.6	25	24	75	0.4	34	7.5
	Max	70	135	198	1.8	150.0	131	104	196	1.6	2890	9.1
ALK21 -009	Min	43	55	155	0.5	63.5	11	13	25	0.2	10	NA*
	Median	53	83	173	0.8	115.3	19	20	72	0.4	32	NA*
	Max	76	110	183	1.3	150.0	145	249	303	1.6	613	NA*
Overall	Min	18	45	150	0.3	29.4	4	10	25	0.2	7	5.8
	Median	42	78	173	0.8	121.3	3	23	74	0.4	31	7.5
	Max	76	135	198	1.8	150.0	145	249	303	1.6	2890	9.1

No pediatric (<18 years of age) subjects have been studied. Overall, 2% of subjects were 65 years or older at the start of treatment. The study population was 69% white and 59% male. Except for study ALK21-009 (conducted in subjects with mild to moderate hepatic dysfunction), subjects with clinically significant liver impairment were routinely excluded from all studies. Most subjects had either normal renal function or mild renal impairment for any given age group. Studies typically excluded subjects with significant laboratory or clinical abnormalities.

2.3.1 What intrinsic factors influence exposure?

a) Pediatrics

Pharmacokinetics of Vivitrol have not been evaluated in pediatric population.

b) Renal impairment

Based on naltrexone PK following Vivitrol microsphere administration, dose adjustment may not be necessary for subjects with renal impairment.

Effect of renal impairment on the pharmacokinetics of Vivitrol was not evaluated in separate study. Renal function (as measured by creatinine clearance) was evaluated as a covariate in the population pharmacokinetic analysis. However, the majority of subjects (426 out of 453) had normal renal function; twenty five subjects with mild renal impairment (creatinine clearance of 50-80 mL/min); one subject with moderate renal impairment and one subject with severe renal impairment.

Following oral administration, naltrexone is extensively metabolized to 6β-naltrexol which is eliminated primarily in urine. In the population PK analysis, naltrexone clearance did not change with changes in renal function; while, a decrease in creatinine clearance correlated with a decrease in apparent 6β-naltrexol clearance. The final model predicts clearance of 6β-naltrexol in subject with alcohol/polysubstance abuse would decrease from 88 L/hr to 62 L/hr (30% reduction) as creatinine clearance decreased from 150 to 29 mL/min. Since the exposure to 6β-naltrexol is still considerably lower than that observed with oral naltrexone, dosing adjustment may not be necessary.

c) Hepatic impairment

Exposure of naltrexone was not significantly different in subjects with mild and moderate hepatic impairment compared to healthy subjects, following Vivitrol administration. With regard to severe hepatic deficiency, administration of a deep IM injection such as Vivitrol suspension in subjects with could result in an increased risk of bleeding or significant hematoma at the site of injection if the subjects have coagulation disorders. Hence, subjects with severe hepatic impairment were excluded from all clinical pharmacology, clinical safety and efficacy studies. No dosage adjustment is required in patients with mild and moderate hepatic impairment. Use of Vivitrol with caution in severe hepatic impairment is recommended.

In Study ALK21-009, the effect of mild and moderate hepatic impairment on the pharmacokinetics of naltrexone following 190 mg Vivitrol administration was evaluated. This Phase I study was an open-label, parallel-group design to evaluate the PK of Vivitrol in subjects with mild or moderate hepatic impairment compared with healthy subjects. To minimize the impact of factors other than hepatic impairment, healthy subjects were matched to subjects with hepatic impairment with regard to gender, age, and weight.

Based on healthy subject matching, $AUC_{0-\infty}$ is 7% higher in patients with mild hepatic impairment and C_{max} is increased by 85%. $AUC_{0-\infty}$ is not altered in subjects with moderate hepatic impairment compared to matched healthy subjects; however, C_{max} decreased 45%. While the changes in C_{max} in mild and moderate hepatic impairment are confounding, the impact of this observation appears minimal as overall exposure (AUC) is not significantly different from healthy subjects.

Comparison of Naltrexone Pharmacokinetic Parameters between Subjects with Mild and Moderate Hepatic Impairment and Matched Healthy Subjects

PARAMETER	GROUP	N	GEOMETRIC MEAN	ratio % (90% ci)[b]
C_{max} (ng/mL)	Mild Impairment	6	15.2	185.80 (109.23, 316.39)
	Matched Healthy Subjects	6	8.19	
	Moderate Impairment	6	7.50	55.34 (32.52, 94.19)
	Matched Healthy Subjects	6	13.5	
$AUC_{0-\infty}$ (ng*days/mL)	Mild Impairment	6	84.2	107.57 (81.07, 142.74)
	Matched Healthy Subjects	6	78.3	
	Moderate Impairment	6	77.2	97.00 (72.10, 130.50)
	Matched Healthy Subjects	5	79.6	

As evidenced by the prolongation of the elimination half life compared to oral naltrexone, naltrexone PK following IM administration with Vivitrol appear to depend on the release from microspheres. Hence, it can be presumed that naltrexone clearance to 6β-naltrexol is naltrexone plasma appearance dependent or naltrexone release rate-dependent. Following oral administration of naltrexone, plasma 6β-naltrexol levels are generally 15- to 30-fold higher compared to naltrexone. However, following IM administration of Vivitrol the plasma 6β-nalrexone levels are approximately 2- to 4-fold compared to naltrexone. In this study, the 6β-naltrexone:naltrexone ratio in all treatment groups is

M. Bertolotti et al.

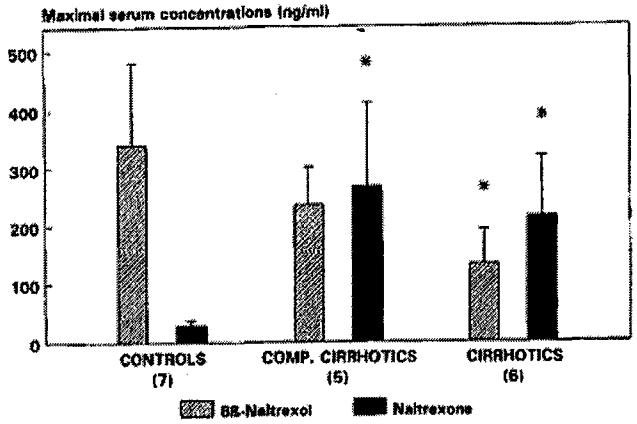


*Fig. 2. Maximal serum concentration (Cmax) of naltrexone and 6β-naltrexol in control subjects, patients with compensated and decompensated cirrhosis after oral administration of 100 mg of naltrexone. Data indicate mean value and SD. * p<0.01 vs controls, Student's t-test for unpaired data.*

approximately 2, suggesting lack of effect of hepatic impairment on metabolism of naltrexone.

Previously, Bertolotti et. al. (Journal of Hepatology 27: 505-511) demonstrated that although delayed, extent of naltrexone metabolism to 6β-naltrexol in cirrhotic subjects is comparable to healthy subjects (see figure below).

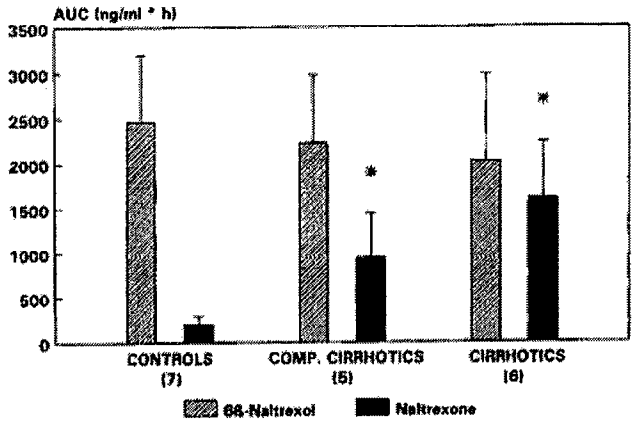


*Fig. 3. Area under the curve (AUC) of naltrexone and 6β-naltrexol in control subjects, and patients with compensated cirrhosis and decompensated cirrhosis after oral administration of 100 mg of naltrexone. Data indicate mean value and SD. * $p<0.01$ vs controls, Student's t-test for unpaired data.*

This indicates that extra-hepatic sites may also play a major role in the clearance of naltrexone to 6β-naltrexol. Aldo-Keto-reductases (AKRs), the enzymes responsible for conversion of naltrexone to 6β-naltrexol, are expressed primarily in liver but also in brain, heart, kidney, lung, prostate, skeletal muscle, small intestine, spleen and testis (O'Connor et. al., Biochem. J. 343:487-504, 1999).

d) Gender

Naltrexone and 6β-naltrexol C_{max} were lower in females than males; whereas, naltrexone and 6β-naltrexol AUC_{0-28} were similar between females and males following a single dose of 380 mg Vivitrol. Dosage adjustment is not necessary based on gender of the subject.

In study ALK21-005, gender differences in PK parameters (C_{max} and AUC_{0-28}) of naltrexone and 6β-naltrexol following single 380 mg dose of Vivitrol administration were analyzed using an ANOVA model. The ratio of PK parameters was obtained by exponentiating the difference in the LS means of the natural log-transformed parameters. As shown in the table below C_{max} of both naltrexone and 6β-naltrexol in women are ~ 30% lower than that seen in men. However, AUC_{0-28} was similar in both women and men.

ANALYTE	PARAMETER	RATIO[a]	90% CI[b]
Naltrexone	C_{max}(ng/mL)	0.677	0.469, 0.979
	AUC_{0-28} (ng×days/mL)	1.039	0.823, 1.313
6β-naltrexol	C_{max}(ng/mL)	0.742	0.536, 1.027
	AUC_{0-28} (ng×days/mL)	1.042	0.822, 1.321

e) Age

Effect of age on the pharmacokinetics of Vivitrol was not evaluated.

The majority of subjects included in the population pharmacokinetic analysis were under 65 years of age (445 out of 453). Utilizing data from these subjects, age was not identified as a significant covariate which impacts Vivitrol pharmacokinetics.

f) Race

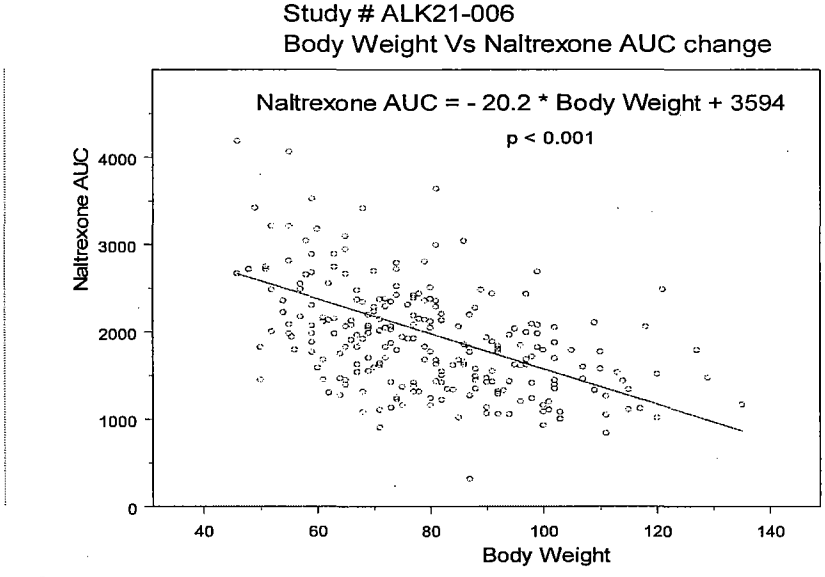
Effect of race on the pharmacokinetics of Vivitrol was not evaluated.

Majority of the subjects included in the population pharmacokinetic analysis were Caucasian (329 out of 453) followed by 67 Hispanics and 49 Blacks. With the information available the population PK analysis suggests that race was not identified as a significant covariate which impacts Vivitrol pharmacokinetics.

g) Body Weight

Increased naltrexone clearance is noted with increase in body weight. Dose adjustment is not suggested as safety and efficacy of Vivitrol doses above 380 mg have not been studied.

Study ALK21-006 had 245 subjects in the weight range of 46 to 135 kg. The AUC_τ (AUC over first four weeks of drug administration) calculated using the sparse sampling from each of these subjects decreased with the increase in body weight of subjects.



A 50% decrease in AUC is noted with increased body weight in the range studied (46 kg to 135 kg). Additionally, population PK analysis confirmed that a 1.8-fold increase in clearance of naltrexone is noted in the 46 to 135 kg weight range; this increase in clearance coincided with a 2-fold increase in volume of distribution.

Clinical efficacy study # ALK21-003 comprised of male and female subjects that had an average body weight of 88 ± 18 Kg, 71 ± 16 Kg in all treatment groups. The study may not be powered to detect difference in efficacy with respect to body weight of subjects.

2.4 Extrinsic Factors

Drug-Drug Interactions

Naltrexone is an opioid antagonist and hence patients expecting to use opioid pain management drugs should not receive Vivitrol. Since the metabolism of naltrexone is not mediated by CYP enzymes, drug-drug interactions related to coadministration of CYP inhibitors is not expected.

The sponsors' approach of using fluorogenic substrates in a high throughput CYP inhibition assay is not acceptable. The study has to be repeated using conventional substrates of CYP enzymes.

CYP3A4 and CYP1A2 induction potential of naltrexone should be evaluated in vitro in human hepatocyte model.

CYP inhibition or induction related drug interactions are not reported in the past 20 years of oral naltrexone use. However, there is difference in plasma PK profile of naltrexone following Revia and Vivitrol administration. Naltrexone release with Vivitrol 380 mg is continuous over a period of 28 days and the overall exposure (AUC) is 4-fold higher compared to that observed following oral dosing.

In a Type C industry meeting on July 11, 2002, the sponsor was advised that initially *in vitro* studies should be conducted to evaluate the potential for drug interactions. If there is an indication of drug-drug interactions in the in vitro assay, additional clinical studies may be required.

CYP inhibition:

CYP inhibition studies were conducted employing fluorogenic substrates and cDNA expressed CYP enzymes *in vitro*. While the use of fluorogenic substrates is not acceptable, the following are the conclusions from the study. Assuming the highest plasma concentration (I) of 50 ng/mL or 146 nM, observed in ALK21-005, the I/IC_{50} ratio for CYP2D6 inhibition is ~ 0.04, indicating that there is remote possibility for drug interaction. However, since the use of fluorogenic substrates is not acceptable the sponsor should repeat the studies using conventional CYP substrates *in vitro*.

Positive controls included furafylline (CYP1A2), quercetin (CYP2C8), sulfaphenazole (CYP2C9), tranylcypromine (CYP2A6, CYP2B6, CYP2C19), quinidine (CYP2D6), 4-methylpyrazole (CYP2E1) and ketoconazole (CYP3A4).
Substrate include 7-ethoxycourmarin (CEC), 7-ethoxy-4-trifluoromethylcoumarin (EFC), 7-methoxy-4-trifluoromethylcoumarin (MFC), 3-[2-(N, N-diethyl-N-methylamino)ethyl]-7-methoxy-4-methyl-coumarin (AMMC), dibenzylfluorescein (DBF), coumarin, and 7-benzyloxy-4-trifluoromethylcoumarin (BFC). These substrates release a fluorescent moiety following enzymatic degradation.

IC_{50} values for CYP inhibition by naltrexone, 6β-naltrexol and positive controls.

Enzyme/Substrate	Naltrexone	6b-Naltrexol	* Positive control
CYP1A2/CEC	> 100, > 100	> 100, > 100	1.1, 1.3
CYP2A6/Coumarin	> 50, > 50	> 50, > 50	0.28, 0.35
CYP2B6/EFC	> 100, > 100	> 100, > 100	26, 38
CYP2C8/DBF	> 100, > 100	> 100, > 100	6.0, 7.8
CYP2C9/MFC	> 100, > 100	> 100, > 100	0.10, 0.12
CYP2C9/DBF	> 100, > 100	> 100, > 100	0.12, 0.12
CYP2C19/CEC	40, 53	> 100, > 100	3.5, 3.3
CYP2D6/AMMC	3.2, 3.0	30, 35	0.005, 0.005
CYP2E1/MFC	> 100, > 100	> 100, > 100	20, 34
CYP3A4/BFC	> 100, > 100	> 100, > 100	0.014, 0.015
CYP3A4/DBF	> 100, > 100	>100, > 100	0.002, 0.002

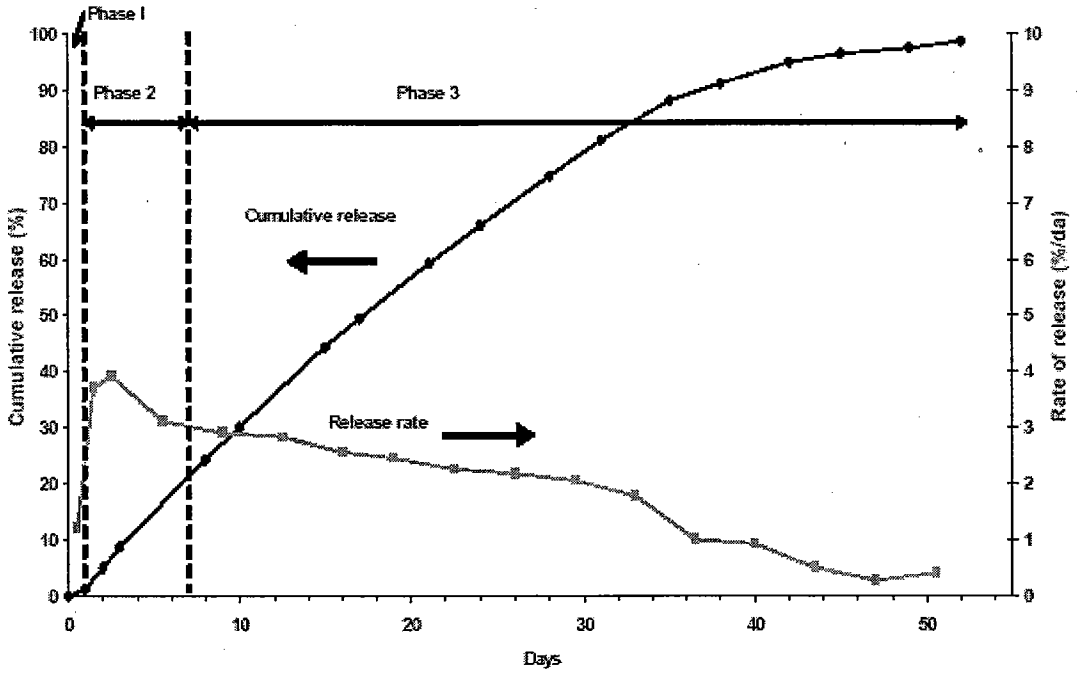
CYP induction: Experiments were not conducted to evaluate the CYP induction potential of naltrexone in vitro.

2.5 General Biopharmaceutics

Vivitrol Drug Release Characteristics

The Vivitrol microsphere formulation is intended to release naltrexone in a controlled fashion with release kinetics appropriate for a one month dosing interval. To accomplish this, the formulation is designed to undergo drug release accompanied by degradation and resorption of the polymer over a 4 to 6 week period via a three phase mechanism.

Phase 1 Initial Release	The Initial Release phase takes place during the first day following exposure of the Microspheres to an aqueous environment. A small quantity of drug at or near the surface is released. [redacted] are selected to minimize the amount of naltrexone released during this phase.
Phase 2 Hydration	The Hydration phase occurs during the first week. Physical erosion of the microspheres begins and some subsurface drug is released. It is desirable to maintain a release rate during this phase that is similar to the rate of release during the subsequent Sustained Release phase in order to provide a constant exposure throughout the dosing interval.
Phase 3 Sustained Release	The Sustained Release phase takes place from Week 2 until drug release is complete and is governed by polymer erosion. The Sustained Release phase constitutes the majority of the release profile both in terms of overall duration and quantity of drug released. The objective of this phase is to release the remaining encapsulated drug at a steady rate.



igure Legend: *In Vitro* Release Rate and Cumulative Release Profile for Vivitrol Microspheres

2.4.1 Are the clinical trial and to-be-marketed formulations adequately linked?

As per Agency's recommendation, the sponsor demonstrated that drug release from — lots used in clinical trials are similar to the — batch manufactured for marketing by means of a modified F2 comparability test.

Clinical Pharmacology, Phase II and Phase III safety and efficacy studies were conducted employing a — pilot scale batches of Vivitrol. The final to-be-marketed formulation lots were manufactured in the scale of a — batch.

The Agency indicated that bioequivalence study will not be necessary if the Sponsor provides stability data as well as comparative multi-point dissolution testing data using an acceptable dissolution testing method.

Rationale for using a modified f2- test:

Vivitrol microspheres release drug in different phases. Per Agency's suggestion (CMC meeting with sponsor on 2 February, 2005) the sponsor developed a modified f_2 similarity factor in order to address the deficiencies of the conventional f_2 similarity factor when applied to sustained release drug products that exhibit multiple phases of release. The modified f_2 approach compares percent cumulative release for each **phase** of release independently of the previous phase. As a result, transient variations in the release rate that may occur early in the release profile are not propagated into subsequent phases. As with the conventional f_2 similarity factor, the comparison is performed between the test batch (T) and a reference batch (R). The modified f_2 calculation is expressed as follows:

As with the standard f_2 calculation, the comparison includes one data point after 85% release of one of the samples.

Three reference batches were selected for use as a basis for comparison with the development/comparability batches. These batches were selected on the basis of:

(1) Frequency of use in the ALK-21-003 safety and efficacy study (lot 233-3341A),

(2) *In vitro* release characteristics representing central tendencies of the batch population (n=30) used in support of critical clinical and stability studies (lot 233-3031A), and

(3) Use in the ALK-21-005 single and multi-dose PK study (lot 233-3262A).

Alkermes has produced three development/comparability batches for the purpose of establishing chemical comparability, and one comparability (registration) batch. Please refer to the CMC review for details of the scale-up process development, including critical process parameters, comparability of the and scale based upon chemical analyses.

In vitro release data for the development/comparability batches were compared to each of the three eference batches using both standard and modified f_2 calculations (see results tabulated below). One of the lots (04-009-020) had a standard f_2 value of ≥ 50 when compared to all three reference batches. The remaining two batches displayed $f_2 \geq 50$ values when compared to two of the reference batches, and slightly below 50 compared to the third reference batch. Based on modified f_2 test, all three of the reference batches had similarity factors of ≥ 50 compared to all three reference batches. Thus, the *in vitro* release profiles for all three development/ comparability batches are comparable to the eference batches when the three phases of release are considered independently.

Summary for Comparability Lots versus Reference Lots

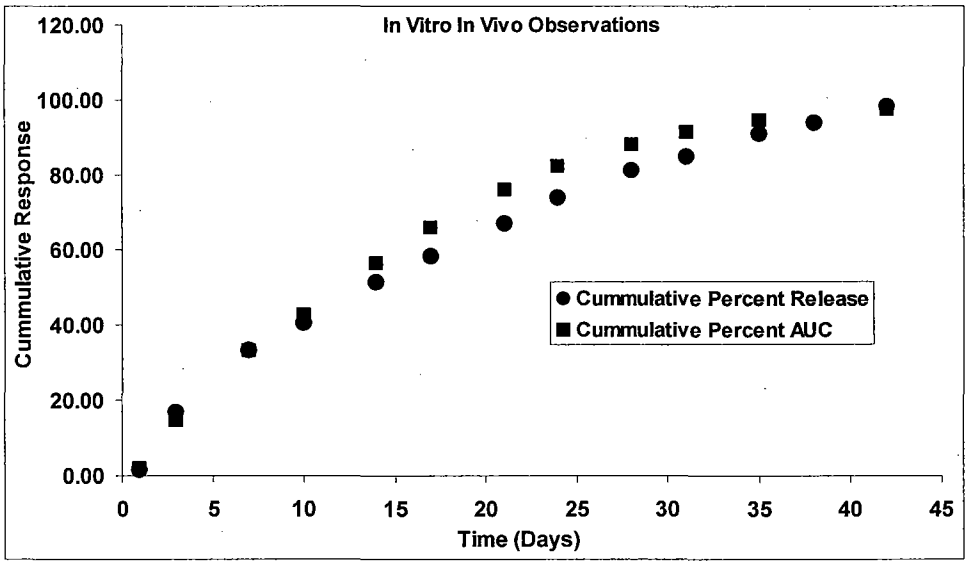
		STANDARD F2			MODIFIED F2		
LOT # ↓ / LOT # →	USE	233-3031A	233-3262A	233-3341A	233-3031A	233-3262A	233-3341A
1064-094	Dev/ Comp 1	47	52	65	63	67	66
04-009-020	Dev/ Comp 2	52	59	66	59	64	56
04-009-026	Dev/ Comp 3	48	54	66	63	66	63

The sponsor is assuming that the Day 7 to Day 14 sampling will be representative of the remaining 14 days of drug release. About 26 – 75 % of drug from various lots of Vivitrol was released by day 14 from real time release method; hence additional sampling up to

30 days may be necessary depending on the stability of the drug in solution. Consistent product performance over 28 days is pivotal for the safety and efficacy of this drug.

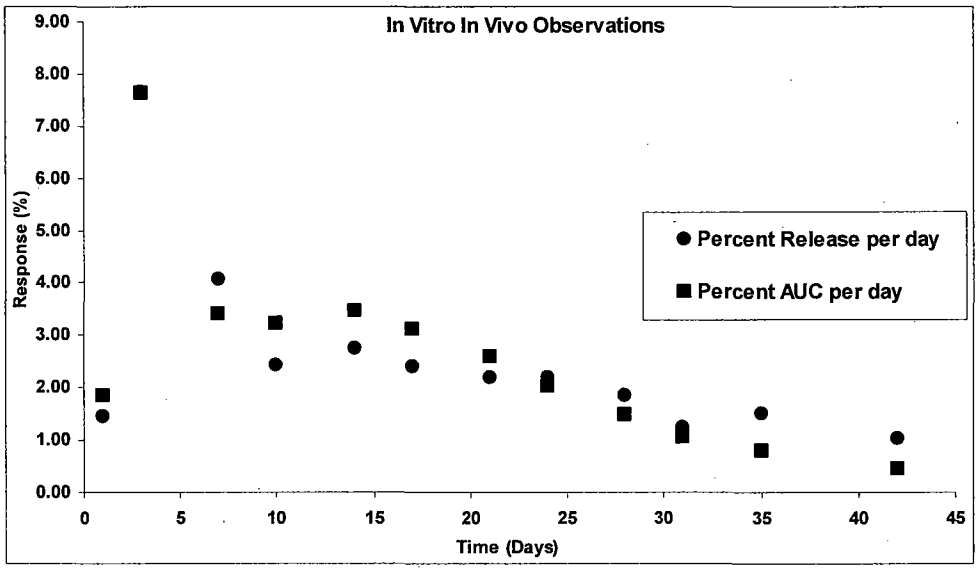
Pharmacokinetics of naltrexone following Vivitrol administration may be release dependent.

Based on the average drug release data generated from limited number of [redacted] lots used in PK study ALK21-005 and the clinical PK observations from ALK21-005 suggest that the drug disposition may be drug release rate dependent. The cumulative AUC observations from study ALK21-005 were plotted against the cumulative drug release

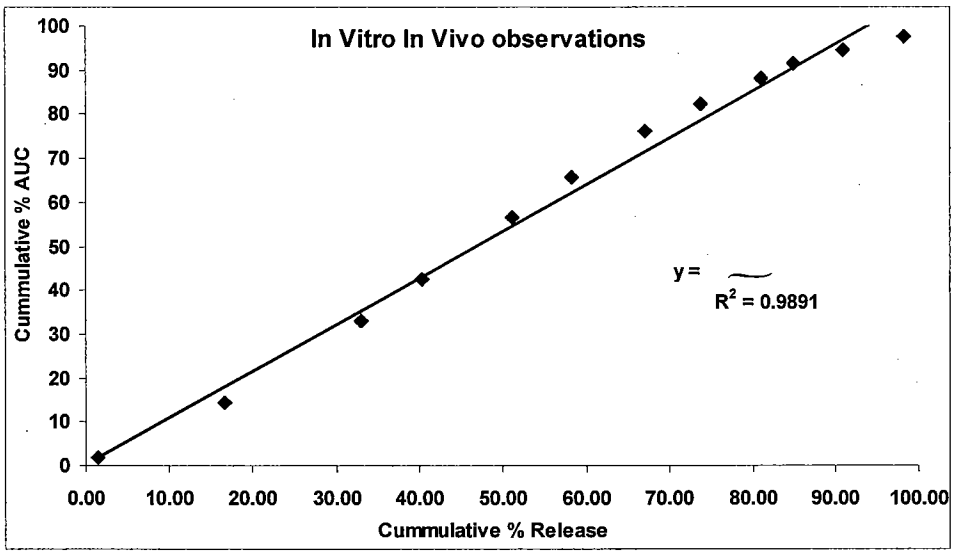


from a test batch of Vivitrol, used in the validation of drug release method (Figure above).

It appears that the percentage of drug release corresponds with the percentage of AUC per day (see Figure below).



The correlation between the mean in vitro release and mean in vivo AUC increase is a linear relationship (see Figure below).



2.4.1 Is the proposed in vitro release method and specifications appropriate for this product?

Sponsor has adequately validated a real time in vitro drug release method. However, additional sampling is necessary for better comparison of drug release characteristics between different batches of Vivitrol. In addition, tighter release specifications are necessary.

The sponsor employed two separate *in vitro* release methods, described below, for the development of drug product specifications.

Real time *in vitro* release method:

This method is used to determine the *in vitro* profile [initial phase, secondary (hydration) phase and sustained release phase] of Vivitrol microspheres in the presence of buffered aqueous media (release media) at physiological pH (7.4) and temperature (37°C). The samples were prepared in the release media and were placed in a 37°C water bath that is maintained at 37.0°C ± 0.3°C. The samples were taken at the specified time points and analyzed for naltrexone content using a UV/Vis spectrophotometer. The percent cumulative release for each sampling day was calculated. The percent cumulative release was reported for Day 1, Day 7 and Day 14. Additionally the difference between Day 14 and Day 7 is reported. The selection of the proposed days is based on the timing of the polymer degradation over time as described above and summarized as follows.

1. Cumulative percent released at Day 1 (Initial Release Phase)
2. Cumulative percent released at Day 7 (Hydration Phase)
3. Percent released between Day 7 and Day 14 (Sustained Phase)

The proposed drug release specifications are as follows:

TEST*	PROPOSED RELEASE CRITERIA	PROPOSED SHELF-LIFE CRITERIA
Real Time *In Vitro* (37°C) UV/Vis: Method #	Day 1: Day 7: ΔDay 7 – Day 14:	Day 1: Day 7: ΔDay 7 – Day 14:

The sponsor is assuming that the Day 7 to Day 14 sampling will be representative of the remaining 14 days of drug release. About 26 – 75 % of drug from various lots of Vivitrol was released by day 14 from real time release method; hence additional sampling up to 30 days may be necessary depending on the stability of the drug in solution. Consistent product performance over 28 days is pivotal for the safety and efficacy of this drug.

Release Medium monobasic monohydrate sodium phosphate, anhydrous dibasic sodium phosphate, sodium chloride, Tween 20 or suitable substitute), and sodium azide dissolved in 1 Liter of deionized water.

Validation of the UV/Vis spectrophotometric method of sample analysis employed in the Drug Release Testing

The sponsor adequately validated UV spectrophotometric method used for the drug release studies for accuracy, repeatability, detection limit, quantitation limit, linearity, range, and intermediate precision (report attached). However, the stability of working standards prepared in the release medium was studied at ambient temperature for up to 33 days. As indicated above, real time and accelerated *in vitro* release methods employ 37^0C and 42^0C temperature, respectively.

Robustness of the real time *in vitro* release of Vivitrol microspheres using a 37°C water bath (*In Vitro* Method, SOP

The effect of slight pH (7.2, 7.4, 7.6), temperature (36.5, 37 & 37.5^0C), and osmolarity changes (250, 270 & 290 Osm), on naltrexone release from Vivitrol using the real time *in vitro* method was determined. The range studied for each parameter was either greater or the same as the range specified in the method. The results indicate that the drug release shows less fluctuation (<5%) within the ranges studied for pH (7.2 to 7.6) and osmolarity (250 Osm to 290 Osm). With regard to temperature changes (see table and figure below), from the start, the samples in the 36.5°C water bath released slower than the samples in the 37.0°C; while faster release is seen with samples in the 37.5°C baths. This difference is noticeable, particularly, during the Phase 3 of the drug release, between days 14 and 30. Hence, the real time release method requires tighter temperature control around 37.0°C.

2.6 Analytical Section

1. Is the analytical method adequately validated?

The sponsor has employed adequately validated analytical methods for the detection of naltrexone and its major metabolite 6β-naltrexol.

Plasma concentrations of naltrexone and 6β-naltrexol were measured employing high performance liquid chromatography (HPLC) methods with tandem mass spectrometry (MS/MS) detection. Naloxone was employed as the internal standard. The analytical method validation information is indicated in the table below:

VALIDATION REPORT REFERENCE	CLINICAL STUDY SUPPORTED	FULL OR PARTIAL VALIDATION	METHOD TYPE	MATRIX	VALIDATION SUMMARY
AV-21-01	--	Full	LC-MS-MS	Human plasma	**Naltrexone** Range: 0.2 to 20.0 ng/mL Accuracy (interday): 1.3 to 5.7% Precision (interday): 3.1 to 7.7% **6β-naltrexol** Range: 2.00 to 200 ng/mL Accuracy (interday): 1.6 to 3.5% Precision (interday): 5.4 to 8.6%
AV-21-03	ALK21-001	Full	LC-MS-MS	Human plasma	**Naltrexone** Range: 0.2 to 125 ng/mL Accuracy (interbatch): 1.66 to 8.39% Precision (interbatch): 2.41 - 11.1% **6β-naltrexol** Range: 0.2 to 125 ng/mL Accuracy (interbatch): 2.92 to 11.7% Precision (interbatch): 3.22 to 10.6%
AV-21-04	--	Partial (as an addition to AV-21-01)	LC-MS-MS	Human plasma	**Naltrexone** Range: 0.200 to 100 ng/mL Accuracy (intraday): 0.78 to 7.8% Precision (intraday): 1.2 to 4.0% **6β-naltrexol** Range: 1.00 to 500 ng/mL Accuracy (intraday): 1.2 to 4.5% Precision (intraday): 1.5 to 4.8%
AV-21-08	ALK21-002 ALK21-004 ALK21-005 ALK21-006 ALK21-009	Partial (as an addition to AV-21-04)	LC-MS-MS	Human plasma	**Naltrexone** Range: 0.200 to 100 ng/mL Accuracy (intraday): 2.9 to 10.3% Precision (intraday): 3.7 to 4.2% **6β-naltrexol** Range: 0.500 to 250 ng/mL Accuracy (intraday): 8.8 to 14.9% Precision (intraday): 3.5 to 5.0%

83 Page(s) Withheld

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5 Page(s) Withheld

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4.3 CPB filing/review form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-897**	**Brand Name**	**VIVITREX**
OCPB Division (I, II, III)	**DPE II**	**Generic Name**	**Naltrexone**
Medical Division	**Division of Analgesics, Anesthetics and Rheumatology Products**	**Drug Class**	**Opioid Antagonist**
OCPB Reviewer	**Srikanth C. Nallani, Ph. D.**	**Indication(s)**	**Treatment of Alcohol Dependence**
OCPB Team Leader	**Suresh Doddapaneni, Ph. D.**	**Dosage Form**	**Injectable microsphere suspension**
		Dosing Regimen	**Once every month**
Date of Submission	**3/31/2005**	**Route of Administration**	**Intramuscular Injection**
Estimated Due Date of OCPB Review	**7/31/2005**	**Sponsor**	**Alkermes Inc.**
PDUFA Due Date	**9/31/2005**	**Priority Classification**	**Priority Review**
Division Due Date	**8/31/2005**		

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	**X**			
Reference Bioanalytical and Analytical Methods	**X**	[redacted]	[redacted]	
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	**X**			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**			
multiple dose:	**X**			
Patients-				
single dose:	**X**	1	1	
multiple dose:	**X**	1	1	
Dose proportionality -				
fasting / non-fasting single dose:	**X**	1	1	Food Effect – Not Applicable
fasting / non-fasting multiple dose:				Food Effect – Not Applicable
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:	**X**	1	1	CYP inhibition studies
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	**X**	1	1	Pop PK analysis considers mild only
hepatic impairment:	**X**	1	1	Mild & moderate only
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	**X**	1	1	

Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X	1	1	3 studies (Data pooled from a total of 4 different PK studies)
Data sparse:	X	1	1	1 study
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	2	2	One comparing IM vs Oral One comparing IM vs SC
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X	1	1	
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan	NA			
Literature References	X			
Total Number of Studies		8	8	Total number of actual studies is less as some evaluated more than one clinical pharmacology aspect

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?	X	Comments have been sent to firm (or attachment included). FDA letter date if applicable. Comment for 74 day letter IR "Address QT prolongation potential by vivitrex from available sources including published literature, drug history including other members of the class, pre-clinical data, Phase III data, EKG's from IND's pertinent to current indication or other indications being studied."
QBR questions (key issues to be considered)	**Dosage appropriateness in special populations** **Rationale for dose selection of the depot formulation**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

4.4 Consent of Supervisor for the proposed Phase IV commitments

Nallani, Srikanth

From: Doddapaneni, Suresh
Sent: Friday, November 18, 2005 8:34 AM
To: Nallani, Srikanth
Subject: FW: Srikanth's NDA-Naltrexone depot formulation!

Srikanth

Print out this e-mail and attach it to the review as Division Director's concurrence. This is in line with OCPB's procedure.

Thanks, Suresh

-----Original Message-----
From: Malinowski, Henry J
Sent: Friday, November 18, 2005 8:28 AM
To: Doddapaneni, Suresh
Subject: RE: Srikanth's NDA-Naltrexone depot formulation!

Suresh,
Looks fine...Hank

-----Original Message-----
From: Doddapaneni, Suresh
Sent: Thursday, November 17, 2005 12:44 PM
To: Malinowski, Henry J
Subject: Srikanth's NDA-Naltrexone depot formulation!

Hank

The review for depot naltrexone product is being finalized. We had the briefing on this on Tuesday. I have extracted from the review, the recommendation/phase IV commitment related language that Srikanth and I drafted. Please provide your feedback.

Thanks, Suresh

1.1 Recommendation

From a Clinical Pharmacology and Biopharmaceutics perspective, NDA 21-897 is acceptable provided that a mutually satisfactory agreement can be reached between the Agency and Alkermes regarding the (a) language in the package insert (b) *in vitro* drug release method, and (c) post marketing commitment to further investigate potential of this product to inhibit or induce CYP enzymes. Specifically,

a) The drug release specifications should be revised with addition of Day 14 and Day 28 drug release information.
b) Conduct *in vitro* CYP inhibition studies using conventional substrates as the submitted data used florescent substrate(s) which tends to introduce non-specificity in detection.
c) Conduct *in vitro* studies in human hepatocytes to evaluate potential of naltrexone to induce CYP3A4 and CYP1A2.

1.2 Phase IV Commitments

a) Conduct *in vitro* CYP inhibition studies using conventional CYP substrates and validated analytical methodology.
b) Conduct *in vitro* studies in human hepatocytes to evaluate potential of naltrexone to induce CYP3A4 and CYP1A2.

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/s/

Srikanth Nallani
11/21/2005 11:09:54 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
11/21/2005 01:47:33 PM
BIOPHARMACEUTICS