8 NOMENCLATURE ISSUES

The original proprietary name proposed by Alkermes was — (naltrexone long-acting injection). The name — was deemed unacceptable by the Office of Drug Safety — .lkermes' alternative, VIVITROL, was found acceptable. However, the Labeling and Nomenclature Committee determined that the established name should be revised from "naltrexone long-acting injection" to "naltrexone for extended-release injectable suspension."

9 CONCLUSIONS AND RECOMMENDATIONS

Alkermes has provided efficacy data from only one adequate and well-controlled clinical study of Medisorb Naltexone. The data demonstrate a pharmacologic effect of the product at the 380 mg/month dose. However, exploration of the finding suggests that the effect is driven largely by favorable results in the very small subpopulation of patients who were able to abstain from drinking during the week before treatment initiation. In fact, in these patients, even the lower dose, 190 mg/month, appears beneficial. Only minor reductions in the event rate of heavy drinking compared to placebo are apparent in the >90% of subjects who were drinking at treatment initiation. In these subjects, attainment of a non-risky drinking pattern (absence of heavy drinking days) or even drinking patterns involving several heavy drinking days per month was unusual and an effect of naltrexone was not clear.

Tempting as it may be to approve the product with labeling stipulating that it is helpful only to subjects abstinent at baseline, I do not think the exploratory analyses supporting this conclusion should be relied upon without further confirmation in an additional study; ideally one that would confirm the efficacy of the lower dose of Medisorb Naltrexone. In particular, it seems important to determine how the subset of patients likely to respond would be identified. It should be established whether the determining factor is a motivational one (i.e., only patients capable of abstaining for a week on their own) or merely the absence of alcohol (such that patients could receive an initial dose of Medisorb Naltrexone prior to discharge from an environment which enforces abstinence). Furthermore, it should be explored whether the 190 mg dose, which appears safer, is, in fact sufficient for treatment.

The safety data suggest that, consistent with its mechanism of action, naltrexone increases the risk of developing or worsening depression, and may increase the risk of suicidality. Other significant findings was a lack of notable advantage of Medisorb Naltrexone over oral naltrexone with respect to hepatic effects. Only minor hepatic abnormalities were observed with either formulation; however, oral naltrexone has been associated with hepatic abnormalities, including post-marketing reports of liver failure and other life-threatening hepatic events. Yet to be completely explained is the observation that Medisorb Naltrexone appears to be associated with a variety of allergic responses, from urticaria and angioedema to two cases of pneumonia (including one bronchoscopically-diagnosed case of eosinophilic pneumonia) and a case of injection site necrosis requiring extensive surgical excision. These last three were serious events and

very concerning. In addition, patients using Medisorb Naltrexone commonly experience injection site reactions, gastrointestinal symptoms, headache, asthenia, and anorexia. Many of these events are less common at the lower dose (190 mg) than at the dose proposed for marketing in the present submission (380 mg).

Of particular concern is the risk of eosinophilic pneumonia. Although this rare condition responds reliably to treatment with steroids, patients who are actively drinking heavily may be less likely to seek treatment for medical illnesses, and could develop this serious illness and go untreated. This raises the important issue of the risk/benefit ratio of the product, and how the use of this drug could be restricted to those who are more likely to benefit. The protocol-specified primary analysis involved group-wise comparisons in the occurrence of heavy drinking days. Although the primary comparison did show a statistically significant effect of the 380 mg dose, there are several concerning aspects to the results:

- A subset analysis of the *fully 91% of the population* that was actively drinking at baseline did not yield a statistically significant result; the hazard ratio (sponsor's analysis) was 0.79, suggesting an overall modest reduction compared to that which could be accomplished without naltrexone. This is not to say that the treated patients continued to drink at baseline levels—they did markedly reduce their drinking compared to baseline. However, so did patients who received only placebo and the concomitant BRENDA therapy.
- Exploratory analyses of various responder definitions in this subgroup also showed that naltrexone treatment did not appreciably improve a patient's chances of restricting heavy drinking occasions to 4 or fewer per month, compared to placebo treatment.

It has been frequently argued that many drugs are approved on the basis of group-wise analyses, such as antihypertensives and lipid-lowering agents, and that the application of a responder analysis to an alcoholism treatment drug represents the imposition of a "higher approval standard." However, it must be noted that, for an individual patient treated for hypertension or hypercholesterolemia, a clinician can easily determine whether the drug is having the intended effect: the patient either is or is not normotensive; the patient's lipid levels are or are not in the desireable range. If a clinician were to treat an alcoholic patient with Medisorb Naltrexone with the expectation that response would be defined by the patient drinking less frequently than he otherwise would be drinking, it would be quite difficult to determine whether to discontinue the drug due to non-response. For a drug intended for chronic administration, which appears to confer a risk of some significant safety events, the lack of a readily-assessed marker of benefit is a significant concern. For this reason, it seems prudent to suggest that only patients who are abstinent at baseline be treated with this product, because, in this group, relapse to heavy alcohol drinking (particularly frequent, e.g., more than 4x/month, drinking) could be viewed as a marker for non-response to treatment and would prompt the clinician to discontinue the therapy[5]. It should be remembered that the original

[5] Of the 17 patients in the 380 mg group who were abstinent at baseline, 82% drank heavily on 4 or fewer occasions per month.

clinical trials supporting approval of oral naltrexone for alcohol dependence treatment were conducted in patients abstinent at baseline, and demonstrated an effect on improving the likelihood of maintaining abstinence. Although it had been theorized that naltrexone's effect was exerted through helping patients to moderate their drinking, the data do not appear to bear this out. It is possible that the disappointing clinical experience with oral naltrexone reflects not simply poor compliance (as generally believed), but also the fact that, perhaps, naltrexone simply helps abstinent patients stay abstinent.

However, I remain reluctant to recommend approval even for this subset without confirmation in an additional trial. In particular, I would like to see an evaluation of whether enforced (i.e. inpatient) abstinence from alcohol is sufficient, or whether only patients capable of spontaneous abstinence for a week can benefit.

Further weighing against approval is the lack of specific non-clinical information about the naltrexone-PLG microspheres. An increased appreciation of the interaction between the active ingredient and the polymer have led to uncertainty about the applicability of information about the safety of PLG in other drug products.

Therefore, I recommend the application not be approved until:

- additional efficacy data is provided confirming the effect of Medisorb Naltrexone 190 mg and/or 380 mg and determining the patient characteristics predictive of success (i.e. enforced vs. spontaneous abstinence),
- additional safety data is provided to establish the expected frequency of very serious allergic reactions, such as injection site necrosis and eosinophilic pneumonia, and
- pre-clinical data deemed necessary by the pharmacology/toxicology team are provided.

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/s/

Celia Winchell
12/22/2005 05:33:49 PM
MEDICAL OFFICER

1 ST Cycle

CLINICAL REVIEW

Application Type	N 21-897
Submission Number	000
Letter Date	March 31, 2005
Stamp Date	March 31, 2005
PDUFA Goal Date	December 30, 2005
Reviewer Name	Mwango Kashoki, MD, MPH
Review Completion Date	December 8, 2005
Established Name	Medisorb Naltrexone
(Proposed) Trade Name	Vivitrol
Therapeutic Class	Opioid antagonist
Applicant	Alkermes
Priority Designation	P
Formulation	Depot naltrexone
Dosing Regimen	380 mg IM q month
Indication	Alcohol dependence
Intended Population	Alcohol dependent adults

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This application does not contain sufficient information to support the efficacy of Medisorb Naltrexone, when used in conjunction with a psychosocial treatment program, in the treatment of alcohol dependence among individuals — abstinent —— at treatment initiation.

The 505(b)(2) new drug application for Medisorb Naltrexone rested, in part, on the Agency's previous finding of efficacy of oral naltrexone. The previous finding of efficacy was based on trials of oral naltrexone in recently detoxified patients, or those otherwise abstinent for at least 10 days prior to treatment. All patients in the oral naltrexone efficacy trials also participated in a psychosocial treatment program.

In addition, the NDA relied upon the Agency's previous finding of safety of polyactide-go-glycolide (PLG), the biodegradable matrix in which the naltrexone was embedded. However, the NDA lacked information regarding the reproductive, genetic, and carcinogenetic potential for the "naltrexone + PLG" combination.

The effect of Medisorb Naltrexone in patients either abstinent or actively drinking at baseline was measured using an endpoint that the Division found to be of unclear clinical relevance, namely the "event rate of heavy drinking." Using this endpoint, a difference in effect between the Medisorb Naltrexone 380-mg and the placebo groups was observed. However, the difference appeared to have been driven by the substantial effect among a small subset of patients who were abstinent from drinking in the 7 days prior to treatment initiation.

The Division re-evaluated the effect of Medisorb Naltrexone using an endpoint considered of greater clinical significance and easier interpretability: "absence of any heavy drinking during the treatment period." Based on this endpoint, there was no considerable difference in effects between the active and placebo groups. However, sizeable differences in treatment effect were noted when data from the small sub-group of patients abstinent at baseline were analyzed. Again, this suggested that the drug is efficacious only in that specific population.

In addition to the lack of substantial evidence of efficacy, there is insufficient demonstration of safety of Medisorb Naltrexone. The information in the NDA indicates that the drug is associated possibily life-threatening reactions such as hypersensitivity reactions at the injection site with subsequent tissue necrosis, eosinophilic pneumonia requiring steroids and ventilatory management, as well as angiodema. The available data do not allow for conclusive elimination of an underlying allergic or hypersensitivity mechanism for these reactions. Furthermore, the magnitude of the risk of an allergic reaction, as well as the risk factors for the reactions cannot be ascertained from the available data.

Altogether, the data do not clearly demonstrate a benefit of treatment in the studied population, and suggest considerable risks of drug administration. Also, non-clinical information regarding toxicological aspects of the formulation is lacking. Thus, approval of this product is not recommended.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Beyond labeling, no formal risk management program or tools are recommended for Medisorb Naltrexone. Labeling should emphasize the need for clinical monitoring of patients for emergence of depressive symptoms, caution prescribers and patients that, due to blockade at the opioid receptor, [redacted] as well as caution prescribers and individuals with a history of opioid abuse that there is a risk of overdose should attempts be made to overcome the blockade effect with increasing doses of opioids.

1.2.2 Required Phase 4 Commitments

- CYP inhibition studies should be repeated using conventional substrates and analytical methods.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

Medisorb Naltrexone is a depot formulation of naltrexone intended for intramuscular injection. Naltrexone is a non-selective antagonist at the opioid receptor, and an oral formulation has been approved for treatment of opiate and alcohol dependence. The mechanism of action of naltrexone is believed to be due to blockade of endogenous opioids at the mu-opioid receptor, resulting in inhibition of the reward pathways and reduction in the euphoric and reinforcing effects of alcohol.

Previous research has shown that patients are poorly compliant with the oral naltrexone regimen. Also, treatment with oral naltrexone has been associated with elevated transaminases. The Medisorb Naltrexone formulation was developed because it was anticipated that monthly injections would increase compliance and, due to the by-passing of first pass metabolism, would decrease the risk of hepatocellular injury.

1.3.1 Brief Overview of Clinical Program

Product name: Medisorb Naltrexone injection.
Drug class: Opioid antagonist.
Route of administration: Intramuscular injection.

Indication sought: Treatment of alcohol dependence, as part of an appropriate program for alcohol dependence.
Population studied: Adults with alcohol dependence, who were either abstinent from drinking or were actively drinking at treatment initiation.

Number of efficacy trials: Two: 1 Phase II trial; 1 Phase III trial.
Number of safety trials: Four (4), two of which were on-going at the time of NDA submission.

The sole Phase III trial enrolled 627 patients, and 624 were given at least one dose of study drug. There were 205 patients treated with Medisorb Naltrexone 380-mg, 210 patients treated with 190-mg, and 214 patients given placebo. Treatment duration for this trial was 6 months, and 64% of the treated patients were treated for all 6 months.

As of the cut-off date for the 120-day Safety Update, a total of 1065 individuals had been given at least one dose of Medisorb Naltrexone. Of these, 942 were patients with a history of alcohol and/or opiate abuse. There were 400 patients treated with the proposed to-be-marketed dose (380-mg) for at least 6 months, and 229 patients treated with this dose for at least 1 year.

1.3.2 Efficacy

A single Phase III trial was submitted in support of efficacy of Medisorb Naltrexone. Subjects were randomized to monthly treatments of Medisorb Naltrexone (190-mg or 380-mg) or placebo for six months, and also participated in a psychosocial management program. Efficacy was assessed using the endpoint "event rate of heavy drinking", and analyzed using a multiple event time analytic approach. This novel endpoint was intended to evaluate both the number and the timing of drinking events. However, the Division deemed the endpoint inadequate for several reasons. First, the endpoint is not clinically intuitive – the clinical meaning of a reduction in the "event rate" of heavy drinking is not clear. Also, the magnitude of a reduction in the event rate of heavy drinking that is associated with clinical improvement is not known. Also, the endpoint is a result of a group mean analysis, and does not provide information on the effects of treatment on an individual patient level. Finally, recent (unpublished) data from the National Institute of Alcohol Abuse and Alcoholism, found that sustained absence of heavy drinking over the treatment period was associated with few drinking consequences. As such, the optimal definition for treatment success in alcoholism trials is now considered to be 'absence of heavy drinking.'

An issue that arose upon inspection of four selected sites was the possibility of biased reporting in drinking behavior, due to the fact that at two of the sites, the same individual who conducted the psychosocial counseling also collected the drinking data. This practice was a violation of the

protocol instructions, and raised the issue of possibility that the drinking data from these sites was unreliable and should not be included in the efficacy analysis. When the sites were excluded, the study 'failed' on both the Applicant's primary endpoint (event rate of heavy drinking) and on the Division's optimal endpoint (sustained absence of heavy drinking). However, further evaluation of the severity and impact of the violations found that exclusion of the two sites was not fully warranted. Therefore, conclusions about efficacy were based on information from all of the participating sites.

My review of the efficacy data found that there were no numerical or statistical differences between either dose of Medisorb Naltrexone and placebo with respect to the proportion of patients who were able to refrain from heavy drinking during the treatment period. However, treatment response was evaluated based on drinking status at study initiation (i.e. actively drinking vs. abstinent from any drinking), the proportion of patients meeting the definition of treatment success was greatly increased, and a difference between the Medisorb Naltrexone and placebo groups was suggested for patients abstinent at baseline. The efficacy results are summarized in the table below:

Actual number of heavy drinking days per month	N (%)			P value	
	Placebo	190 mg	380 mg	190mg vs. placebo	380-mg vs. placebo
All patients (abstinent and non-abstinent at baseline)					
0	11 (5%)	15 (7%)	14 (7%)	0.4325	0.5107
Patients abstinent at baseline					
0	2 (11%)	6 (35%)	6 (35%)	0.1212	0.1212

Thus, my efficacy analysis suggests that Medisorb Naltrexone is efficacious primarily in patients who are abstinent at baseline. Evaluation of the baseline characteristics of these patients found that they were not severely dependent on alcohol and/or had recently undergone detoxification. Thus, this appears to be a selective group of patients for whom the drug will have a clinically meaningful effect. Additional larger studies in patients abstinent at baseline (whether due to detoxification or quitting 'cold turkey') are needed to explore this further.

1.3.3 Safety

In the Medisorb Naltrexone trials, all spontaneously reported, elicited, and observed adverse events were recorded on the Case Report Form. In the original NDA submission, the safety database comprised all patients who took at least one dose of study drug (placebo or Medisorb Naltrexone).

Overall, the mortality rate across the studies was low (n = 5, total), with no considerable increased risk of death in patients treated with Medisorb Naltrexone compared to placebo patients (0.4% vs. 0%). Causes of death were variable (coronary atherosclerosis, pancreatic

cancer, homicide, and completed suicide). The cases of suicide both occurred in Medisorb Naltrexone-treated individuals, however these patients also had depression and suicidal ideation. Thus a relationship to study treatment to suicide is suggested, rather than strongly indicated.

Serious adverse events that associated with treatment included eosinophilic pneumonia, local hypersensitivity reaction with tissue necrosis at the injection site, and an increased risk of suicidal ideation and suicide attempt. Medisorb Naltrexone could have allergic potential, causing reactions such as inflammatory-type injection reactions, eosinophilia, urticaria, and angioedema. A causal association between Medisorb Naltrexone and the reactions, the risk factors for allergic reactions following treatment, and the potential magnitude of these reactions cannot be completely determined from the data.

The most common adverse reactions were injection site reactions. Other common effects were those known to occur with oral naltrexone treatment, including gastrointestinal effects (nausea, vomiting, and diarrhea), as well as headache, dizziness, and somnolence. Medisorb Naltrexone injections were also more likely than placebo to be associated with asthenia, arthralgia, and muscle cramps.

Because of its blockade effects at the opioid receptor, naltrexone is not considered to have abuse potential. There is a risk of opioid overdosage, should opioid abusers attempt to overcome the blockade effects of Medisorb Naltrexone with higher doses of opioids. The risk of overdose increases as the blockade effects wane. The risk of overdose with Medisorb Naltrexone itself is minimized by the fact that patients are dosed by a health practitioner and are only dosed at monthly intervals. Previous research has shown that use of naltrexone during pregnancy and lactation should be avoided. There have been no studies of Medisorb Naltrexone in pediatric patients.

While the common effects of Medisorb Naltrexone appear to have been adequately described, there is still uncertainty about the severity of the allergic potential of the drug. Since this is a depot formulation, with prolonged release of drug, and no methods for drug removal following injection, ascertainment of those at risk for an allergic reaction, as well as methods to treat the reaction is necessary in order to more fully describe the safety of the product.

Altogether, given the lack of definitive evidence of efficacy in the intended population, the incompletely elucidated safety of the product, as well as the availability of other products to treat alcohol dependence, further study of the Medisorb Naltrexone is indicated.

1.3.4 Dosing Regimen and Administration

The Applicant proposed monthly dosing with Medisorb Naltrexone 380-mg. Per its own analyses, the Applicant did not find the 190-mg dose to be efficacious. I agree with the Applicant that monthly dosing with 380-mg results in a similar pharmacokinetic profile as that seen when the dose was given every 28 days. Dosage adjustment does not appear to be indicated for individuals with renal impairment, or those with mild-to-moderate hepatic impairment.

However, due to the risk of bleeding, intramuscular injections should not be given to patients with severe hepatic impairment. Medisorb Naltrexone was not studied in pediatric patients.

Thus, should efficacy be shown in another adequate and well-controlled trial, a monthly dosing regimen of 380-mg IM would be acceptable.

1.3.5 Drug-Drug Interactions

Naltrexone is primarily metabolized at extra-hepatic sites. Thus, inhibitors of CYP enzymes are not likely to affect the pharmacokinetics of Medisorb Naltrexone. Drug interactions using Medisorb Naltrexone were not performed. However, *in vitro* studies of naltrexone suggest that the drug does not inhibit CYP enzymes and therefore naltrexone will not alter the pharmacokinetics of drugs metabolized by these enzymes.

Because naltrexone blocks opioid receptors, dosage adjustment may be necessary for patients administered opioids for pain. Also, since Medisorb Naltrexone showed neuropsychiatric effects such as sedation, dizziness, anxiety, and insomnia, care should be taken when co-administering drugs with similar effects.

1.3.6 Special Populations

See Sections 1.3.3 and 1.3.4.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Medisorb Naltrexone is a new intramuscular depot formulation of naltrexone. Naltrexone is a non-selective opioid antagonist with no agonist activity, and an oral formulation of the drug is currently approved for use in opiate dependence and alcohol dependence.

The Medisorb Naltrexone formulation is a combination of extended-release microspheres of naltrexone and a diluent that are injected intramuscularly (IM). The microspheres comprise naltrexone that is incorporated into a biodegradable matrix of polylactide-co-glycolide (PLG). PLG is a biodegradable medical polymer which is used in several FDA-approved products.

- Drug established name: Medisorb Naltrexone Injection
- Chemical name: Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-(5α)
- Proposed trade name: Vivitrol
- Drug class: non-selective opioid antagonist
- Proposed indication: Treatment of alcohol dependence, as part on an appropriate program for alcohol dependence
- Dose: 380-mg IM q month
    - Injections are to be administered by a health care professional. Injections are to be to the gluteal muscle, alternating buttocks with each administration.
- Age groups: Adults
    - Studies in children waived
    - Studies in adolescents deferred

2.2 Currently Available Treatment for Indications

Alcohol dependence and abuse are commonly treated with non-pharmacologic psychosocial therapy and/or mutual self-help groups (e.g. Alcoholics Anonymous). When pharmacologic treatment is used, the usual practice in the United States is to combine medication with psychosocial treatment.

There are three drugs approved for the treatment of alcoholism: disulfiram, naltrexone (oral), and acamprosate.

Disulfiram
Disulfiram (Antabuse) is a DESI drug approved prior to the requirement of evidence of efficacy. It works through a mechanism unlikely to be approved by today's standards: disulfiram interferes with the hepatic oxidation of acetaldehyde resulting in a 5- to10-fold increase serum acetaldehyde concentrations with associated aversive physical symptoms. Disulfiram's efficacy

is limited by poor compliance, and it is generally used only in highly motivated individuals or in compulsory treatment settings. In addition, the product label notes that hepatic toxicity, including hepatic failure resulting in transplantation or death, has been reported. Severe and sometimes fatal hepatitis associated with disulfiram therapy may develop even after many months of therapy. Hepatic toxicity has occurred in patients with or without prior history of abnormal liver function."

Naltrexone (oral)
The oral dosage form of naltrexone, approved initially for the blockade of exogenously administered opioids, received supplemental approval for the treatment of alcoholism in 1995. Efficacy was demonstrated in patients who are abstinent from alcohol at initiation of treatment. The efficacy of oral naltrexone is limited by problems with compliance, and its post-approval acceptance by patients has been limited. Oral naltrexone's label also carries a warning concerning hepatic toxicity.

Acamprosate
Acamprosate (Campral) is a synthetic molecule that has been internationally available for the maintenance of abstinence from alcohol post-withdrawal since 1987. It was approved for use in the United States as a treatment for alcoholism in 2004, in patients who are abstinent at treatment initiation. Information regarding efficacy and treatment compliance among US populations is limited. Data from international populations show that acamprosate increases the likelihood of maintaining abstinence following detoxification. The drug is generally well-tolerated.

2.3 Availability of Proposed Active Ingredient in the United States

Naltrexone is commercially available in the United Sates in an oral dosage form. It is sold in the US under the trade names ReVia®, Depade®, and Naltrexone Hydrochloride®,

See Section 2.2 for the marketing experience with naltrexone.

2.4 Important Issues with Pharmacologically Related Products

Not applicable.

2.5 Presubmission Regulatory Activity

The IND for Medisorb Naltrexone was first submitted to the Division of Anesthetic, Analgesic, and Addiction Drug Products on October 19 2000. The initial desired indication was treatment of alcohol dependence.

Key milestones in the clinical development program are noted below:

06/15/2000 Pre IND meeting	The Division made several recommendations regarding the proposed development plan: • For the NDA, a single adequate trial may be sufficient, with reference to the Agency's previous finding of efficacy for oral naltrexone. • Conduct of comparative bioavailability studies of multiple doses of oral naltrexone vs. a single dose of Medisorb Naltrexone was recommended. • Evaluation of the effect of hepatic impairment on the pharmacokinetics of Medisorb Naltrexone was necessary. • *In vitro* and *in vivo* evaluations of the metabolism of naltrexone were required. • Because alcoholism is a chronic disorder, Medisorb Naltrexone will be a chronically administered drug. Therefore safety information in at least 300 patients treated for 6 months, and 100 patients treated for 1 year would be required for NDA filing. • Subjects with conditions common in the target population (e.g. polysubstance abuse) were to be included in the safety database. • The proposed endpoint "reduction" in heavy drinking was not acceptable. • Possible efficacy endpoints included a responder rate with respect to abstinence from heavy drinking, complete abstinence, and abstinence from drinking more than the NIAAA "safe" level of drinking. • If only a single efficacy trial were conducted, the concomitant behavioral therapy was to be as realistic as possible (i.e. not standardized). •
10/19/2000	Submission of initial IND – Phase II study of Medisorb Naltrexone 400 mg in alcohol dependent patients (study ALK21-002).
11/16/2000 30-day IND safety review	The Division provided comments regarding study ALK21-002: A 2-3 day run-in period with oral naltrexone prior to administration of Medisorb Naltrexone was recommended in order to assess tolerability of naltrexone.
04/10/2001 Type C meeting	The Division provided advice regarding the Applicant's proposal for

(Clinical development milestones, continued)

10/03/2001 Advice Letter	The Division commented on the Applicant's proposed sole Phase III efficacy study in patients with alcohol dependence: • The proposed primary efficacy endpoint, the event rate of heavy drinking, was deemed acceptable. • Justification of a statistically significant decrease in the event rate of heavy drinking in the absence of a significant difference between groups with respect to a decrease in the event rate drinking above the NIAAA "safe" level would be required. • The statistical analysis plan was to pre-specify how missing data would be defined and handled. • The Applicant was to demonstrate that the proposed psychosocial treatment, BRENDA, was suitable for primary care settings. • The 3-day oral naltrexone run-in period could be removed if data from the Phase II trial, ALK21-002, indicated that safety and tolerability were not compromised by the lack of an oral naltrexone run-in. • If there was no pharmacokinetic difference between administration of the product every four weeks versus every 30-31 days (i.e., every month), then a labeled dosing interval of "monthly or every 4 weeks" might be acceptable.
10/07/2004 Type B meeting Pre-NDA	The Division informed the Applicant that: • [redacted] would be a matter for NDA review. • Pediatric studies could be deferred until after NDA approval. • A responder analysis, using various definitions of treatment response, should also be performed as part of the efficacy analysis. • Definition of treatment response as "≥ 50% decrease in the percent heavy drinking" was not acceptable. • Because of the prior agreement with the Applicant, finding of treatment efficacy would be based on the primary analysis.
03/31/2005	NDA submission.

2.6 Other Relevant Background Information

Not applicable.

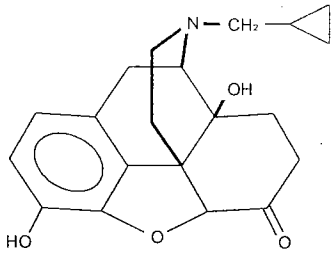
3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC and Clinical Microbiology

Much of the information below is based on the Applicant's NDA summary, and the proposed product label. Information provided following discussion with the Chemistry Reviewer is also included.

Medisorb Naltrexone is comprised of sterile, off-white to light-tan microspheres of naltrexone base encapsulated in polylactide-co-glycolide (PLG), mixed in a 75:25 ratio. The naltrexone is the active ingredient.

Naltrexone:
Generic name: Naltrexone
Chemical name: Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-(5α)
Molecular formula: $C_{20}H_{23}NO_4$
Molecular weight: 341.41 (in the anhydrous form, i.e. < 1% maximum water content)
Chemical structure:



The Medisorb Naltrexone microspheres are combined with a colorless diluent composed of carboxymethylcellulose sodium salt, polysorbate 20, sodium chloride, and water. The microspheres are suspended in the diluent, and a properly mixed suspension will be milky white without particulates. The combination of the microspheres and the diluent is intended for intramuscular injection, and the dosage strength of the injection is 380-mg naltrexone per vial.

Medisorb Naltrexone is to be provided in single use kits. Each kit will contain one 380 mg vial of Medisorb Naltrexone microspheres, one vial containing 4.0 mL (to deliver 3.4 mL) diluent for the suspension of Medisorb Naltrexone, one 5 mL syringe, one ½" 20 gauge needle, and two 1½" 20 gauge needles with safety device: NDC 65757-402-05.

Key issues identified during the CMC review were:

1. *Stability of drug product*
   The Applicant used — batches of drug product during clinical development, and provided stability data at 12 months and 18 months for these batches. The Applicant recently scaled up to — batches however, at the time of the NDA submission; there were only 2 months of "real time" stability data for the larger batches. Stability information was to be extrapolated from the — batches. The Chemistry Review found that extrapolation could only be done up to —

   REVIEWER COMMENT: The finding of only 12-month stability for the — batches will limit the expiry for the product, but should not impact drug approval.

2. *Drug release*

The data show that the rate and amount of drug release both increase with increasing temperatures (e.g. ≥ 40°C). Thus, there is the potential for rapid drug release and increased exposure in patients with elevated temperatures, e.g. during a fever.

The data also showed that, on average, about 30% of naltrexone is released during the first 7-10 days. This corresponds to release of approximately 114 mg of naltrexone in the initial 1-2 weeks. The variation in drug release / dissolution specifically at day 7 could partially be due

, thereby affecting the day 7 to day 14 dissolution rates. The Applicant proposes an upper limit drug release specificication of about — This means that there is the potential for release of approximately — ng of naltrexone in the first 2 weeks.

REVIEWER COMMENT:
The finding of increased drug release with high temperatures should be factored into the evaluation of the safety of the product.

The current drug release data showing release of 114 mg of naltrexone over 1 to 2 weeks is acceptable. Patients have previously been dosed with similar doses of oral naltrexone, without significant adverse effects. However, the Applicant's proposal to have drug release specifications such that — of the drug is released over a short period of time is unacceptable. Higher doses of naltrexone have previously been associated with adverse events, such as oral toxicity. The drug release specifications should remain as 'tight' as can be reasonably achieved.

3. *Drug kit*
   The kit contains two 20-gauge 1½ inch safety needles. Only one needle appears necessary for drug administration.

   REVIEWER COMMENT: I agree that only one needle appears necessary. Inclusion of an extra needle could be problematic in terns of diversion of needles for drug abuse, and the potential for needle-stick injuries should unused needles be thrown away with the packaging material.

The Division requested that the microbiology review team in the Office of New Drug Chemistry evaluate the data regarding the sterility process and microbial testing for naltrexone base, as well as for the Medisorb Naltrexone microspheres. The conclusions from the microbiology review are described in Section 6.1.5.

3.2 Animal Pharmacology/Toxicology

See the Pharmacology/Toxicology reviews for a detailed discussion of the non-clinical issues related to this product.

The Applicant intended this 505(b)(2) NDA to rely in part on previous Agency findings of safety for products containing either naltrexone or PLG, or on non-clinical data for naltrexone and for PLG that was already available in the published literature. Non-clinical studies that were specifically conducted by Alkermes were those related to the pharmacokinetics, acute toxicity, and the repeat dose toxicity of Medisorb Naltrexone.

An important issue that emerged during the review process was whether or not the referenced data were sufficient to provide non-clinical information about Medisorb Naltrexone. The application relied upon multiple sources of data for the reproductive toxicology, genetic toxicology, and carcinogenicity of naltrexone and PLG individually, however there were no such data for the combined Medisorb Naltrexone product. The Pharmacology/Toxicology review evaluated whether the information on the individual components was sufficient, or whether specific studies for the Medisorb Naltrexone formulation were required.

A significant concern for the review was whether the data from the referenced studies were even applicable to the Medisorb Naltrexone product. Some of the referenced information was based on a specific ratio of "drug + PLG" that was different from the "naltrexone + PLG" ratio of Medisorb Naltrexone. Since [redacted] the combination of naltrexone with PLG is anticipated to result in a different pattern of PLG biodegradation than that of "other drug + PLG" combinations. As a result, the toxicology data from the combinations of other drugs and PLG may not be applicable to Medisorb Naltrexone.

Furthermore, due to the higher exposure (AUC) experienced with the Medisorb Naltrexone formulation compared to the exposure with oral naltrexone (see Section 5.1), the referenced carcinogenicity and reproductive toxicology studies using oral naltrexone may not be applicable to the Medisorb product.

An important result of the Applicant's non-clinical studies was the occurrence of injection site reactions:

Key safety finding of Medisorb Naltrexone - Injection site reactions:

In monkeys and rabbits, both SC and IM injections of Medisorb Naltrexone and placebo microspheres resulted in a clinically visible injection site enlargement which the Applicant attributed to the mass of test material and pathological evidence of a foreign body reaction at the depot site. The enlargement was more pronounced for SC than IM injections.

In the 1-month rabbit studies, microscopic findings at the sites of both SC and IM injections of the Medisorb Naltrexone and placebo microspheres were foreign body reactions which were characterized by granulomatous inflammation and fibrosis surrounding the residual polymer material. Microscopic examination of the IM sites showed minimal to slight edema and minimal hemorrhage, minimal to slight lymphoplasmacytic infiltrate (at the Medisorb Naltrexone sites, Day 30), as well as minimal to moderately-severe muscle degeneration with subsequent muscle regeneration. Alkermes concluded that the muscle degeneration was due to local pressure caused by depot material at the injection site.

In the IM and SC 8-month local tolerance study in rabbits, necropsies conducted at 8 and 30 days after dosing revealed that the IM and SC sites consisted mainly of residual test material. Clinically and by gross pathological examination, it was suggested that the test materials were gradually resorbed. Microscopically, the polymer microspheres were progressively degraded, with accompanying foreign body response and fibrosis at the injection sites.

In a repeat-dose monkey study, granulomatous inflammation consisting of macrophages, multinucleated giant cells, and fibrosis were observed at injection sites at the 3-month sacrifice. These responses were considered to be resolving by the 6 month sacrifice.

In a 10-month local tolerance study in dogs, a dose and volume of Medisorb Naltrexone comparable to that proposed for human dosing was administered: 394 mg naltrexone; 1144 mg microspheres; 4 mL dose volume. All animals received active drug. No systemic toxicity was apparent however, prominent injection site reactions occurred in all animals. The local reaction consisted of skin swelling approximately 1 to 5 cm in diameter. An area of discoloration up to 7 cm in diameter was also noted at the injection sites of some animals. Residual test material within the muscle and in some cases on the proximal muscle surface was observed at all necropsy intervals and at all injection sites. Adhesions between the skin and skeletal muscle were also observed grossly at the injection sites in some animals sacrificed 2 weeks after dosing.

Histopathology from the dog study showed an inflammatory reaction with fibrosis at the injection sites. At 2 weeks post-dose, a chronic active inflammatory reaction was observed (macrophages, multinucleated giant cells, neutrophils, eosinophils and lymphoplasmacytic cells). The injection site reactions in dogs were apparent soon after administering the first dose and were most severe between 1 to 3 weeks post-dose. At 6 to 7 months post-dose, granulomatous inflammation was the primary histopathological change observed. The inflammatory response and accompanying fibrosis diminished over time.

Alkermes considered the injection site reactions observed in the dog to be unexpected. Therefore local tolerance studies were repeated in dogs and rabbits using the same lot material that elicited significant reactions in the initial 10-month dog study. Alkermes found that IM administration of the treatment to rabbits was well tolerated, and that there were no clinical or gross injection site reactions after 2 weeks. However, in dogs, the IM injections caused significant and dose-related injection site reactions at 2 weeks. Alkermes concluded that, based on the earlier experience of reasonable local tolerance in the monkey studies, the dog is unusually sensitive to IM Medisorb Naltrexone.

REVIEWER COMMENT:
The review found that the major safety pharmacology concern for Medisorb Naltrexone was inflammatory injection site reactions which were common across all 3 animal species tested. The review also found that the referenced non-clinical data do not completely describe the reproductive, genetic, and carcinogenetic potential of Medisorb Naltrexone. However, such information is not available for the individual naltrexone and PLG components. Nevertheless,

these are approved and marketed products. The Pharmacology/Toxicology reviewer is of the opinion that the non-clinical information that is lacking on the combined "naltrexone + PLG" product is required for consideration of NDA approval.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This review relied upon summary reports and datasets of one Phase 2 trial, one Phase 3 trial, and two open-label extension studies using Medisorb Naltrexone. The datasets were utilized for confirmatory data analysis, as well as for additional exploratory analyses. The Applicant's summaries of efficacy and safety data for oral naltrexone were also examined.

4.2 Tables of Clinical Studies

The tables below list the studies conducted by the Applicant and submitted in support of the New Drug Application. Only the Phase 3 trial (ALK 21-003) was reviewed for demonstration of efficacy. Data from the all of studies were evaluated for safety.

Table 4.2 Tabular listing of clinical studies

TYPE OF STUDY; OBJECTIVE(S) OF THE STUDY	ID; LOCATION OF STUDY REPORT	STUDY DESIGN AND TYPE OF CONTROL	TEST PRODUCT(S); DOSAGE REGIMEN; ROUTE OF ADMINISTRATION	NUMBER OF SUBJECTS	HEALTHY SUBJECTS OR SUBJECT DIAGNOSIS	DURATION OF TREATMENT*	STUDY STATUS; TYPE OF REPORT
Safety & tolerability; Single dose PK estimation	ALK21-001 Section 5.3.3.1	Randomized, double-blind, dose escalation Placebo-controlled (for injected drug only)	Vivitrex, 141, 269, or 530 mg, single dose, SC Vivitrex, 141, 269, 530, or 784 mg, single dose, IM Naltrexone, 50 mg, multiple dose (daily), oral	48 (35 Vivitrex, 6 oral naltrexone, 7 placebo)	Healthy subjects	Single dose (Vivitrex) 5 days (oral naltrexone)	Complete;Full
Steady state and single dose PK; Safety & tolerability	ALK21-005 Section 5.3.3.1	Randomized, double-blind Placebo and active-controlled	Cohort A: Vivitrex, 190, or 380 mg, single dose, IM Naltrexone, 50 mg, single dose, oral Cohort B: Vivitrex, 380 mg, q 28 days, IM Naltrexone, 50 mg, daily, oral	42 (Cohort A: 28 [12 Vivitrex 190 mg, 12 Vivitrex 380 mg, 4 placebo]; Cohort B: 14 [12 Vivitrex 380 mg, 2 placebo])	Healthy subjects	Cohort A: single dose oral naltrexone followed by single dose* Vivitrex Cohort B: 5 days oral naltrexone followed by 4 IM doses (q 28 days) Vivitrex	Complete;Full

TYPE OF STUDY; OBJECTIVE(S) OF THE STUDY	ID; LOCATION OF STUDY REPORT	STUDY DESIGN AND TYPE OF CONTROL	TEST PRODUCT(S); DOSAGE REGIMEN; ROUTE OF ADMINISTRATION	NUMBER OF SUBJECTS	HEALTHY SUBJECTS OR SUBJECT DIAGNOSIS	DURATION OF TREATMENT*	STUDY STATUS; TYPE OF REPORT
PK; Safety & tolerability	ALK21-009 Section 5.3.3.3	Parallel-group, open-label	Vivitrex, 190 mg, single dose, IM	25	Mild or moderate hepatic impairment; matched healthy controls	Single dose	Complete;Full
Population PK	ALK21-011 Section 5.3.3.5	Pooled analysis of PK data from: ALK21-004, ALK21-005, ALK21-006 ALK21-009	Vivitrex, variable dosages, IM	453	Healthy subjects and alcohol and/or opiate dependcence	Single dose up to 6 months	Complete; Full
Safety & tolerability; PK estimation; Data collection methodology assessment	ALK21-002 Section 5.3.5.1	Randomized, double-blind Placebo-controlled	Vivitrex, 400 mg, q 28 days, IM	30 (25 Vivitrex, 5 placebo)	Alcohol dependence	4 months	Complete;Full
Efficacy; Safety & tolerability	ALK21-003 Section 5.3.5.1	Randomized, double-blind Placebo-controlled	Vivitrex, 190 or 380 mg, q 28 days, IM Placebo, q 28 days, IM	627 (624 dosed; 210 Vivitrex 190 mg; 205 Vivitrex 380 mg; 209 placebo)	Alcohol dependence	6 months	Complete;Full

TYPE OF STUDY; OBJECTIVE(S) OF THE STUDY	ID; LOCATION OF STUDY REPORT	STUDY DESIGN AND TYPE OF CONTROL	TEST PRODUCT(S); DOSAGE REGIMEN; ROUTE OF ADMINISTRATION	NUMBER OF SUBJECTS	HEALTHY SUBJECTS OR SUBJECT DIAGNOSIS	DURATION OF TREATMENT*	STUDY STATUS; TYPE OF REPORT
Long term safety & tolerability; Outcome measures	ALK21-003-EXT Section 5.3.5.2	Extension of ALK21-003 Uncontrolled	Vivitrex, 190 or 380 mg, q 28 days, IM	332‡ (102 Vivitrex 190 mg; 115 Vivitrex 380 mg; 115 placebo)	Alcohol dependence	1 year	Complete;Full
Long term safety & tolerability;	ALK21-006 Section 5.3.5.2	Randomized, open-label Active-controlled	Vivitrex 380 mg, q 28 days, IM Naltrexone, 50 mg, daily, oral	436‖ (373 Vivitrex, 63 oral naltrexone)	Alcohol and/or opiate dependence	1 year	Complete; Interim
Long term safety & tolerability	ALK21-010 Section 5.3.5.2	Extension of ALK21-003-EXT Open-label Uncontrolled	Vivitrex, 190, or 380 mg, q 28 days, IM	99‡‖ (53 Vivitrex 380 mg; 46 Vivitrex 190 mg)	Alcohol dependence	3.5 years	Ongoing; Interim
Demonstration of biological activity; Safety & tolerability; PK	ALK21-004 Section 5.3.5.4	Randomized, double-blind Uncontrolled	Vivitrex, 75, 150, or 300 mg, single dose, IM	27 (9 Vivitrex 75 mg; 8 Vivitrex 150 mg; 10 Vivitrex 300 mg)†	Non-dependent opioid-using adults	Single dose*	Complete;Full

TYPE OF STUDY; OBJECTIVE(S) OF THE STUDY	ID; LOCATION OF STUDY REPORT	STUDY DESIGN AND TYPE OF CONTROL	TEST PRODUCT(S); DOSAGE REGIMEN; ROUTE OF ADMINISTRATION	NUMBER OF SUBJECTS	HEALTHY SUBJECTS OR SUBJECT DIAGNOSIS	DURATION OF TREATMENT*	STUDY STATUS; TYPE OF REPORT
Exploratory evaluation of psychosocial information	ALK21-003RET Section 5.3.5.4	Retrospective data collection	NA	256 (received at least 1 dose of study drug from ALK21-003)	Alcohol dependent subjects from ALK21-003	One time survey	Complete; Full

*Vivitrex is a long-acting product; a single dose is expected to provide exposure for approximately 1 month.
†Of the 27 randomized subjects, 2 were randomized twice, once at each study center. Thus, a total of 25 unique individuals participated in the study.
‡Subjects in ALK21-003-EXT are a subset of subjects from ALK21-003. Subjects in ALK21-010 are a subset of subjects from ALK21-003-EXT.
‖As of 31 August 2004
NA = not applicable
PK = pharmacokinetics

Vivitrex = Vivitrol = Medisorb Naltrexone

Type of study; Objective(s) of the study	**Study ID**	**Study design and type of control**	**Test product(s); dosage regimen, route of administration**	**Number of subjects**	**Healthy subjects or subject diagnosis**	**Duration of treatment**	**Study status; type of report**
Long-term safety and tolerability	ALK21-006-EXT	Extension of ALK21-006; Uncontrolled	Medisorb Naltrexone 380 mg	0 (at time of data cut-off)	Alcohol and/or opiate dependence	3 years	Study not initiated (at time of data cut-off)

4.3 Review Strategy

For this 505(b)(2) NDA application, Alkermes conducted only one Phase 3 efficacy study, ALK 21-003. Together with literature cited by the Applicant, and the Agency's previous finding of efficacy of naltrexone (oral dosage form), data from this study were used to evaluate the efficacy of Medisorb Naltrexone as treatment for alcohol dependence.

Review of the efficacy was conducted together with Dr. Dionne Price, Division of Biometrics II. Dr. Price evaluated the Applicant's analyses of the primary endpoint, and performed additional alternate analyses of the effects of treatment on drinking patterns, including a comparison of treatment response rates between the active and placebo groups. Key findings from Dr. Price's analyses are included in this review. A detailed description of all analyses and findings can be found in Dr. Price's review.

The primary electronic datasets used for the efficacy analyses were those containing data for study ALK21-003, namely: *drink.xpt, drinkl.xpt,* and *effisub.xpt.*

Data from all Phase 2 and Phase 3 trials were utilized in the integrated safety analysis. The safety review focused on adverse events, particularly hepatic changes and injection site reactions. The Integrated Summary of Safety (ISS) datasets that were used for the safety review are listed in Section 7.1

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) inspected four sites for inspection, each located in the United States. The sites were selected for inspection if

- Either Study ALK21-003 (the sole efficacy study) or Study ALK21-006 (a 1-year open label safety study of Medisorb Naltrexone and oral naltrexone) was conducted there;
- A relatively high number of patients was enrolled; and
- There was a fairly high association between the site and the treatment outcome.

DSI noted irregularities at all of the four inspected sites:

Study ALK21-003

Notable protocol features were as follows:

- The protocol was amended such that the same person who administered study drug could not conduct any of the safety or efficacy assessments.
- The protocol was also amended to disallow collection of the drinking data and conduction of the psychosocial counseling by the same person.
- The IRB specifically requested that all adverse events of grade 3 or above be reported within 48 hours.

Site # 215

- Of 36 consented patients, 12 subject records were reviewed. It was found that 9 subjects had the same person perform physical examinations and collect drinking data.
- The person who performed the physical examinations was not licensed to practice medicine in the United States.
- All 12 of the subject records showed that the same person conducted the psychosocial counseling and collected drinking information
- Twenty-one subjects did not sign all available consent form revisions during the participation in the study. Several of the versions included updated safety and adverse event information.

Site # 217

- Of 46 enrolled patients, 15 patients' records were reviewed. Among the 15 patients, here were 4 who had 8 instances in which the same person perform psychosocial counseling and collect drinking data.

Site # 214

- Records for 12 of 35 randomized patients were reviewed. The review found that the SAEs for 7 subjects were reported to the IRB 16 to 119 days after they occurred: hospitalization occurred for exacerbation of alcohol dependence (5 subjects; pleurisy (1 subject); and death (homicide – 1 subject).

Study ALK21-006

Site # 214

- Of 16 enrolled patients, two SAEs for one patient (hospitalized for scalp lacerations and exacerbation of alcohol dependence) were reported to the IRB 178 and 194 days after they occurred.

Site # 245

There were 40 subjects randomized and 8 patient records reviewed. Three protocol deviations were noted:

- The first 14 subjects enrolled in the study (subjects 001 – 014) received Medisorb Naltrexone or oral naltrexone before the results of the coagulation group test values were received and reviewed by the investigator.
    - The 14 subjects were listed as protocol deviations on the firm's electronic deviation log as "subjects randomized without coagulation results, and the "corrective action" listed on the electronic deviation log was "issue discussed with investigator; IRB notified." However, the list of protocol deviations supplied by the Applicant does not contain these entries. DSI concluded that this appears to be a sponsor issue, not a clinical investigator problem.

- The Medisorb Naltrexone powder was stored outside of the protocol specified temperature range (2 – 8°C). Temperatures reached 13.7°. The length of time the drug was stored is unknown.
- The protocol specified the study drug injection site to alternate between right and left buttocks. Subject 008 received two consecutive injections in the left buttock.

There were also numerous occurrences of inaccurate record keeping at this site:

Subj No.	Start/Stop Date	Info in Source Doc	Info in CRF	Problem
032		Yes	No	Use of 3 concomitant medications (valium, benadryl, xanax) not recorded in CRF
008		Yes	No	Stop date for concomitant med use (orthocyclin) not in CRF
008		Yes	No	Stop date for concomitant med use (lexapro) not in CRF
014		Yes	No	Stop date for concomitant med use (prevacid) not in CRF
014		Yes	No	Stop date for concomitant med use (neurontin) not in CRF
014		Yes	No	Stop date for concomitant med use (phentiramine) not in CRF
014		Yes	No	Stop date for concomitant med use (zyrtec) not in CRF
032		20 ultram tablets, PO, qd	Ultram, 20-unk units PO, 1x,	Day and amount of concomitant med differ
032		Cogentin, 2-mg, IM, tid	Cogentin, 6-mg, IM, 1x,	Dosage amount and (although total dose is times differ same)
032		Benadryl 50-mg, PO, qd	Benedryl, 1x 100-mg, PO	Dosage amount and (although total dose is times differ same)
032		Benedryl, 25-mg IM qd	Benedryl, IM, 25-mg, prn	Dosage times differ
028		"Continuous"	Blank	Reported frequency of the AE of anxiety differs
014				Stop date for concomitant med use (prednisone) differ
032				Date for concomitant med use (haldol) differ
032				Date for AE (agitation) differ
032				Date for AE (insomnia) differ

Subj No.	Start/Stop Date	Info in Source Doc	Info in CRF	Problem
016	[redacted]	Blank	"No"	Question whether bilateral sciatic pain was an SAE
010	[redacted]	Blank	"No"	Question whether headaches was SAE
032		"Continuing"	"Resolved"	Question regarding outcome of insomnia AE
008		Blank	"Continuing"	Question regarding outcome of lower back pain AE
014		Blank	"Continuing"	Question regarding outcome of urticaria AE
014		Blank	"Continuing'	Question regarding outcome of fatigue AE
024	Screening visit	[redacted]	[redacted]	Date of screening visit differs

In addition, several instances were found where Data Clarification Forms from the sponsor resulted in the changing of concomitant medication use data or AE data on the CRFs but not on the original source.

Based on the type and severity of the irregularities, DSI recommended that data from sites 215 and 217 be excluded from the NDA evaluation.

REVIEWER COMMENT:
Although the Medisorb Naltrexone was stored at a temperatures greater exceeding the recommended range, the CMC data suggest that the drug is still stable at those temperatures. Therefore, this protocol violation is not likely to have had an effect on the efficacy or safety data provided from patients treated using that sample of drug.

The failure to promptly report SAEs to the IRB, while concerning, is not likely to have affected the studies' safety data. With regards to the enrollment of patients into Study ALK21-006 prior to receipt of the results of the patients' coagulation tests, it was noted that none of the subjects had prolonged prothrombin time and all were eligible for the study. Therefore this irregularity did not have an affect on the safety data.

The violations and irregularities that are concern include the instances where the same person collected the drinking data and conducted the psychosocial therapy or performed safety evaluations and the inconsistencies in data recording. The collection of drinking (efficacy) data and safety/psychosocial assessments by one individual is problematic because there is the potential for bias in safety and efficacy reporting. For example, reporting bias may have occurred if patients chose to minimize the number of drinks reported because the person collecting the drinking data is the same person who is counseling and encouraging them to reduce their intake. Also, investigator bias may have occurred if the person conducting the counseling elicited drinking information in such a manner that fewer drinks were reported or recorded. In addition, inaccuracies in record keeping could diminish the assurance in the accuracy and validity of the data. Overall, imperfections in data collection make it difficult to accept conclusions made about the data.

The Division's assessment of the impact of the violations at sites 215 and 217 on the NDA review is discussed in Section 6.

4.5 Compliance with Good Clinical Practices

All of the studies, including the one efficacy study, appeared to be conducted under acceptable ethical standards, and patients (with the known exception of patients at site 215) appear to have been appropriately informed prior to consenting to participation. Besides the violations found upon DSI site inspection, there were minor protocol violations in the efficacy study which were not considered to have an influence on the study results (see Appendix Section 10.1 for details).

4.6 Financial Disclosures

Alkermes provided financial disclosure information for the principal and sub-investigators who participated in the sole efficacy study, ALK21-003. Only one investigator reported significant financial interest:

Dr. — (PI, site — reported financial interest for receipt an excess of $25,000 for "consultant fees." A total of — patients — were enrolled into the study.

Because only one of the numerous principal and sub-investigators had significant financial interest, and because the total enrollment from this site was only a small fraction of the total enrollment, financial incentive is not considered to have adversely affected the integrity of the data.

5 CLINICAL PHARMACOLOGY

Much of the material below is taken from the Clinical Pharmacology Reviewer's NDA review.

For this 505(b)(2) application, Alkermes relied in part on the clinical pharmacology data already available for the FDA-approved oral naltrexone (Revia). In addition, the Applicant submitted five clinical pharmacology studies evaluating:

- The relative bioavailability of a single dose of Medisorb Naltrexone
- Multiple dose pharmacokinetics of Medisorb Naltrexone
- Pharmacokinetics of Medisorb Naltrexone in patients with mild and moderate renal impairment
- The extent of opioid blockade by Medisorb Naltrexone
- The effect of covariates (e.g. age, sex, weight, polysubstance use) on Medisorb Naltrexone pharmacokinetics (a population PK study)

Based on the microsphere formulation of Medisorb Naltrexone, drug is hypothesized to occur in three phases:

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.

5.1 Pharmacokinetics

After IM administration of Medisorb Naltrexone, peak plasma levels of naltrexone are observed in about 5 hours to 2 days. The C_{max} of naltrexone is highly variable following oral and Medisorb Naltrexone administration. For Medisorb Naltrexone, in the range of 141 – 784 mg, there appeared to be a dose-proportional increase in AUC of naltrexone. Plasma protein binding (21%) did not appear to change with the IM route of administration compared to oral administration. Elimination of naltrexone after IM dosing appears to be dependent on the rate of release from the Medisorb Naltrexone microspheres: whereas the elimination half life for the product is approximately 8 days; the half-life for oral naltrexone is 5 hours.

The proposed dose of Medisorb Naltrexone is 380 mg over 28 days. The total dose of oral naltrexone (50 mg/day) over that same time period would be 1400 mg. Thus the total dose IM Medisorb Naltrexone is approximately one third of the oral naltrexone dose. However, the *exposure* to naltrexone (AUC_{0-28}) over 28 days following a single Medisorb Naltrexone dose 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 administering drug via the IM route.

> REVIEWER COMMENT: In the NDA, Alkermes argued that the concern about the potential toxicities of Medisorb Naltrexone was alleviated by several factors, including the smaller total monthly dose compared to daily oral naltrexone dosing. However, the finding of a much larger total exposure to naltrexone following Medisorb Naltrexone administration compared to oral naltrexone refutes this argument. Instead, the exposure data suggest the potential for greater risks with Medisorb Naltrexone than with oral naltrexone.

Orally administered naltrexone undergoes extensive first-pass metabolism to the active metabolite, 6β-naltrexol. Cytochrome P450 enzymes are not involved in the metabolism of naltrexone. Compared to oral naltrexone (50 mg), dosing with IM Medisorb Naltrexone (380mg) results in much less formation of 6β-naltrexol formation.

REVIEWER COMMENT: Like the parent drug, 6β-naltrexol is renally excreted. Therefore, there is the potential for 6β-naltrexol accumulation in patients with renal impairment. However, metabolism of Medisorb Naltrexone results in substantially lowered formation of and exposure to β-naltrexol compared to oral naltrexone. Thus any accumulation in renal impairment is not likely to have clinically significant effect.

Although naltrexone is not metabolized by CYP enzymes and thus altered pharmacokinetics due to co-administration with CYP inhibitors is not expected, it is unknown whether naltrexone itself inhibits CYP enzymes. While CYP inhibition related drug interactions have not been reported with use of oral naltrexone, due to the evidence of continuous naltrexone from the Medisorb Naltrexone microspheres, with higher exposure to naltrexone compared to that from oral naltrexone, the Applicant was asked to conduct in vitro CYP inhibition studies. Alkermes conducted these studies using fluorogenic substrates, and found that naltrexone may not inhibit most CYP enzymes.

REVIEWER COMMENT: The use of fluorogenic substrates is not acceptable for demonstration of CYP enzyme inhibition since these are non-specific. Instead, conventional substrates are required.

Alkermes found that mild and moderate hepatic impairment did not affect pharmacokinetics of naltrexone following Medisorb Naltrexone administration. Due to the risk of bleeding following IM injection to patients with severe renal impairment and coagulopathy, pharmacokinetic data was not acquired in this population of patients. Data from population PK analyses showed that dosage adjustment is not necessary based on gender of the subject, as the pharmacokinetics were not significantly altered.

5.2 Pharmacodynamics

Doses of Medisorb Naltrexone ≥150 mg demonstrated blockade of opioid effects of hydromorphone challenge test over 28 days. Data summarized from the literature did not show reports of QT prolongation or any cardiac safety events.

5.3 Exposure-Response Relationships

No tests for an exposure-response relationship were performed.

5.4 Drug release

Alkermes assumed that drug release data obtained via sampling on Days 7 to 14 would be representative of the remaining 14 days of drug release. However, review of the data showed that 26 – 75 % of drug from various lots of Medisorb Naltrexone was released by day 14 based

on real time release methods. Hence the Applicant's assumption is not valid. Additional sampling for drug release up to 30 days may be necessary, depending on the stability of the drug in solution. Evidence of consistent product performance over 28 days is pivotal for the safety and efficacy of Medisorb Naltrexone.

5.5 Dosing interval

In the Phase II and III trials, Medisorb Naltrexone was administered ever 28 days. For ease of prescribing, the Applicant is seeking labeling for "monthly" drug administration.

Naltrexone's mechanism of action in the treatment of alcohol dependence is based on its blockade of the mu opioid receptor. Alkermes found that single and multiple doses of Medisorb Naltrexone (≥ 150 mg) block exogenously administered opioids for more than 28 days. These data were considered sufficient to support the proposed dosing interval.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Medisorb Naltrexone is a depot formulation of naltrexone. The oral formulation of naltrexone has been marketed since 1995 for the treatment of alcohol dependence, as part of an appropriate management plan for addiction. The Agency's finding of efficacy was based on trials of oral naltrexone in recently detoxified patients, or those otherwise abstinent for at least 10 days at baseline.

The proposed indication for Medisorb Naltrexone is also "treatment of alcohol dependence." The proposed Physician's Package Insert adds that "

The Applicant evaluated the efficacy of Medisorb Naltrexone included patients who were either abstinent or actively drinking at the time of study enrollment.

6.1.1 Methods

The Applicant submitted study ALK 21-003 in support of the efficacy of Medisorb Naltrexone as treatment for alcohol dependence. The Division considered submission of a single adequate efficacy study, with reference to the previous Agency finding of efficacy for oral naltrexone, acceptable for an NDA submission.

6.1.2 General Discussion of Endpoints

Historically, the efficacy evaluation in alcohol treatment studies has primarily involved alcohol consumption. Measures (counts) of how much and how frequently patients drink have been obtained. The ideal efficacy endpoint in trials of treatments for alcohol dependence is complete abstinence from drinking (i.e. zero drinks) during the treatment period. This is because sobriety is associated with maximal psychosocial functioning and physical health. Also, complete abstinence from drinking is the most straightforward and easily interpreted endpoint. Complete abstinence should be sustained over the entire duration of treatment, and should be verified using biological markers of alcohol exposure.

However, it is evident that achievement and maintenance of complete abstinence is extremely difficult for most alcohol dependent patients. More commonly, patients display other patterns of drinking, including relapses, episodic heavy drinking, or frequent but reduced alcohol intake. Additionally, there is evidence that patterns of drinking other than complete abstinence can be associated with very significant improvements in psychosocial function. Consequently, assessment of the effects of an alcohol treatment may rely on efficacy endpoints other than complete abstinence.

In the past, researchers have used endpoints such as drinks per drinking day (DDD), percent days abstinent (PDA), heavy drinking days (HDD), and percent heavy drinking days (PHDD). In addition to these consumption-related endpoints, researchers have evaluated the time to the first drinking event or heavy drinking day (i.e. time to relapse to drinking). However, until recently, the most appropriate endpoint remained unclear because it was unknown which of these "partial abstinence" endpoints correlated best with clinically relevant improvements in psychosocial functioning. Selection of the appropriate endpoint was also difficult because the endpoints did not necessarily take into account the variation in patterns of drinking over time. Nevertheless, the Division did not consider an endpoint assessing time to relapse to be salient because a delay in drinking within the time frame practical for a clinical trial (i.e. a few months) was not believed to be the most appropriate therapeutic goal.

The Division previously considered PDA to be the most reasonable endpoint for alcohol treatment trials because it captured the ideal outcome (complete abstinence), assessed the durability of a treatment's effect, and incorporated all periods of drinking. Inclusion of complete abstinence as a binary outcome (yes/no) was also recommended. Also, an analysis of treatment responders (or successes) was also desirable. A responder analysis using various definitions of a treatment responder would allow for exploration of treatment effects involving drinking patterns other than complete abstinence. A responder analysis would also allow for prediction of an individual patient's response Suggested responder definitions included "absence of heavy drinking" and drinking below the NIAAA 'safe' level of drinking (> 2 drinks/day (men) and > 1 drink/day (women)). (The NIAAA 'safe' limits are based on the epidemiological observation that the aforementioned drinking levels are associated with a lowered risk of heart disease.)

Alkermes proposed the "event rate of heavy drinking" as its primary endpoint, where an event is a drinking day on which alcohol consumption is $\geq$ 5 drinks/day (men) and $\geq$ 4 drinks/day

(women). This endpoint is based on a multiple event time analytic approach, and was selected because it evaluates both the number of drinking events and the timing of these events. Alkermes is of the opinion that, for alcohol treatments, all the drinking events and the time to each event are relevant measures of treatment response.

Following discussion with the Division, Alkermes amended its sole efficacy trial to include a responder analysis, using various categories of success where patients were classified as treatment responders depending on the number of heavy drinking days they had per month. "Heavy drinking" was defined as ≥ 4 drinks/day (women), and ≥5 drinks/day (men).

Together with the FDA, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) has sought to determine the most appropriate, empirically-based outcomes for use in trials of treatments for alcohol dependence. Especially important has been characterization of the relationship between specific amounts and frequencies of drinking, and the subsequent physical and psychosocial consequences. Such knowledge would allow for identification of the level of drinking, apart from complete abstinence, that is associated with the least amount of risk. To that end, NIAAA recently sponsored two separate investigations of existing data on alcohol consumption (Project MATCH and the National Alcohol Survey (1995 and 2000)) (data not published). Project MATCH was a trial evaluating the effects of two behavioral interventions (Cognitive Behavioral Therapy (CBT) and Motivational Enhancement Therapy (MET)) on patients' drinking, social, and functioning outcomes. The National Alcohol Survey (NAS) is a nation-wide survey of alcohol use among current drinkers.

Key findings from the re-analysis of the Project MATCH data were:

- Following 3 months treatment with behavioral intervention, 30% of patients are able to achieve complete abstinence from any drinking up to 1 year later.
- Sustained absence of heavy drinking (≥ 3 drinks/day (women) and 4 drinks/day (men)) was the best predictor of treatment success, as measured by a low score on a scale of drinking consequences. However, similar success was also observed among patients not drinking more than 4 (women) or 5 (men) drinks per day.
- The more often a patient experiences a heavy drinking day (e.g. 1HDD, 3 HDDs, 5-10 HDDs, 11-20 HDDs), the greater the amount of alcohol consumed and the greater the consumption-related consequences.
- Total drinks consumed and PHD are indicators of alcohol consumption that best predict drinking related problems, particularly when considering lower scores on Drinker Inventory of Consequences (DrInC) scale.

The NAS data reanalysis showed that:

- Volume and frequency of heavy drinking are important in determining the risk of meeting DSM-IV criteria for alcohol dependence.
- Previously treated or concerned drinkers who restrict their intake to no more than 2 drinks per week, and who never exceed 4 (women) or 5 (men) drinks per day have a low risk of alcohol dependence or abuse.

- The single best criterion for non-consequential drinking is never exceeding daily heavy drinking levels.

Essentially, the Project MATCH and NAS re-analyses both concluded that the general population and the treated/concerned alcohol patients can safely drink up to 2 drinks per day (men) and 1 drink per day (women) if they never exceed a limit of 4 drinks (men) or 5 drinks (women) during the treatment or observation period.

Based on these findings, the Division now considers a responder analysis using absence of heavy drinking (≥ 4/5 drinks per day) as the optimal definition of treatment success. This definition and analyses were utilized in the review of the Applicant's efficacy trial. The results were compared to those obtained using the slightly more stringent definition of heavy drinking, ≥ 3/4 drinks per day

6.1.3 Study Design

Study ALK21-003 was a randomized, double-blind, and placebo controlled trial in adults who met DSM-IV criteria for alcohol dependence, were either abstinent from or actively drinking at baseline, and whose treatment goal was either complete abstinence or occasional alcohol use. Patients were treated with study drug (Medisorb Naltrexone (190-mg or 380-mg) or placebo) for 6 months.

The Medisorb Naltrexone doses comprised microspheres of naltrexone and polylactide-co-glycolide (PLG) suspended in aqueous diluent. The 190-mg dose was suspended in 2-mL of diluent, and the 380-mg dose in 4-mL of diluent. To maintain the blind, subjects in the placebo group were randomly assigned to placebo 2-mL or placebo 4-mL.

Data on alcohol use was collected at each clinic visit using the Time Line Follow Back (TLFB) method. Laboratory testing with breath alcohol concentration (BAC), carbohydrate-deficient transferrin (CDT), and γ-glutamyltransferase (GGT) was also performed for biological verification of drinking status. Clinic visits occurred weekly for the first 4 weeks, then every 2 weeks for the remainder of the trial.

The Applicant's study design is consistent with the Division's requirements and recommendations for alcohol treatment trials. Enrollment of both patients who are abstinent and patients who are actively drinking at baseline is recommended, since inclusion of only abstinent patients may select for those individuals who are able to stop drinking and have a lower level of dependence, thereby biasing the study results in favor of treatment. Long durations of treatment (≥ 6 months) are required, since alcoholism is a chronic relapsing disease, and since data have shown that drinking patterns are quite variable over time. Use of a validated measure, such as the TLFB, that reliably captures day-by-day drinking data is strongly recommended. Accuracy of alcohol consumption and adherence to therapy is enhanced by frequent clinical assessments. Since patients' self-report of alcohol use is subject to recall bias, biological verification of reported alcohol use is also necessary.

In study ALK21-003, the TLFB data were the primary source of drinking status information. Drinking status was to be verified using biological markers (specifically, BAC and CDT). BAC testing was done prior to obtaining TLFB information, and only patients with a BAC level of zero were allowed to provide drinking data. Because an elevation in CDT reflects heavy drinking, therefore this information could be used to confirm that patients were accurately/truthfully reporting drinking less than 4 or 5 drinks per day. However, CDT is limited in its utility because it does not give information to pinpoint when or how frequently the heavy drinking occurred. The Applicant did not explain how CDT levels would be used to reconcile reported drinking behavior.

6.1.4 Efficacy Findings

The Applicant's primary efficacy outcome was the event rate of heavy drinking ($\geq$ 4 (women) and $\geq$ 5 (men) drinks per day). The analysis was performed on all heavy drinking events captured using the TLFB measure during the treatment period (i.e. from the first treatment day up to 30 days following the last dose of study medication).

6.1.4.1 Protocol ALK21-003

(Refer to the Appendix for a detailed description of the study design, protocol amendments, statistical analyses, and study results.)

Title: A Phase III, Multi-Center, Randomized, Double Blind, Placebo Controlled Study of the Efficacy and Safety of Medisorb Naltrexone in Alcohol Dependent Adults

Subject disposition:

Overall, there were 627 subjects randomized, and 624 who took at least 1 dose of medication. The 3 subjects who were not administered any study medication were in the Medisorb Naltrexone 380-mg group and were withdrawn due to "investigator judgment."

A total of 402 patients (64%) completed treatment. Among the 222 subjects (36%) who prematurely discontinued study drug, 49 opted to continue with other aspects of the study, including provision of TLFB data: 13 in the placebo group, 14 in the Medisorb Naltrexone 190-mg group, and 22 in the Medisorb Naltrexone 380-mg group. Of those 49 subjects, 33 subsequently completed the study procedures (other than drug administration).

The Applicant was asked to tabulate patient disposition using all available data sources (e.g. termination visit sheet, adverse event sheet, drug administration sheet) in order to determine the actual reason for dropout, particularly in cases where dropout was initially listed as "lost to follow up," "investigator decision," or "other." Reclassification of the reason for dropout was to be done if necessary. Also, patients who dropped out due to events related to alcohol use (e.g. "alcoholism," "detoxification") were to be reclassified as dropping out due to lack of efficacy.

Table 6.1.4.1.a shows the patient disposition, and the reasons for early study termination. The most common reason for trial discontinuation was loss to follow up (83 patients, 13%), followed by adverse events (52 patients, 8%), withdrawal of consent (42 patients, 7%), and lack of treatment efficacy (34, 5%). More patients in the Medisorb Naltrexone 380-mg group withdrew for adverse events (13%) compared to patients in the 190-mg and placebo groups (6%, each). Twice as many placebo patients withdrew due to lack of efficacy (8%) than did patients in the Medisorb Naltrexone groups (4% each).

Table 6.1.4.1.a: Subject disposition – Treatment completion status - ALK21-003

		Placebo			Medisorb Naltrexone	
	All subjects	**2 mL**	**4 mL**	**Pooled**	**190-mg**	**380-mg**
N Randomized	627	105	104	209	210	208
N Dosed	624	105	104	209	210	205
N(%) [1] completed treatment 2	402 (64)	62 (59)	73 (70)	135 (65)	137 (65)	130 (63)
Reason [3] for discontinuation, N(%) [1]						
Lost to follow-up	83 (13)	19 (18)	9 (9)	28 (13)	31 (15)	24 (12)
Adverse events	58 (8)	7 (7)	6 (6)	13 (6)	12 (6)	27 (13)
Subject withdrew consent	42 (7)	8 (8)	5 (5)	13 (6)	14 (7)	15 (7)
Lack of efficacy	34 (5)	7 (7)	9 (9)	16 (8)	9 (4)	9 (4)
Investigator judgment	4 (1)	1 (1)	1 (1)	2 (1)	2 (1)	0
Protocol violation	2 (0)	0	0	0	2 (1)	0
Other [#]	5 (1)	1 (1)	1 (1)	2 (1)	3 (1)	0

[1] Percentages are out of number of subjects dosed
[2] Includes Subject 214-013 who missed one injection and enrolled to ALK21-003EXT
[3] Reason for discontinuation was reclassified using all applicable information on each subject
[#] "Other" includes: incarceration (n = 2); too far out of dosing window to receive an injection (n = 3)

(Source: Applicant's Table 1.1.1, Applicant's July 29 2005 response to an Information Request, P. 6)

Extent of exposure/Dosing information

Of the 624 patients treated with study drug, 410 patients (64.3%) were administered all 6 six doses. The percentage of subjects who took all 6 doses was similar across treatment groups (approximately 64%). Due to the long-acting properties of Medisorb Naltrexone, exposure was expected to last approximately 1 month after dosing. Therefore, subjects who took all 6 doses were exposed for 24 weeks.

Among the 223 subjects who did not receive all 6 doses, 57 subjects (9.1%) received 1 dose; 68 (10.9%) received 2; 36 (5.8%) received 3; 38 (6.1%) received 4; and 24 subjects (3.9%) received 5 doses. Overall, subjects had a median of 140 days from first dose to last dose, representing an exposure of over 168 days. Some subjects had one or more late doses of study medication, resulting in a maximum of 205 days from first to last dose.

See the Appendix for a tabulation of patient exposure.

Demographics:

Baseline characteristics were similar for the 3 treatment groups. Mean age was 44.7 years with a range of 19-79 years. The proportion of males to females was approximately 2:1 for all treatment groups. Most subjects were Caucasian (83.5%).

The majority of subjects (571/624, 91.5%) reported lead-in drinking1. During the 30 days prior to the first dose, subjects reported a mean of 22.9 drinking days, and a mean of 19.5 heavy drinking days. This corresponds to 76.4% drinking days and 64.9% heavy drinking days over that one month period. Treatment goals were similar among treatment groups. Nearly three quarters of subjects reported baseline treatment goals of total abstinence (43.3%) or occasional use (30.6%). Nearly half of the subjects (48.6%) were enrolled at an addiction treatment center; 34.0% enrolled at a research center; and 17.5% enrolled at a combination addiction/research center.

The Alcohol Dependence Scale (ADS) was added to the protocol in April 2002, following initiation of enrollment. Subjects who were enrolled prior to this date did not complete the Scale, and so ADS data were collected for 306 of the 624 subjects (49%) in the ITT population. The mean ADS score among these subjects was 17.1; this score was similar among treatment groups.

The Appendix contains tables detailing the demographic and baseline characteristics of the patient population.

1 Lead-in drinking was defined as daily drinking over a pre-defined period (7 days or 30-days) before randomization

Applicant's Efficacy Analysis:

Overview:
The Applicant found that, with respect to the primary endpoint, treatment with Medisorb Naltrexone 380-mg was associated with a 25% decrease in the event rate of heavy drinking compared to treatment with placebo, and the difference was statistically significant. The event rate of heavy drinking in the 190-mg group was also less than placebo (17% less). However, this difference did not reach statistical significance. Similar results were obtained with the definition of heavy drinking was made slightly more stringent ($\geq$ 3/4 drinks per day instead of $\geq$ 4/5 drinks per day).

Among patients abstinent at baseline, the event rate of heavy drinking was even more reduced in the Medisorb Naltrexone 190- and 380-mg groups. Again, however, the difference was statistically significant only for the 380-mg group.

The effects of treatment on an individual patient basis were explored using a responder analysis. Treatment response was defined using various cut-offs of the average number of heavy drinking days per month. Alkermes found that there were more responders in the 380-mg group than in the 190-mg or placebo groups, especially at the broader (i.e. less stringent) cut-offs for treatment response.

Due to the DSI findings of protocol violations at sites 215 and 217 that could potentially have led to reporting or assessment biases, the Applicant was asked to reanalyze the efficacy data after excluding subjects from these two sites. Alkermes found that the reduction in the event rate of heavy drinking in the Medisorb Naltrexone groups was lower than that observed upon analysis of the entire database (reduction in heavy drinking compared to placebo was 6% for the 190-mg group and 12% for the 380-mg group). Alkermes considered these results to still show a positive overall treatment effect.

In summary, based on its analyses, Alkermes concluded that treatment with Medisorb Naltrexone 380-mg (but not 190-mg) is efficacious in the treatment of alcohol dependence.

Primary Efficacy Analysis: Event rate of heavy drinking

a) Medisorb Naltrexone vs. pooled placebo group

The primary efficacy analysis was performed on all heavy drinking events from the first day of treatment up to 30 days following the last dose of study drug. A heavy drinking event was defined as a day on which alcohol consumption was $\geq$ 5 drinks (men) and $\geq$ 4 drinks (women). The analysis used 8 strata corresponding to predefined factors used in the dynamic randomization: gender (male/female), lead-in-drinking (yes/no), treatment goal of abstinence (yes/no).

The table below displays hazard ratios for the event rate of event drinking for the Medisorb Naltrexone 190-mg and 380-mg groups, compared to the pooled placebo group. The table shows that, compared to placebo, treatment with Medisorb Naltrexone 380-mg was associated with a

25% decrease in the event rate of heavy drinking and this difference was statistically significant (p = 0.0123). Treatment with Medisorb Naltrexone 190-mg resulted in a 17% decrease in the event rate of heavy drinking, but this difference was not statistically significant (p = 0.744).

Table 6.1.4.1.b: Applicant's Analysis: Event rate of heavy drinking (≥ 4 drinks/day (women) or ≥ 5 drinks/day (men)) vs. pooled placebo groups – Study ALK21-003

Analysis*	Medisorb Naltrexone 190-mg vs. Placebo			Medisorb Naltrexone 380-mg vs. Placebo		
	Estimate	Hazard ratio (95% CI)	P value	Estimate	Hazard ratio (95% CI)	P value
Stratified by 8 strata	-0.186	0.83 (0.68, 1.0)	0.0744	-2.87	0.75 (0.60, 0.94)	0.0123

* Not adjusted for baseline percent heavy drinking
(Source: Applicant's ALK21-003 Study Report, Appendix Tables, Table 14.2.1, P. 39)

The effect of placebo volume on the event rate of heavy drinking was also evaluated. The difference between the 2-mL and the 4-mL placebo group with respect to the event rates of heavy drinking was not statistically significant, regardless of which stratification method was utilized. The Applicant concluded that since the two placebo groups had comparable outcomes, it was reasonable to pool them when comparing the effects of treatment with Medisorb Naltrexone.

REVIEWER COMMENT: On its face, this method to evaluate the effect of placebo volume on the primary efficacy outcome appears reasonable, and use of the pooled placebo groups for comparison of efficacy is acceptable.

c) Imputing Heavy Drinking Days for Missing Data

Alkermes constructed a sensitivity analysis for the event rate of heavy drinking, in which missing data during the middle of the study (i.e., between randomization and discontinuation) were imputed as heavy drinking days. A total of 136 applicable drinking days were imputed to a heavy drinking day: 21 in the placebo group, 64 in the Medisorb Naltrexone 190 mg group, and 51 in the Medisorb Naltrexone 380 mg group. Alkermes found statistically significant reductions with Medisorb Naltrexone 380 mg versus placebo. These results were similar to those of the primary efficacy analysis in which no imputation strategy was implemented for missing data.

REVIEWER COMMENT: Data missing due to premature withdrawal from the study (i.e. prior to Day 168) were not imputed as heavy drinking days. As already shown, 222 patients discontinued treatment prematurely, and these patients' missing days of data were not accounted for in the Applicant's sensitivity analysis. Therefore, this was neither an adequate nor an appropriate strategy to evaluate the effect of missing data on the efficacy results.

Supplemental analyses of the primary efficacy endpoint, event rate of heavy drinking

a) Sensitivity analysis of the definition of heavy drinking

The rate of heavy drinking was reanalyzed using a modified definition of heavy drinking (≥4 drinks/day for males and ≥3 drinks/day for females). The event rate of heavy drinking was calculated using the pooled placebo group for comparison. Results for this analysis were similar to those of the primary analysis: there was a 20% decrease in the event rate of heavy drinking in the Medisorb Naltrexone 380-mg group compared to placebo, and this difference was statistically significant. The 190-mg group had an 7% decrease in the event rate of heavy drinking which did not reach statistical significance.

Table 6.1.4.1.c: Applicant's Analysis: Event rate of heavy drinking - Alternate definition of heavy drinking (≥ 4/3 drinks per day)

Medisorb Naltrexone 190-mg vs. Placebo			Medisorb Naltrexone 380-mg vs. Placebo		
Estimate	Hazard ratio (95% CI)	P value	Estimate	Hazard ratio (95% CI)	P value
-0.075	0.928 (0.768,1.120)	0.4222	-0.222	0.801 (0.656,0.978)	0.0292

(Source: Applicant's ALK21-003 Study Report, Appendix Tables, Table 14.2.8.1, P. 75)

b) Controlling for baseline percent heavy drinking

The primary efficacy endpoint was re-calculated after controlling for heavy drinking at baseline (baseline was defined as 30 days prior to the first drug dose). The analysis showed that patients in the Medisorb Naltrexone 380 mg group experienced a 25% reduction in the event rate of heavy drinking compared with subjects in the placebo group ($p = 0.0047$). That is, the hazard ratio of the event rate of heavy drinking for the 380-mg group vs. the placebo group was 0.748. Patients in the Medisorb Naltrexone 190 mg group showed a 14% reduction in the event rate of heavy drinking compared with subjects in the placebo group (hazard ratio 0.861) that was not statistically significant ($p = 0.1060$).

When baseline heavy drinking was re-defined as daily heavy drinking during the 7 days prior to randomization, the results for the Medisorb Naltrexone 380-mg group were greater: there was a 36% decrease in the event rate of heavy drinking (hazard ratio 0.638) compared to treatment with placebo which was statistically significant ($p < 0.001$).

FDA Requested Analyses

a) Responder Analysis

Alkermes conducted a responder analysis using different definitions (or categories) of a treatment responder. Response (or treatment success) was based on the extent to which patients could refrain from heavy drinking, where heavy drinking was defined as ≥ 5 drinks/day (men) and ≥ 4 drinks/day (women). The average monthly proportion of responders in each treatment group was calculated, and the proportions in the Medisorb Naltrexone groups compared to those in the pooled placebo group. The results are shown below:

Table 6.1.4.1.d Applicant's Analysis: Responder Rates – ALK21-003

Post-Baseline[1] Heavy Drinking Days per Month[2]	N(%) All	Placebo	190mg	380mg	P-Value* 190mg vs. Placebo	380mg vs Placebo
All Subjects	N=611	N=204	N=206	N=201		
0	86 (14%)	23 (11%)	29 (14%)	34 (17%)	0.3938	0.1026
0-1	165 (27%)	44 (22%)	53 (26%)	68 (34%)	0.3217	0.0058
0-2	205 (34%)	56 (27%)	68 (33%)	81 (40%)	0.2205	0.0063
0-3	248 (41%)	68 (33%)	83 (40%)	97 (48%)	0.1442	0.0022
0-4	289 (47%)	84 (41%)	95 (46%)	110 (55%)	0.3133	0.0063

[1] Drinking data up to 30 days after the last dose.
[2] Heavy Drinking Days per Month = (Percent Heavy Drinking Days*30.4)/100.
* Chi-Square test.

(Source: Applicant's Table 25, Clinical Study Report ALK21-003, P. 92)

REVIEWER COMMENT:
The table above presents response rates on an "average number of heavy drinking days per month" basis, and shows the proportion of patients in each treatment arm that met varying cut-offs of monthly average number of heavy drinking days. Acritical limitation of the Applicant's analysis is that it is based on observed data only. No imputations were made for missing data, including data missing following premature discontinuation from the trial. Additionally, this analysis did not require that patients never exceed the specified number of heavy drinking days in a given month; instead, all of the patients' heavy drinking days during the observation period were divided by 30 to calculate an "average monthly number of heavy drinking days."

The difference in the proportions of responders between the Medisorb Naltrexone 190-mg and placebo groups was numerically small and not statistically different at any definition of treatment success (i.e. cut-off for average number of heavy drinking days per month).

While there were more Medisorb Naltrexone 380-mg patients (17%) than placebo patients (11%) who showed a sustained absence of heavy drinking over the treatment period (i.e. 0 average monthly heavy drinking days), this difference was not statistically significant. Among persons who averaged up to 1 heavy drinking day per month (i.e. up to 6 heavy drinking days, on average, during the treatment period), the difference between the Medisorb Naltrexone 380-mg and placebo groups was numerically large and reached statistical significance. Similar results were observed at the higher cut-offs of monthly average number of heavy drinking days.

Although these findings may suggest a beneficial treatment effect, it is important to keep in mind that the results of the Project MATCH and NAS re-analyses showed a greater likelihood of adverse drinking-related consequences when patients display drinking patterns

other than a sustained absence of heavy drinking over the course of therapy. Therefore the most relevant results of this analysis are the results of the first row in the table ("0 post-baseline heavy drinking days per month"): a numerically small and statistically non-significant difference between Medisorb Naltrexone 380-mg and placebo with respect to the proportion of patients who averaged no heavy drinking days each month.

c) Event rate of any drinking over the 24-week period
The Division also requested that the Applicant calculate the event rate of any drinking, regardless of quantity. Alkermes found that, in the overall population, there was no significant difference in the event rate of any drinking between either of the 2 Medisorb Naltrexone doses and the pooled placebo group.

After reanalyzing the data based on pre-randomization drinking behavior, the Applicant showed that for both the 190-mg and the 380-mg groups, prior abstinence (i.e. abstinence 7 days prior to randomization) was associated with a considerable decrease in the event rate of any drinking. Treatment with 190-mg was associated with a 79% decrease in the event rate of any drinking compared to placebo (hazard ratio 0.21; $p = 0.002$). Patients in the 380-mg group showed a 70% decrease in the event rate of heavy drinking (hazard ratio 0.30; $p = 0.008$).

Efficacy re-analyses following the findings of the DSI inspection

As described in Section 4.4, the Division of Scientific Investigations (DSI) noted protocol violations at all 4 of the sites inspected. Violations that could potentially impact the efficacy data were noted at two sites: 215 and 217. The specific violations were collection of drinking data and conduct of psychosocial treatment by the same person, as well as collection of drinking data and performance of safety evaluations by the same person. These violations could have biased the efficacy data in that patients might have been motivated to report less drinking to the behavioral therapist who was recording their drinking patterns. Also, the behavioral therapist could have reported less drinking for individuals they suspected to be in the active treatment group. Based on the inspection findings, DSI recommended that data from patients at sites 215 and 217 be excluded from the efficacy analysis.

At the Division's request, the Applicant conducted additional analyses of the event rate of heavy drinking and the proportions of treatment responders, after excluding sites 215 and 217 from the dataset. Alkermes concluded that the results were consistent with the findings from the original NDA analyses, and argued against exclusion of the sites. As further support of this argument, Alkermes provided testimony from a well-known researcher in alcohol dependence as well as evidence from a published study that stated that having the same person collect the drinking and conduct the psychosocial therapy should not negatively impact the data or introduce bias.

Key findings from the Applicant's re-analyses are summarized below. See the Statistical Review for a detailed discussion of the re-analyses.

a) *Table 6.1.4.1.e Event rate of heavy drinking, Anderson-Gill stratified analysis – Including results of the original NDA submission and results after excluding sites 215 and 217*

	Hazard ratio (95% CI)	p-value
Medisorb Naltrexone 190-mg vs. Placebo		
Original NDA	0.830 (0.677, 1.018)	0.0744
Excluding sites 215 and 217	0.941 (0.754, 1.175)	0.5931†
Medisorb Naltrexone 380-mg vs. Placebo		
Original NDA	0.751 (0.600, 0.940)	0.0123*
Excluding sites 215 and 217	0.879 (0.687, 1.125)	0.3050†

† Re-randomization p-value could not be calculated
* Unadjusted

REVIEWER COMMENT: The table shows that, when sites 215 and 217 are excluded, the reduction in the event rate of heavy drinking for the 190-mg group changes from 17% to 6%, neither of which is statistically significant. The reduction in the event rate of heavy drinking for the 380-mg group decreased from 25% to 12%. The p-value for the 12% reduction in the event rate of heavy drinking did not reach statistical significance.

b) *Table 6.1.4.1.f Responder analysis, heavy drinking days per month[1] - Imputing missing data as heavy drinking days, excluding sites 215 and 217*

Post-Baseline[2] Heavy Drinking Days per Month	All	N (%)			P value*	
		Placebo	190 mg	380 mg	190mg vs. placebo	380-mg vs. placebo
0	14 (3%)	2 (1%)	5 (3%)	7 (4%)	0.2553	0.0836
0-1	88 (16%)	24 (13%)	28 (15%)	36 (20%)	0.5635	0.0694
0-2	132 (24%)	38 (21%)	43 (23%)	51 (29%)	0.5473	0.0817
0-3	162 (30%)	48 (26%)	51 (28%)	63 (36%)	0.7480	0.0588
0-4	188 (35%)	57 (31%)	59 (32%)	72 (41%)	0.8500	0.0646

[1] Heavy Drinking Days per Month = (Percent Heavy Drinking Days*30.4)/100.
[2] With drinking data for at least 168 days. Missing data was imputed as heavy drinking days.
* Chi-Square test.

REVIEWER COMMENT: Compared to the results of the original NDA analysis, the proportions of treatment responders, regardless of the cut-off for treatment response, are lower across all treatment groups (refer to Table 6.1.4.1.e). With respect to the proportions of patients who had an average of zero heavy drinking days per month, fewer than 5% of patients in each treatment group were able to achieve this level of reduced drinking (compared to 11% to 17% in the original NDA calculation). The proportions of these treatment responders in the Medisorb Naltrexone groups were not statistically different from the proportion of placebo responders.

Across the other less stringent, definitions of treatment success (i.e. > 0 heavy drinking days per month), the differences in the response rates between the Medisorb Naltrexone 190-mg and placebo groups were numerically small and not statistically significant. With respect to the 380-mg group, there were more responders at the other cut-offs for treatment response compared to the placebo group (differences of 7% to 10%), but these were not statistically significant.

Of note, the Applicant calculated response frequencies using *at least* 168 days (i.e. 24 weeks) of data for each patient. In the study, drinking data was to be collected for each day since the clinic visit. Patients who had their last assessment later than scheduled (i.e. more than 28 days since the last dose) would therefore contribute more days of drinking data than patients who attended the last assessment on time. Since, on a pharmacological basis, Medisorb Naltrexone is not considered to be efficacious beyond 28-31 days post- dose, any drinking data collected beyond 168 days would not be expected to be reflective of drug efficacy. Thus, per the Applicant's analysis, patients who had more than 168 days of data and drank on one or more occasions beyond Day 168 might be "unfairly" classified as a non-responder.

Reviewer's Efficacy Analysis:

As discussed in Section 6.1.2, based on the recent analyses of the NAS and Project MATCH data, the best empirically supported definition of treatment success is sustained absence of heavy drinking over the treatment duration, where heavy drinking is defined as ≥ 4 drinks/day for women, and ≥ 5 drinks/day for men. The Division is interested in the effects of treatment on an individual patient level, and not only in group mean changes. This kind of information can be obtained using a responder analysis, in which the proportions of treatment successes are compared.

The Division reanalyzed the Applicant's data, performing responder analyses based on both the "≥ 4/5 drinks/day" and "≥ 3/4 drinks per day" definitions of heavy drinking. The effect of baseline abstinence from any drinking on efficacy was also explored. In addition, given that it might take some time for patients to respond to therapy and therefore experience early lapses, a grace period was incorporated in the analysis. Data were presented using cut-offs for the average monthly number of heavy drinking days, as well as the actual number of heavy drinking days per month. A reanalysis of the Applicant's primary endpoint, the event rate of heavy drinking, was also done using the alternate definition of heavy drinking, ≥ 3/4 drinks per day.

One of the key issues in the efficacy analysis was how missing data were handled. Missing data were not a factor in the primary analysis, the event rate of heavy drinking. However, they were important to consider for the responder analysis. An imputation strategy was necessary for data missing due to patients discontinuing the trial prior to the Day 168 termination date, not just to days missing during the middle of the study (i.e., between randomization and discontinuation). With this method, patients contribute the same number of days of data to the analysis (i.e. 168). Responder analyses were conducted in which a heavy drinking day was imputed for all missing data points.

Following the report of protocol violations at sites 215 and 217, the Division requested re-analyses of the primary efficacy endpoint (the event rate of heavy drinking) and on the responder analyses, in order to assess the effect of excluding data from the two sites on these outcomes.

Dr. Dionne Price, the Statistical Reviewer, performed all of the efficacy analyses.

Overview:

The Division found that, with respect to the optimal efficacy endpoint, the proportion of patients who are able to sustain an absence of heavy drinking, when data from all randomized patients are included, and missing days are imputed as heavy drinking days, there is no significant numerical or statistical difference between the Medisorb Naltrexone groups and the placebo group. This was true regardless of whether heavy drinking was defined as ≥ 4/5 drinks/day or ≥ 3/4 drinks/day.

However, among patients who were completely abstinent from drinking 7 days prior to treatment, the proportions of treatment successes were considerably greater in the Medisorb Naltrexone groups than in the placebo group. Since there were only 53 patients abstinent at baseline, the results of this analysis cannot be used to make definitive conclusions about the efficacy of Medisorb Naltrexone in this sub-group of alcohol dependent patients.

A 2-month grace period was incorporated into the responder analysis. The grace period was incorporated to allow for early lapses back to drinking –naltrexone has been shown to decrease the craving and reinforcing effects of alcohol. Therefore, patients may sample drinking early, but gradually learn to discontinue sampling because the reward effects have been reduced. Incorporation of the grace period into the analysis showed that the differences in responder rates were even larger for patients abstinent at baseline. Again, however, the small size of patients in this sample limits the conclusions that can be made about the effects of Medisorb Naltrexone.

Given the Division's finding of a greater proportion of treatment responders in patients abstinent at baseline, as well as the Applicant's finding of a very large reduction in the event rate of heavy drinking in this sub-group, it was considered that perhaps the Applicant's result of a positive effect of Medisorb Naltrexone 380-mg on the event rate of heavy drinking was actually being driven by the efficacy of the drug in the abstinent-at-baseline patients. Therefore the event rate of heavy drinking was re-calculated for patients *not abstinent* at baseline. The analysis showed that neither the 190-mg nor the 380-mg dose produced a statistically significant reduction in the event rate of heavy drinking.

After consideration of the type and severity of protocol violations at sites 215 and 217, it was concluded that exclusion of data from these sites was not indicated, and that conclusions regarding efficacy were to be based on the entire efficacy database.

Reviewer's Responder Analysis – Actual number of heavy drinking days per month

The Applicant's responder tables were based on different definitions of responders, depending on the cut-off of the average number of heavy drinking days per month. This method, however, does not capture the actual number of heavy drinking days per month. Therefore the responder analysis was repeated where patients were considered responders based on whether or not they were able to have no more than 0,1,2,3 or 4 heavy drinks for each of the 6 months of treatment. Again, heavy drinking days were imputed for all missing data, and the two different definitions of a heavy drinking day were utilized.

This analysis differs from the one above in that a subject with 2 heavy drinking days in the observation period would be considered a non-responder at the 0-1 level if these drinking days both occurred in the same month. The analysis above represents an "average," or essentially the "total number of heavy drinking days/6 months"

1. *Responder analysis: Actual number of heavy drinking days each month. (Heavy drinking is defined as ≥ 4/5 drinks per day and all missing data were imputed as HDDs)*

As expected, there was no change in the results with respect to the proportions of patients who had no heavy drinking days during each month of treatment. Otherwise the results were not dissimilar from those shown in Table 6.1.4.1.j, with greater proportions of patients meeting the definition of treatment responder at higher cut-offs for allowable HDDs per month.

Table 6.1.4.1.g: Responder analysis: Actual monthly heavy drinking days (HDDs), where heavy drinking is defined as ≥ 4/5 drinks per day

Actual number of HDDs each month	Placebo (n=204)	Medisorb Naltrexone		P - value	
		190 mg (n=206)	380 mg (n=201)	190 mg vs. placebo	380 mg vs. placebo
0	11 (5%)	15 (7%)	14 (7%)	0.4325	0.5107
0-1	24 (12%)	27 (13%)	29 (14%)	0.6806	0.4269
0-2	30 (15%)	38 (18%)	45 (22%)	0.3086	0.0466
0-3	34 (17%)	44 (21%)	51 (25%)	0.2261	0.0315
0-4	41 (20%)	48 (23%)	60 (30%)	0.4315	0.0233

2. *Responder analysis: Actual number of heavy drinking days each month, including a 2-month grace period. (Heavy drinking is defined as ≥ 4/5 drinks per day and all missing data were imputed as HDDs)*

A 2-month grace period was incorporated into the analysis to allow for the possibility of early drinking lapses and the need for time for the drug to take effect. The table below shows that allowing for a grace period increases the proportions of patients who were able to completely refrain from drinking heavily during each of month of the study (i.e. had 0 heavy drinking days per month). However, the differences across groups were negligible, both numerically and statistically. The greatest differences in treatment responders were noted at the higher cut-offs of treatment response (e.g. 3+ heavy drinking days per month, or 18+ heavy drinking days during the treatment period). However, this finding is of limited clinical value, given the high likelihood of drinking-related consequences associated with this pattern of drinking.

Table 6.1.4.1.h: Responder analysis: Actual monthly heavy drinking days (HDDs), including a 2-month grace period

Actual number of HDDs each month	Placebo (n=204)	Medisorb Naltrexone		P - value	
		190 mg (n=206)	380 mg (n=201)	190 mg vs. placebo	380 mg vs. placebo
0	22 (11%)	25 (12%)	26 (13%)	0.6675	0.5031
0-1	36 (18%)	37 (18%)	39 (19%)	0.9338	0.6492
0-2	47 (23%)	51 (25%)	61 (30%)	0.6834	0.0963
0-3	52 (26%)	59 (29%)	70 (35%)	0.4728	0.0406
0-4	56 (28%)	65 (32%)	79 (39%)	0.3625	0.0114

Reviewer's Responder Analysis – Patients abstinent from drinking at baseline

Per the Applicant's own analysis, a greater proportion of patients who were abstinent from drinking at baseline showed a reduction in any drinking compared to patients who were not abstinent. Also the difference in the event rate of any drinking during the treatment period was significantly greater for the Medisorb Naltrexone groups than the placebo group. This suggested that drinking status at baseline was a key determinant of treatment efficacy.

It was theorized that perhaps a difference across groups in sustained absence of heavy drinking over the study duration could not be shown because all 168 treatment days were included in the analysis. The majority of patients (91%) were drinking at study onset, with a substantial proportion of subjects experiencing heavy drinking at baseline. These patients may have been unable to reduce their drinking to no more than 3 or 4 drinks per day during the initial weeks of the study. Consequently, if all 168 days are considered in the responder analysis, hardly any patients would qualify as treatment successes early in the study.

A responder analysis was therefore performed among patients who were abstinent at baseline, with and without incorporation of a grace period of 2 months (this grace period was arbitrarily selected). The number of abstinent patients was small (n = 53), hence definitive conclusions cannot be made from these analyses.

3. *Responder analysis, patients abstinent at baseline: Actual number of heavy drinking days each month, (Heavy drinking is defined as ≥ 4/5 drinks per day; all missing data were imputed as HDDs)* -,

Among patients abstinent at baseline, more than three times as many patients in the Medisorb Naltrexone groups than in the placebo group (35% vs. 11%) were able to refrain from drinking heavily during each month of the study. At this definition of treatment response, the proportion of responders in the Medisorb Naltrexone patients is more than double that in the combined abstinent/non-abstinent population.

At less stringent definitions of treatment response (e.g. 2+ HDDs per month, or 12+ HDDs during the treatment period), upwards of 70% of patients in the Medisorb Naltrexone 380-mg group were responders, compared to 40% of the placebo group. At these cut-offs, the differences between the two groups was statistically significant. However, the less stringent definitions of response are also the least clinically meaningful.

Table 6.1.4.1.i: Responder analysis, patients abstinent at baseline - Actual monthly heavy drinking days (HDDs), where HDD is ≥ 4/5 HDDs per day

Actual number of HDDs each month	Placebo (n=18)	Medisorb Naltrexone		P - value	
		190 mg (n=17)	380 mg (n=17)	190 mg vs. placebo	380 mg vs. placebo
0	2 (11%)	6 (35%)	6 (35%)	0.1212	0.1212
0-1	5 (28%)	9 (53%)	9 (53%)	0.1288	0.1288
0-2	6 (33%)	10 (59%)	12 (71%)	0.1303	0.0275
0-3	7 (39%)	10 (59%)	12(71%)	0.2383	0.0599
0-4	7 (39%)	10 (59%)	13 (77%)	0.2383	0.0247

REVIEWER COMMENT:
The finding of a much larger proportion of treatment "successes" in patients abstinent from any drinking at baseline, and randomized to therapy with Medisorb naltrexone implies that patients abstinent at baseline may selectively be those who are able to stop drinking and/or have a lower level of alcohol dependence. The demographic data were therefore explored to ascertain whether there were considerable differences in severity of alcoholism between those abstinent and non-abstinent at baseline.

At screening, severity of alcohol dependence was determined by the Alcohol Dependence Scale (ADS). (Scores for this scale can range from 0-49, with a high score indicating severe dependence). However, this measure was an amendment to the protocol, and so not all the patients in the study were assessed/had a score.

Among the 53 patients abstinent at baseline (i.e. those who had no drinking in the 7 days prior to randomization/treatment), 23 had an ADS score. Of these, the ADS scores ranged from 11-42. The number of patients with a specific ADS score was as follows:

ADS score	# Patients	ADS score	# Patients
11	3	22	1
12	3	24	1
16	2	25	1
17	2	27	3
19	1	34	1
20	1	38	1
21	2	42	1
		NR	30

NR = no score recorded

Severity of alcohol dependence was also estimated based on the average number of drinks in the 90 days prior to enrollment. Excluding the 7-day lead in period, those abstinent at baseline appear to have had slightly more drinks/day than those non abstinent, particularly patients in the Medisorb Naltrexone groups.

Average # drinks...	Abstinent at baseline N = 53			Not abstinent at baseline N = 571		
	PBO	190mg	380mg	PBO	190mg	380mg
During the 90 days prior to randomization	7.78	8.50	9.21	7.46	7.03	6.82
During the 90 days prior to randomization, excluding the 7-day lead in period	8.44	9.21	9.96	7.58	7.19	6.97
During the 7-day lead in period	0	0	0	6.04	5.10	5.05

I searched the 'medical history' dataset for any information regarding prior detoxification. The detoxification history was obtained from the verbatim comments in the *mxcoded.xpt* dataset. For some patients, the date of detoxification was not provided, so their detoxification was presumed to be distant to the first injection.

The available data showed that, among the patients abstinent at baseline, 20 (38%) were detoxified within days to weeks of their first dose of study drug (6 in the placebo group, 7 in the 190-mg group, and 7 in the 380-mg group). Two patients were detoxified within months of their first dose, and 1 patient reported detoxification 2 years prior to the first dose. Among patients *not* abstinent at baseline, 20 patients (3.5%) were detoxified within days to weeks of their first dose of study drug.

Overall however, the ADS data as well as the medical history information were were insufficient to provide and understanding as to whether baseline differences in severity of alcoholism explained the differences in efficacy observed between patients who were abstinent or non-abstinent at study initiation.

4. *Responder analysis, patients abstinent at baseline: Actual number of heavy drinking days each month, 2-month grace period included*

Incorporation of a 2-month grace period into the responder analysis resulted in considerably more patients in the Medisorb Naltrexone groups meeting the "zero HDDs each month" definition of a treatment responder. In this analysis, 41% of the 380-mg group and 59% of the 190-mg group were able to sustain an absence of heavy drinking, compared to 11% of the placebo group. These differences reached, or nearly reached, statistical significance. At higher cut-offs for treatment response, the proportion of responders in the placebo and 380-mg groups increased, but not in the 190-mg group.

Table 6.1.4.1.j: Responder analysis, patients abstinent at baseline - Actual monthly heavy drinking days (HDDs), where HDD is ≥ 4/5 HDDs per day; 2-month grace period included

Actual number of HDDs each month	Placebo (n=18)	Medisorb Naltrexone		P - value	
		190 mg (n=17)	380 mg (n=17)	190 mg vs. placebo	380 mg vs. placebo
0	2 (11%)	10 (59%)	7 (41%)	0.0030	0.0599
0-1	5 (28%)	10 (59%)	9 (53%)	0.0636	0.1288
0-2	7 (39%)	10 (59%)	12 (71%)	0.2383	0.0599
0-3	8 (44%)	10 (59%)	12 (71%)	0.3949	0.1183
0-4	8 (44%)	10 (59%)	14 (82%)	0.3949	0.0204

Reviewer's Analysis: Event rate of heavy drinking (≥ 4/5 drinks per day) in patients *not abstinent* at baseline

The Reviewer's responder analysis suggests that Medisorb Naltrexone is most efficacious in patients who are abstinent at baseline. Also, Applicant's found a much lower event rate of heavy drinking in abstinent patients compared to the entire study sample (see "Applicant's efficacy analysis: supplemental analyses of the primary efficacy endpoint"). Thus, to evaluate whether the Applicant's finding of a positive treatment effect was driven by the effect in the abstinent patients, the event rate of heavy drinking was recalculated for patients *not* abstinent at baseline.

The recalculation showed that among the non-abstinent patients, treatment with Medisorb Naltrexone 190-mg resulted in a 6% decrease in the event rate of heavy drinking, compared to placebo. Treatment with 380-mg was associated with a 17% decrease in the event rate of heavy drinking. Neither finding reached statistical significance.

Table 6.1.4.1.k: Event rate of heavy drinking (≥ 4/5 drinks per day) in patients *not abstinent* at baseline

	Estimate	Hazard ratio	Unadjusted p-value	Adjusted p-value
190 mg vs. placebo	-0.061	0.941	0.5685	0.5685
380 mg vs. placebo	-0.192	0.826	0.1105	0.2211

Efficacy re-analyses following the DSI findings of protocol violations

The results of the reanalysis (following exclusion of the 2 sites where violations were noted) of the primary endpoint, the event rate of heavy drinking, and of the responder analysis are briefly described under "Applicant's Efficacy Analysis" (see above). A more detailed description of the Applicant's reanalysis can be found in the Statistical Review.

Overall, unlike the Applicant, the Division found that with respect to the primary efficacy endpoint, exclusion of the sites resulted in a lower reduction in the event rate of heavy drinking between the 190-mg and 380-mg Medisorb Naltrexone groups compared to the placebo group. These differences were not statistically significantly different. Therefore, contrary to the Applicant, the Division found that exclusion of the two sites caused the study to "fail" on its primary endpoint.

With respect to the comparison of treatment response, the Division found that the Applicant's own reanalysis showed that there were much fewer treatment responders when sites 215 and 217 were excluded compared to the number calculated by the Division. This was because Dr. Price conducted a slightly different responder analysis from the Applicant, in which only 168 days of data were included for each patient, with days missing data imputed as heavy drinking days. (In its reanalysis, the Applicant included *at least* 168 days of data for each patient. This resulted in some patients contributing more than 168 days of data, with imputation missing days as heavy

drinking days. Thus, the Applicant's approach is more stringent and likely to result in fewer persons meeting criteria for treatment response.)

Table 6.1.4.1.1: *Reviewer's analysis – Responder analysis: average monthly heavy drinking days, with imputation of missing days as heavy drinking days and where each patient has 168 days of data – excluding sites 215 and 217*

Average number of HDDs each month	N (%)			p-value	
	Placebo (n=178)	190 mg (n=180)	380 mg (n=174)	190mg versus placebo	380 mg versus placebo
0	10 (6%)	13 (7%)	14 (8%)	0.5359	0.3662
0-1	33 (19%)	38 (21%)	41 (24%)	0.5417	0.2475
0-2	42 (24%)	46 (26%)	56 (32%)	0.6667	0.0723
0-3	51 (29%)	55 (31%)	66 (38%)	0.6932	0.0646
0-4	60 (34%)	64 (36%)	75 (43%)	0.7133	0.0699

The Reviewer's analysis above differs from the Applicant's in that there were more treatment responders in each group, for every definition of treatment response. Similar to the Applicant, the Reviewer's analysis showed that as the cut-offs for treatment response became less stringent, the proportions of responders increased, with numerically more responders in the Medisorb Naltrexone 380-mg group than in the placebo group. There were no considerable numerical differences in response rates between the 190-mg and the placebo group.

As regards the proportion of patients who averaged zero heavy drinking days per month, the proportions of responders were low and comparable across the treatment arms: 6% in the placebo group, 7% in the 190-mg group, and 8% in the 380-mg group.

Overall, the differences in the proportions of responders in the active and placebo groups did not reach statistical significance for any of the definitions of treatment response.

Dr Price also calculated the response rates for only patients abstinent at baseline, excluding sites 215 and 217. Similar to what was found in the analysis of the entire efficacy dataset, the reanalysis showed that treatment response was dramatically increased among patients who were abstinent at the beginning of the study, at each definition of treatment response. It is important to note, however, that the absolute numbers of patients abstinent at baseline (n = 47) and of treatment responders (n = 13) were small. The response rates must therefore be interpreted with caution.

REVIEWER COMMENT ABOUT THE IMPACT OF THE DSI FINDINGS:
Ultimately, the re-analyses efficacy following exclusion of sites 215 and 217 showed that neither dose of Medisorb Naltrexone was more efficacious than placebo with respect to reducing the event rate of heavy drinking, or with respect to the current optimal definition of treatment response (absence of heavy drinking during the treatment period). The re-analyses suggested, as did the original NDA analyses, that Medisorb Naltrexone is only efficacious in patients who are *abstinent at the initiation of therapy.*

Given these findings, I considered whether or not exclusion of the data from the two sites, as recommended by DSI, was indeed warranted. After reviewing the type and severity of the protocol violations, I concluded that exclusion was not indicated for several reasons. First, to exclude the sites would be to assume that they were the only locations at which the noted violations occurred, which is unlikely. Furthermore, if the violations were common across all sites, one would either have to discard the results from the entire study or else assume that having the same person perform the efficacy and safety assessments systematically introduced a bias in favor of the active treatment group. Again, this is unlikely given that the therapists/data collectors were blinded to patients' treatment assignment. Also, the study was not structured such that patients would feel compelled to report better drinking behavior than was actually experienced.

Consequently, perhaps the best statement that can be made about the protocol violations is that it appears that across the study, some individuals occasionally had their drinking data collected by their behavioral therapist, or by the person performing the safety assessments. Presumably these sorts of violations occurred similarly across all locations, and did not systematically occur in favor of the treatment group. Thus, conclusions about efficacy may be based upon the entire dataset, without exclusion of information from sites 215 and 217.

6.1.5 Clinical Microbiology

The manufacturing and packaging process Medisorb Naltrexone comprises [redacted]

The Microbiology Review Team was consulted regarding sterility issues related to Medisorb Naltrexone. Preliminary review found that the NDA contained insufficient information regarding:

- [redacted]

This information is necessary to determine the extent, if any, of microbial and/or endotoxin contamination of the drug product. Therefore the Applicant was asked to provide additional information addressing these concerns. The additional information was found to satisfactorily show the adequacy of the product from the standpoint of product quality microbiology.

6.1.6 Efficacy Conclusions

The Applicant used a relatively novel efficacy analysis and endpoint, the event rate of heavy drinking, to evaluate the effect of treatment with Medisorb Naltrexone in patients with alcohol dependence. The analytical method had some limitations, most importantly how missing data were handled (see Dr. Price's review for a detailed discussion of the analytical approach). Additionally, the endpoint is a group mean outcome, and does not provide information on the effects of treatment on an individual patient level. Finally, the clinical relevance of a reduction in the "event rate" of heavy drinking is not easily interpretable and therefore its utility in clinical practice is uncertain.

Hence, the Division focused its evaluation of the efficacy of Medisorb Naltrexone on the most recently defined, and best empirically supported, definition of treatment response: absence of heavy drinking during the treatment period, where heavy drinking is defined as $\geq$ 4/5 drinks per day. The Division's analysis found that neither the Medisorb Naltrexone 190-mg nor the 380-mg groups showed a difference in the proportion of responders compared to the placebo group.

However, at broader definitions of treatment response (i.e. 1+ heavy drinking days during the treatment period), there were numerical increases in the proportions of responders in the treatment groups, with a greater difference between the 380-mg and placebo arms, compared to the 190-mg and placebo arms.

Furthermore, an exploration of efficacy in the small sub-group of patients abstinent at baseline showed a great increase in the proportion of responders (approximately 5 times the percentage o responders, compared to that in the "all comers" analysis). The response rates were even higher when a 2-month grace period was incorporated into the analyses. These exploratory data suggest that Medisorb Naltrexone is efficacious primarily in patients who are abstinent at baseline. However, it must be kept in mind that patients abstinent at baseline may selectively be those who are able to stop drinking and/or have a lower level of alcohol dependence. Therefore, in these patients, study results may be biased in favor of treatment. Additional larger studies in patients abstinent at baseline would be required to explore this further.

Ultimately, the Division's analyses are evidence of a pharmacological effect of treatment with Medisorb Naltrexone in patients with alcohol dependence. However, the effect is difficult to explain clinically: while there was a positive result with respect to the event rate of heavy drinking (particularly for the 380-mg dose), the actual number of patients who were able to sustain non-risky patterns of drinking was small and not considerably different across treatment arms. Thus the data are not overwhelming for a clinically relevant effect of Medisorb Naltrexone (either 190-mg or 380-mg) as a treatment for alcohol dependence.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

In support of this New Drug Application, Alkermes is relying in part on the Agency's previous finding of safety of oral naltrexone. Additional safety information on naltrexone is based on a synopsis of the post-marketing experience with oral naltrexone, as well as summaries of and datasets from trials using both oral and Medisorb Naltrexone.

The Applicant's summarized 22 published trials (20 randomized studies and 2 open-label studies) in patients with alcohol dependence that were conducted between 1992 and 2004. Alkermes focused the literature review on common adverse effects of oral naltrexone, as these would be used in the determination of causality of adverse effects observed using Medisorb Naltrexone.

Alkermes also summarized the published studies that describe the effect of oral naltrexone on the liver. The current product label for oral naltrexone contains a boxed warning regarding the potential for hepatotoxicity with naltrexone treatment. The warning stems from the observation of elevated transaminases following treatment of obese patients with high doses (300-mg/day) of oral naltrexone. Other serious adverse events noted in post-marketing data of oral naltrexone are suicide-related events (e.g. suicide, suicidal ideation, attempted suicide, and depression). Suicide is of concern among naltrexone-treated patients because the antagonist effects of the drug at the mu opioid receptor may cause dysphoria and/or other mood changes leading to suicide. Nevertheless, regardless of treatment with naltrexone, suicide-related behaviors are not uncommon among patients with alcohol and other substance abuse disorders. Also, a causal relationship between suicide and treatment with naltrexone has not been established.

Ultimately, then, the major safety concerns for this review are whether treatment with Medisorb Naltrexone is associated with a risk of hepatocellular injury and suicide. Also of interest are any new risks specific to the formulation and route of administration of the drug.

With respect to the Medisorb Naltrexone trials, data collection on adverse events began after receipt of the first dose of study drug and continued until at least 30 days after administration of the last dose of study drug. Ascertainment of adverse events was done using open-ended questions. For study ALK21-003, AE data were collected for 6 weeks, and for studies -001, -002, -004, -005, and -009 AE data were collected for at least 8 weeks after the last dose was given. AEs were coded using MedDRA version 4.1.

Alkermes analyzed and presented the results of Medisorb Naltrexone safety data by duration of treatment exposure. Overall, this sub-categorization of the study types is acceptable.

Clinical pharmacology studies (1-4 months):
This group comprised studies ALK21-001, ALK21-004, ALK21-005, and ALK21-009. All were single-dose trials (~ 1 month exposure). Studies -001 and -005 were conducted in healthy volunteers; study ALK21-004 was conducted in healthy non-dependent opioid users; and study ALK21-009 was conducted in volunteers with mild-moderate hepatic impairment. With the exception of ALK21-009, all studies were blinded. Although ALK21-004 was blinded, it was uncontrolled.

Studies in alcohol dependent patients (4-6 months' exposure):
This group included studies ALK21-002, ALK21-003, and ALK21-006. ALK21-002 and -003 were double blind and placebo controlled studies in patients with alcohol dependence. These two studies differed in duration (4 vs. 6 months, respectively) and Medisorb Naltrexone dose: patients in ALK21-002 were treated with 400-mg, whereas patients in ALK21-033 were administered either 190-mg or 380-mg.

ALK21-006 was an open-label trial of oral naltrexone and Medisorb Naltrexone 380-mg in patients with mixed alcohol-opioid dependence or alcohol dependence only. At the time of the data cut-off, primarily 6-month interim data were available. Therefore, information from patients dosed up to 6 months is included in this grouping.

Studies in patients with alcohol and/or mixed dependence (> 6 months' exposure):
Three studies comprise this group: ALK21-006, ALK21-003-EXT and ALK21-010. The latter two studies were open label trials of at least 1 year duration and enrolled patients with alcohol dependence. At the data cut-off date, ALK21-010 was ongoing, and only interim data were available. Data from patients in ALK21-006 who were dosed for more than 6 months are also included.

Study ALK21-00-6EXT was not included in the database since no patients had been enrolled by the data cut-off date.

This safety review is based upon Alkermes' analyses, as well as additional analyses conducted using the following ISS datasets:

- Adverse events dataset: iss-ae.xpt, iss-ae-3.xpt
- Discontinuations due to adverse events: aediscon.xpt
- Injection site reactions dataset: iss-isr-xpt, iss-ae.xpt
- Laboratory dataset: iss-labs.xpt, iss-labhz.xpt
- Demographics, dosing and disposition dataset: iss-subj.xpt

Summary of safety findings
The safety data show that the risk of mortality following treatment with Medisorb Naltrexone is low, and comparable to that of placebo (0.4% vs. 0%). Patients died from variable causes:

pancreatic cancer, homicide, coronary atherosclerosis, and completed suicide. Only the completed suicide was suggestive of an association with Medisorb Naltrexone treatment.

The data suggest that Medisorb Naltrexone may have allergic potential. There were two types of serious adverse reactions consistent with an allergic response: eosinophilic pneumonia and a local hypersensitivity reaction at the injection site, with subsequent tissue necrosis. Other non-serious adverse reactions suggestive of an allergic response were eosinophilia, urticaria, angiodema, and inflammatory-type injection site reactions. The data in the NDA do not allow for elucidation of the underlying mechanism for these reactions, nor do they definitively identify risk factors for these reactions to Medisorb Naltrexone. The data suggesting an allergeneity of Medisorb Naltrexone are greatest for the adverse events of urticaria and angioedema.

Additional potential serious risks of Medisorb Naltrexone therapy are suicidal ideation and suicide attempt.

There were no serious episodes of hepatotoxicity. Medisorb Naltrexone treatment was associated with eleveated liver function tests, with similar proportions as those treated with oral naltrexone reporting these events.

Common adverse effects of Medisorb Naltrexone treatment were similar to those of oral naltrexone, including nausea, vomiting, headache, dizziness, and somnolence. Of note, there were cases of protracted nausea and vomiting that resulted in hospitalization for severe dehydration. Other common adverse effects of Medisorb Naltrexone that have not been previously described with oral naltrexone were asthenia, arthralgia, and muscle cramps.

There were no cases of overdose with Medisorb Naltrexone. However, there were reports of non-fatal opioid overdose in opioid abusers who were injected with Medisorb Naltrexone.

7.1.1 Deaths

7.1.1.1 Deaths in published oral naltrexone studies

Alkermes found no deaths reported in the published trials of oral naltrexone.

7.1.1.2 Deaths in Medisorb Naltrexone studies

The initial NDA safety database showed 4 deaths. An additional 1 death was reported during in the Safety Update, thus bringing the total number of deaths in trials using Medisorb Naltrexone to 5 (5/1232, 0.40%). Information regarding these deaths was obtained from patient narratives, Case Report Forms (CRFs), and the Integrated Summary of Safety (ISS) adverse event data set.

All of the five deaths occurred in patients with alcohol dependence and in patients treated with Medisorb Naltrexone (4/1049, 0.38%). Two of the patients who died had less than 6 months' of drug exposure, while the remaining three patients had greater than 6 months of study treatment.

The causes of deaths were completed suicide (n = 2), as well as homicide, pancreatic cancer, and coronary atherosclerosis (n = 1 each)[2]. One suicide occurred in a 56 year old male with whom a previous history of depression and suicidal ideation. The other suicidie occurred in a 52 year old male who also had depression. Given these pre-existing risk factors for suicide, an alternate cause of the death other than treatment with study drug cannot be ruled out. Narratives of the other deaths do not suggest a relationship to study drug. The death narratives are located in the Appendix.

Two of the deaths (Subjects ALK21-003-214-019 and ALK21-003-224-012) occurred during controlled clinical trials. Since both of these deaths were in patients treated with Medisorb Naltrexone, the percentage of deaths in the Medisorb Naltrexone group was 0.38% (4/1049), compared to 0% (0/227) in the placebo group. This difference is not clinically significant.

Three of the 4 deaths occurred more than 30 days after dosing and have an alternate possible explanation other than treatment with Medisorb Naltrexone. The remaining death (Subject ALK21-006-239-012) occurred within 30 days of dosing and, following an autopsy, was deemed not to be drug-related.

Overall, therefore, the data suggest that treatment with Medisorb Naltrexone does not confer a greater risk of death than treatment with placebo.

7.1.2 Other Serious Adverse Events (SAEs)

7.1.2.1 SAEs in oral naltrexone studies

I reviewed the product label for oral naltrexone and found that, in the two 12-week placebo-controlled trials upon which the efficacy and safety of oral naltrexone for alcohol dependence were determined (i.e. the two NDA efficacy supplement trials), patients reported no serious adverse events after treatment with 50 mg/day.

7.1.2.2 SAEs in Medisorb Naltrexone studies

7.1.2.2.1 APPLICANT'S ANALYSIS: SAEs IN STUDIES OF 4-6 MONTHS' EXPOSURE

A total of 1090 patients participated in the studies of 4-6 months' exposure (studies ALK21-002, ALK21-003, and ALK21-006). Alkermes found that in total, 6.8% of patients (71/1049) experienced at least one SAE. None of the patients in ALK21-002 who were randomized to treatment with Medisorb Naltrexone 400-mg experienced an SAE. Therefore, all of the SAEs in the Medisorb Naltrexone group occurred in patients enrolled in studies ALK21-003 and -006.

2 Subject ALK21003-214-019, homicide; Subject ALK21003-224-012, suicide; Subject ALK21003-215-009, pancreatic cancer; Subject ALK21006-239-012, coronary atherosclerosis; Subject ALK21-010-214-008, suicide

The proportion of reported SAEs in the Medisorb Naltrexone group was 6.7% (54/811), and this was comparable to the proportion in the placebo group (7.0%, 15/214). The risk of an SAE was greater for patients treated with Medisorb Naltrexone 380-mg (7.6%, 44/576) than for patients treated with 190-mg (4.8%, 10/210), and only slightly higher than for placebo patients (7.0%, 15/214).

The most frequently reported SAEs were "alcoholism" (23/1049, 2.2%), followed by suicidal ideation, suicide attempt, overdose, pneumonia, detoxification, alcohol withdrawal syndrome, and chronic obstructive airways disease (0.19%, 2/1049, each). Based on its calculations, the Applicant considered the risks of these specific SAEs to be similar across the dose groups.

> REVIEWER COMMENT: Based upon the patient narratives, patients coded as experiencing "alcoholism" actually experienced worsening of their alcohol use and/or underwent supervised detoxification. These experiences are not adverse events, but are more reflective of lack of efficacy of study drug treatment.

7.1.2.2.2 APPLICANT'S ANALYSIS: SAEs IN STUDIES OF >6 MONTHS' EXPOSURE

Altogether, 572 patients in studies ALK21-003-EXT and ALK21-010 were dosed, 36 of who were administered oral naltrexone 50 mg/day. Among these patients, 4.9% (28/572) experienced at least one SAE. The frequency of reported SAEs was slightly higher in the 190-mg Medisorb Naltrexone group (9.6%, 15/157) than in the 380-mg group (2.9%, 11/379) and the oral naltrexone group (5.6%, 2/36).

The most frequently occurring AEs were "alcoholism" (0.5%, 3/572), followed by suicidal ideation and chest pain (0.3%, 2/572). The frequency of alcoholism was greatest in the 190-mg Medisorb Naltrexone group (1.9%, 3/157) than in the 380-mg group (0%, 0/379). The frequency of the other SAEs was similar across the treatment groups.

> REVIEWER COMMENT: Again, "alcoholism" was miscoded as an adverse event. Also, although more patients in the 190-mg group reported more SAEs than patients in the 380-mg group, this result appears to have been due to the higher incidence of worsened drinking and/or detoxification, and not to more occurrences of actual adverse events.

7.1.2.2.3 REVIEWER'S ANALYSIS: SAEs IN STUDIES OF 4-6 MONTHS' EXPOSURE

I reanalyzed the type and frequency of SAEs by study duration and treatment assignment. I also evaluated the Sponsor's summary of SAEs, the adverse event datasets, and the patient narratives for specific SAEs of concern, namely SAEs related to suicide, hepatic disorders, and injection site reactions. In addition, these data sources were reviewed for unusual or unexpected SAEs. Lastly, I provided patient narratives for SAEs that suggest a relationship with active treatment. A list of all SAEs in the trials of 4-6 months' exposure is found in Table 7.1.2.2.3.

Similar to the Applicant, I found that there were 71 patients in these studies who experienced an SAE, none of whom was enrolled in ALK21-002. The most frequently occurring SAE was

"alcoholism." The placebo group had the highest frequency of this SAE (3.3%), followed by the oral naltrexone group (3.1%), the Medisorb Naltrexone 190-mg group (2.4%) and lastly the 380-mg group (1.6%). Review of the CRFs and patient narratives showed that events coded as "alcoholism" were actually worsening of alcohol consumption and/or admission for detoxification. Of note, the CRFs and narratives corresponding to the SAEs "detoxification", and "alcohol withdrawal syndrome" also described increased alcohol use and/or the need for detoxification. As already discussed, these events are more indicative of a lack of treatment efficacy than of an adverse effect of drug therapy.

Following alcoholism, suicide-related events were the next most common SAEs. The frequency of suicide-related AEs was highest in the oral naltrexone group (1.5%), followed by the Medisorb Naltrexone 380-mg group (1.4%), the Medisorb Naltrexone 190-mg group (1%), and the placebo group (0%). However, when patients with depression were removed from the analysis, the frequency of suicidal AEs became highest in the Medisorb Naltrexone 380-mg group. Suicidal ideation was the most commonly reported type of suicide-related SAE.

Although injury was the 3rd most often reported SAE, it was less common in the Medisorb Naltrexone patients (~ 2%) than in the oral naltrexone or placebo patients (~ 3 % each).

Table 7.1.2.2.3: Reviewer's Analysis: Serious Adverse Events (SAEs) in studies of 4-6 months' duration (ALK21-002, -003, and -006)

SOC	PT	Medisorb Naltrexone						Oral NTX N = 65		Placebo N = 214	
		190 N = 210		380 N = 576		All Doses [1]					
		N	%	N	%	N	%	N	%	N	%
Psychiatric disorders	*Alcohol exacerbation - total*	6	2.86	12	2.08	18	2.22	2	3.08	7	3.27
	Alcoholism	5	2.38	9	1.56	14	1.72	2	3.08	7	3.27
	Alcohol withdrawal syndrome	1	0.48	1	0.17	2	0.25	0	0	0	0
	Detoxification NOS	0	0	2	0.35	2	0.25	0	0	0	0
	Suicide-related AEs	0	0	8	1.39	8	0.99	1	1.54	0	0
	Suicidal ideation	0	0	3	0.52	3	0.37	0	0	0	0
	Suicide attempt	0	0	2	0.35	2	0.25	0	0	0	0
	Depression	0	0	0	0	0	0	1	1.54	0	0
	Non-accidental overdose	0	0	1	0.17	1	0.12	0	0	0	0
	Overdose NOS	0	0	2	0.35	2	0.25	0	0	0	0
	Drug dependence [2]	0	0	2	0.35	2	0.25	0	0	0	0
	Agitation	0	0	1	0.17	1	0.12	0	0	0	0
	Delirium	0	0	1	0.17	1	0.12	0	0	0	0
	Insomnia	0	0	1	0.17	1	0.12	0	0	0	0
	Emotional disturbance NOS Emotional distress	0	0	1	0.17	1	0.12	0	0	1	0.47
	Psychotic disorder NOS	0	0	0	0	0	0	0	0	1	0.47
Gastrointestinal disorders	Reflux esophagitis Gastro-esophageal reflux disease	0	0	2	0.34	2	0.24	0	0	0	0
	Rectal hemorrhage Gastrointestinal hemorrhage NOS	0	0	2	0.34	2	0.24	0	0	0	0
	Hemorrhoids	0	0	1	0.17	1	0.12	0	0	0	0
	Constipation	0	0	1	0.17	1	0.12	0	0	0	0
	Perirectal abscess	0	0	1	0.17	1	0.12	0	0	0	0

[1] Comprises patients treated with 190- and 380-mg. There were no patients in the 400-mg group (study ALK21-004) who experienced an SAE.
[2] Detoxification for cocaine

Table 7.1.2.2.3: Reviewer's Analysis: Serious Adverse Events (SAEs) in studies of 4-6 months' duration (ALK21-002, -003, and -006) (continued)

SOC	PT	Medisorb Naltrexone						Oral NTX N = 65		Placebo N = 214	
		190 N = 210		380 N = 576		All Doses [1]					
		N	%	N	%	N	%	N	%	N	%
Injury, poisoning and procedural complications	*Injury - total*	1	0.48	2	0.34	3	0.36	0	0	1	0.47
	Lower limb fracture NOS	0	0	1	0.17	1	0.12	0	0	0	0
	Head injury	1	0.48	0	0	1	0.12	0	0	0	0
	Spinal fracture NOS	0	0	1	0.17	1	0.12	0	0	0	0
	Jaw fracture	0	0	0	0	0	0	0	0	1	0.47
Cardiac disorders	Myocardial infarction	0	0	1	0.17	1	0.12	0	0	0	0
	Chest tightness	0	0	1	0.17	1	0.12	0	0	0	0
	Atrial fibrillation; Atrial fibrillation aggravated	0	0	1	0.17	1	0.12	0	0	1	0.47
General disorders and administration site conditions	Injection site necrosis	0	0	1	0.17	1	0.12	0	0	0	0
	Fatigue	0	0	0	0	0	0	0	0	1	0.47
Nervous system disorders	Ischemic stroke NOS	0	0	1	0.17	1	0.12	0	0	0	0
	Monoplegia	0	0	1	0.17	1	0.12	0	0	0	0
	Convulsions NOS	0	0	1	0.17	1	0.12	0	0	0	0
Infections and infestations; Respiratory, thoracic and mediastinal disorders	Interstitial pneumonia; Pneumonia NOS; Eosinophilic pneumonia acute	1	0.48	2	0.34	3	0.36	0	0	1	0.47
Musculoskeletal and connective tissue disorders	Lumbar disc lesion; Intervertebral disc herniation	0	0	1	0.17	1	0.12	0	0	1	0.47

Table 7.1.2.2.3: Reviewer's Analysis: Serious Adverse Events (SAEs) in studies of 4-6 months' duration (ALK21-002, -003, and -006) (continued)

SOC	PT	Medisorb Naltrexone						Oral NTX N = 65		Placebo N = 214	
		190 N = 210		380 N = 576		All Doses [1]					
		N	%	N	%	N	%	N	%	N	%
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Laryngeal cancer NOS; Inflammatory carcinoma of the breast	1	0.48	0	0	1	0.12	0	0	1	0.47
Respiratory, thoracic and mediastinal disorders	Chronic obstructive airways disease	0	0	2	0.35	2	0.25	0	0	0	0
Blood and lymphatic system disorders	Cervical adenitis	0	0	1	0.17	1	0.12	0	0	0	0
Hepatobiliary disorders	Cholelithiasis	1	0.48	0	0	1	0.12	0	0	0	0
Pregnancy, puerperium and perinatal conditions	Abortion missed	0	0	1	0.17	1	0.12	0	0	0	0

SAEs after excluding patients who experienced hospitalization for alcoholism

Appendix 10.3 shows the results of this analysis. After removing the reports of alcohol-related SAEs from the analysis, I found that there were 47 patients who had an SAE. Psychiatric SAEs were most frequently reported. In particular, suicide-related SAEs occurred with greatest frequency in the Medisorb Naltrexone 380-mg patients (1.4%) than in the placebo patients (0%). Serious injury was relatively infrequent (0.4% of all patients), and the risk of this SAE was similar across treatment groups. The risk of the other reported types of SAEs was either no higher or less for the active groups than the placebo group.

7.1.2.2.3.1 Depression- and Suicide-related SAEs – Studies of 4-6 months' exposure

Together, depression and suicide-related SAEs (suicide attempt, suicidal ideation, and overdose) were the next most commonly occurring SAEs after "alcoholism" (i.e. lack of efficacy). I counted 9 patients who experienced suicide-related SAEs. The oral naltrexone group had the highest proportion (1.5%), followed by the Medisorb Naltrexone 380-mg group (1.4%). No suicide related SAEs occurred in patients treated with 190-mg or placebo.

The patient narratives show that the majority of the suicide-related SAEs occurred in patients with a previous history of depression and/or anxiety. Therefore, it is possible that the events are related to the patients' underlying mood disorder, or even to their substance dependence. However, given that there were no suicide related SAEs reported in the low-dose Medisorb Naltrexone or placebo groups, an association with Medisorb Naltrexone 380-mg cannot be ruled out. Narratives for suicide related AEs are provided in the Appendix:

The association between study treatment and suicide-related AEs (both serious and non-serious) is discussed further in Section 7.1.3.3.

7.1.2.2.3.2 Serious injection site reactions (ISRs) – Studies of 4-6 months' exposure

There was one (1) patient who suffered a serious ISR following treatment with study drug (Medisorb Naltrexone 380-mg):

Subject ALK21-006-246-013 – Injection site reaction/tissue necrosis
This is a 35-year-old female with no known allergies. She received her first and only dose of Medisorb Naltrexone 380-mg for treatment of alcohol dependence on [redacted] On that same day, the patient noted swelling and erythema which progressed. On 27 October she was experiencing induration, redness and tenderness at the injection site. The patient was prescribed antibiotics but the symptoms/signs did not improve. At the scheduled November 6th clinic visit, the injection site reaction was ongoing, and the patient had an elevated white count. Because of the reaction, the subject discontinued participation in the study.

On November 14 ultrasound showed a fluid collection which was aspirated and was negative on culture. Her white count was 15.6 with 12% eosinophils. On [redacted] approximately 43 days after the initial injection), the patient was admitted to the hospital for treatment with IV antibiotics for presumed

infection. On admission, she had a 10x20 cm erythematous swelling on the right hip/buttock with a 2x2cm central eschar. She was afebrile with a white count was 19.9 with 4.77% eosinophils. Cutaneous punch biopsy was performed, and results were consistent with a hypersensitivity reaction (e.g. lymphoeosinophilic infiltrate). A CT scan showed an area of inflammatory stranding/edema extending along the right lower flank subcutaneous tissue for approximately 12 cm. Allergy consultation concluded that the inflammation was due in part to an allergic response to the depot naltrexone injection.

Bedside incision and debridement was unsuccessful (the wound continued to have necrotic edges), therefore on [redacted] he patient underwent wide local excision in the operating room. Approximately 20x15 cm of necrotic tissue from the area surrounding the injection site was removed. It was necessary to excise very near the right hip and joint capsule to remove all of the necrotic tissue. Tissue pathology revealed a 13 x 11 x 9 cm area of fat necrosis. The patient was discharged on [redacted] with acetaminophen and ibuprofen for pain control.

REVIEWER COMMENT:
The patient's signs and symptoms, as well as the timing of the events strongly indicate an allergic/hypersensitivity reaction to the Medisorb Naltrexone. StuThe incidence and severity of the reaction is alarming because, due to the depot formulation, treatment with Medisorb Naltrexone cannot be discontinued once the dose is given. Removal of exposure to the drug can occur only with gradual degradation of the microspheres or, perhaps, with surgical excision of the injected material.

The occurrence of injection site reactions (both serious and non-serious) following study treatment is discussed further in Section 7.1.3.3.

7.1.2.2.3.3 Serious cases of Pneumonia – Studies of 4-6 months' exposure

Pneumonia was the third most common SAE. A total of 4 patients (3 in the Medisorb Naltrexone arm and 1 in the placebo arm) reported pneumonia. Pneumonia is not uncommon among alcoholic patients. Typically, their addiction has caused them to be under-nourished and susceptible to infection. In addition, aspiration pneumonia can also occur.

Although serious cases of pneumonia were more common in the placebo group (0.5%) than in the Medisorb Naltrexone (0.3%) and oral naltrexone (0%) groups, two cases in the Medisorb Naltrexone group were particularly unusual, and without a clear alternate cause: eosinophilic pneumonia (Subject ALK21003-211-021) and interstitial pneumonia (subject ALK21003-212-020):

ALK21-003-211-021 [redacted] Eosinophilic pneumonia
This is a 61-year-old male with a history of sulfa allergy and alcohol dependence who was given his first dose of Medisorb Naltrexone (380 mg) on [redacted] 03. Concomitant medications included His second dose was given on [redacted] and required 3 attempts and a second vial of study medication. That same day, the subject experienced dizziness and blurred vision about which resolved within hours. Over the next 3 days the subject developed general malaise, myalgias, low-grade temperature, burning on urination, cough and pleuritic chest pain. On [redacted] (3 days after the 2nd injection), the subject was hospitalized for presumed pneumonia. He was discharged 2 days later, but developed increasing dyspnea and was readmitted later that day. A chest CT showed diffuse, patchy, ground-glass opacities. Peripheral

white blood cell count was 11,200 with 15% eosinophils. Bronchoscopy with bronchial lavage revealed a white blood cell count of 330 with 65% eosinophils. Testing for parasites was negative. Treatment was begun with intravenous steroids. He improved and was discharged from hospital on [redacted] 10 days after the 2nd injection) on oral steroids and oxygen. Follow-up eosinophil counts were normal on April 8 2003 (1.2%) and May 6 2003 (2.6%). This subject did not receive any further injections after his second dose. He continued participation in all other aspects of the study, and completed the study on 24 September 2003.

REVIEWER COMMENT: The patient's symptoms and signs are consistent with drug-induced eosinophilic pneumonia. This type of pneumonia results from a hypersensitivity reaction to drug exposure.

ALK21-003-212-020/ [redacted] "Interstitial pneumonia"
The subject is a 45-year-old male with a history of asthma, seasonal allergies, eczema, and alcohol dependence. He was given his first dose of Medisorb Naltrexone 380-mg on [redacted] and his third on [redacted] On [redacted] he presented to an urgent care center describing an approximately 1 week history of cough, malaise, and increasing shortness of breath. He reported that a chest x-ray showed bilateral pulmonary infiltrates with hypoxemia, and that he was sent home on oral antibiotics.

His symptoms continued to worsen, and on [redacted] he presented to a hospital emergency room for evaluation. He had marked hypoxemia (62% oxygen saturation on room air), WBC of 13.8 with 7.1% eosinophils, and diffuse bilateral pulmonary infiltrates on chest x-ray. Chest CT showed mediastinal and hilar lymphadenopathy and diffuse ground glass opacities bilaterally. He was admitted to the ICU; the interval from the first dose of study drug until the hospital admission was 67 days. The differential diagnosis included infectious pneumonia, ARDS, or allergic drug reaction. The subject was empirically treated with antibiotics as well as with corticosteroids, bronchodilators, intravenous ranitidine, and diphenhydramine. Sputum culture taken on admission eventually showed scant yeast.

The subject was discharged on [redacted], on steroids and antibiotics. No further study drug was administered. However, the subject continued participation in all other aspects of the study. Prednisone therapy was continued for 2 months. At follow-up with the subject's physician in February 2003, physical examination was normal but the eosinophil count remained elevated at 8.1%. The subject completed the study on May 6. 2003.

REVIEWER COMMENT: The patient's symptoms and test findings are also suspicious of an allergic reaction to study treatment, namely eosinophilic pneumonia. Although the patient had taken 3 doses of Medisorb Naltrexone prior to developing symptoms, drug-induced lung disease can occur after repeated exposure. The patient's response to steroid therapy is also consistent with an allergic reaction.

Together, these two cases are suspicious for an allergic potential of Medisorb Naltrexone, with the possibility of serious and life-threatening respiratory effects.

7.1.2.2.4 REVIEWER'S ANALYSIS: SAEs IN STUDIES OF > 6 MONTHS' EXPOSURE

Studies ALK21-006, ALK21-010 and ALK21-003-EXT were included in this sub-grouping. For studies ALK21-006 and -010, the SAE data are included for only those patients with drug exposure of more than six months by the data cut-off date. None of the studies had a placebo arm; therefore a comparison of the frequency of AEs in treated vs. untreated patients was not possible.

Like the Applicant, I found that 28 patients experienced a total of 33 SAEs (see Table 7.1.2.2.4). The most SAEs occurred in the Medisorb Naltrexone 190-mg group (15/157, 9.5%), followed by the oral naltrexone group (2/36, 5.6%), and then the 380-mg group (11/379, 2.9%) group. As was observed in the 4-6 month trials, the most frequently reported SAE was alcoholism/alcohol detoxification (i.e. lack of treatment efficacy) (n = 4 reports): there were 3 cases of "alcoholism" and all of them occurred in patients treated with Medisorb Naltrexone 190-mg (3/157, 1.9%); one (1) patient in the oral naltrexone group (1/36, 2.7%) was admitted for detoxification.

Suicidal ideation, chest pain, dehydration, and cholycystitis/cholelithiasis were the next most common SAEs (n = 2, each). There was one report each of pneumonia, acute hepatitis, and cellulitis. The remaining SAEs were reported in one patient each.

I reviewed the patient narratives corresponding to these SAEs, and identified those cases suggestive of a relationship to study treatment. These cases are listed below (see the Appendix for complete patient narratives):

SAEs possibly related to study treatment – Studies of > 6 months' exposure

Patient ID	Treatment dose	SAE
ALK21-006-246-001	Medisorb Naltrexone 380 mg	Suicidal ideation
ALK21-003-EXT-229-010	Medisorb Naltrexone 190 mg	Suicidal ideation
ALK21003-210-004	Medisorb Naltrexone 190 mg	Acute hepatitis
ALK21-003-EXT-214-004	Medisorb Naltrexone 190 mg	Dehydration (due to protracted emesis)
ALK21-006-231-009	Medisorb Naltrexone 380 mg	Dehydration (in the context of protracted emesis)
ALK21-006-245-028	Oral naltrexone 50 mg	Anxiety

With respect to the single report of acute hepatitis (subject ALK21003-210-004), the patient developed symptoms and signs after the twelfth (12^{th}) dose of Medisorb Naltrexone, and in the setting of resumed alcohol consunmption and Vicodin use. Therefore, it is possible that patient's signs and symptoms were due to the combination of naltrexone, alcohol, acetaminophen (present in Vicodin), all of which are known to have an effect on the liver.

The two cases of dehydration (subjects ALK21003-EXT-214-004 and ALK21006-231-009) occurred in the setting of protracted emesis. Since nausea, vomiting, abdominal pain, and decreased appetite are known adverse effects of naltrexone, it is possible that the patients' symptoms were due to Medisorb Naltrexone treatment.

REVIEWER CONCLUSION:

The data from the longer term, open label trials also show that treatment with Medisorb Naltrexone 190-mg or with oral naltrexone is associated with a greater frequency of non-efficacy that treatment with Medisorb Naltrexone 380-mg. The data also suggest that treatment with Medisorb Naltrexone may be associated with development of severe nausea and vomiting, and of hepatitis (particularly in the presence of risk factors such as hepatitis C infection and use of acetaminophen).

Table 7.1.2.2.4: Reviewer's Analysis: SAEs in studies of > 6 months' exposure

SOC	Preferred Term	Medisorb Naltrexone				Oral NTX, N = 36	
		190 mg, N = 157		380 mg, N = 379			
		N	%	N	%	N	%
Psychiatric disorders	Drug dependence; Drug abuser NOS	0	0.0	2	0.52	0	0.0
	Suicidal ideation	1	0.64	1	0.26	0	0.00
	Alcoholism; Alcohol detoxification	3	1.91	0	0.0	1	2.78
	Anxiety NEC	0	0.00	0	0.00	1	2.78
Gastrointestinal disorders	Abdominal pain NOS; Abdominal pain upper	0	0.0	2	0.52	0	0.0
	Colitis ischemic	1	0.64	0	0.00	0	0.00
Injury, poisoning and procedural complications	Road traffic accident	1	0.64	0	0.00	0	0.00
	Limb injury NOS	1	0.64	0	0.00	0	0.00
Cardiac disorders	Coronary artery atherosclerosis	0	0.00	1	0.26	0	0.00
	Cardiac failure congestive	0	0.00	1	0.26	0	0.00
	Chest pain	1	0.64	1	0.26	0	0.00
	Angina pectoris	1	0.64	0	0.00	0	0.00
General disorders and administration site conditions	Pyrexia	0	0.00	1	0.26	0	0.00
	Heat exhaustion	0	0.00	1	0.26	0	0.00
Hepatobiliary disorders	Cholecystitis acute NOS; Cholelithiasis	2	1.28	0	0.0	0	0.0
	Hepatitis acute	1	0.64	0	0.00	0	0.00
Infections and infestations	Pneumonia NOS	1	0.64	0	0.00	0	0.00
	Cellulitis	1	0.64	0	0.00	0	0.00

Table 7.1.2.2.4: Reviewer's Analysis: SAEs in studies of > 6 months' exposure (continued)

SOC	Preferred Term	Medisorb Naltrexone				Oral NTX, N = 36	
		190 mg, N = 157		380 mg, N = 379			
		N	%	N	%	N	%
Metabolism and nutrition disorders	Dehydration	1	0.64	1	0.26	0	0.00
Musculoskeletal and connective tissue disorders	Intervertebral disc degeneration NOS	0	0.00	1	0.26	0	0.00
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Pancreatic carcinoma NOS	0	0.00	1	0.26	0	0.00
Respiratory, thoracic and mediastinal disorders	Emphysema	1	0.64	0	0.00	0	0.00
Vascular disorders	Pulmonary embolism	1	0.64	0	0.00	0	0.00

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

7.1.3.1.1 Overall Profile of Dropouts - Studies of 4-6 months' duration

Table 7.1.3.1.1.a shows the subject disposition for the studies of 4-6 months' exposure. Altogether, 38.4% (419/1090) patients in this category of studies prematurely withdrew from the trials. Across all treatment groups, the most common reason for study dropout was "lost to follow up." The oral naltrexone group had the highest proportion of patients withdrawn for this reason. "Adverse events" was the next most common reason for dropout, with more patients discontinuing due to AEs in the higher dose (380/400 mg) Medisorb Naltrexone groups (12%), than in the 190-mg, placebo, or oral naltrexone groups (5-6%). "Lack of efficacy" was slightly more frequently cited among placebo patients (7%) than among the other treatment groups (4-5%).

7.1.3.1.2 Overall Profile of Dropouts - Studies of >6 months' duration

As illustrated in Table 7.1.3.1.2, approximately 39% (223/572) of patients in the studies of greater than 6 months' duration dropped out of the trials. Among all patients, the most common reasons for dropout were subject withdrawal of consent (13%), loss to follow-up (11%) adverse events (7%), and lack of treatment efficacy (7%). Whereas 10% (16/157) of patients in the Medisorb Naltrexone 190-mg withdrew due to lack of treatment efficacy, 6% (21/379) of patients treated with 380-mg, and 3% (1/36) of the oral naltrexone group dropped out for this reason. Also, the proportions of patients who discontinued due to AEs was higher in the Medisorb Naltrexone 380-mg group (8%, 31/379), compared to the 190-mg patients (4%, 7/157) and the oral naltrexone group (3%, 1/36).

Table 7.1.3.1.1: Subject disposition – Studies of 4 - 6 month's exposure

Subject Disposition in 4-6 Month Studies in Dependent Subjects

	All Subjects	Placebo ALK21-003/ALK21-002 2ml	4ml[1]	Pooled	Vivitrex 190mg ALK21-003	380mg ALK21-003	380mg ALK21-006	400mg ALK21-002	380/400mg Combined	Oral Naltrexone ALK21-006
N of Subjects Randomized	1093	105	109	214	210	208	371	25	604	65
N of Subjects Dosed	1090	105	109	214	210	205	371	25	601	65
N(%)[2] of Subjects Completed Treatment[3]	671(62)	62(59)	77(71)	139(65)	137(65)	130(63)	210(57)	20(80)	360(60)	35(54)
Reason# for Discontinuation, N (%)[2]										
Lost To Follow-Up	164(15)	19(18)	9(8)	28(13)	31(15)	24(12)	65(18)	1(4)	90(15)	15(23)
Adverse Events	100(9)	7(7)	6(6)	13(6)	12(6)	27(13)	43(12)	2(8)	72(12)	3(5)
Subject Withdrew Consent	82(8)	8(8)	6(6)	14(7)	14(7)	15(7)	30(8)	1(4)	46(8)	8(12)
Lack of Efficacy	57(5)	7(7)	9(8)	16(7)	9(4)	9(4)	19(5)	1(4)	29(5)	3(5)
Investigator Judgment	6(1)	1(1)	1(1)	2(1)	2(1)	0	1(0)	0	1(0)	1(2)
Protocol Violation	2(0)	0	0	0	2(1)	0	0	0	0	0
Other@	8(1)	1(1)	1(1)	2(1)	3(1)	0	3(1)	0	3(0)	0

SOURCE: J:\BDM\NALTREXONE\NDA\PROG\TABLES\DEV\ISS_DISP6MONTH.SAS 21JUL2005@18:44

[1] Includes 5 subjects dosed in ALK21-002.
[2] Percentages are out of number of subjects dosed.
[3] For ALK21-002 subjects who received 4 injections. For ALK21-003 study those who received 6 injections except subject 214-013 who missed one injection and enrolled to ALK21-003EXT. For ALK21-006 those who continued beyond Week 20 injection/oral dispense visit.
Reason for discontinuation was reclassified using all applicable information on each subject. See Table 2.2 for details.

(Source: Applicant's Table 2.1, Appendix1_NDA_ISS_DISP_Tables, Supplemental information received 8/3/05)

Table 7.1.3.1.2: Subject disposition – Studies of > 6 month's exposure

		Vivitrex					
		ALK21-003Ext and ALK21-010					
	All Subjects	Placebo to 190mg	190mg to 190mg	Placebo to 380mg	380mg to 380mg	ALK21-006 380mg	ALK21-006 Oral Naltrexone
N of subjects dosed	572	55	102	60	115	204	36
N (%)[1] of subjects completed	53 (9)	17 (31)	15 (15)	6 (10)	12 (10)	2 (1)	1 (3)
N (%)[1] of subjects ongoing as of 8/31/2004	296 (52)	9 (16)	32 (31)	14 (23)	35 (30)	175 (86)	31 (86)
N (%)[1] of subjects discontinued	223 (39)	29 (53)	55 (54)	40 (67)	68 (59)	27 (13)	4 (11)
Reason[2] for discontinuation, N (%)[1]:							
Subject Withdrew Consent	75 (13)	15 (27)	22 (22)	9 (15)	20 (17)	8 (4)	1 (3)
Lost To Follow-Up	64 (11)	5 (9)	16 (16)	16 (27)	18 (16)	8 (4)	1 (3)
Adverse Events	39 (7)	1 (2)	6 (6)	10 (17)	14 (12)	7 (3)	1 (3)
Lack of Efficacy	38 (7)	8 (15)	8 (8)	4 (7)	15 (13)	3 (1)	0
Investigator Judgment	4 (1)	0	2 (2)	1 (2)	0	0	1 (3)
Protocol Violation	2 (0)	0	1 (1)	0	1 (1)	0	0
Other[3]	1 (0)	0	0	0	0	1 (0)	0

SOURCE: J:\BDM\NALTREXONE\NDA\PROG\TABLES\DEV\ISS_DISPGT6MONTH.SAS 21JUL2005@16:02
[1] Percentages are out of number of subjects dosed.
[2] Reason for discontinuation was reclassified using all applicable information on each subject. See Table 3.2 for details.
[3] Subject ALK21006-253-003, reported text for reason: 'Incarcerated'.

(Source: Applicant's Table 3.1, Appendix1_NDA_ISS_DISP_Tables, Supplemental information received 8/3/05)

7.1.3.2 Adverse events associated with dropouts

In the clinical studies, the information on patients who discontinued treatment due to adverse events was collected from two separate and independent CRF forms: the Adverse Event (AE) form, and the Study Drug Summary (SDS) form. On the AE form, investigators were to indicate whether or not patients experienced an AE and if this led to study drug discontinuation or withdrawal from the study altogether. On the SDS form, investigators recorded whether patients completed all injections and if not, the reasons for lack of completion. It was noted that the investigator entries in both of these CRFs were not always consistent. Therefore, at the Agency's request, Alkermes again queried the count dataset sources (*iss_ae.xpt* or *iss_subj.xpt*) to re-calculate the total number of discontinuations by dataset. (The updated disposition data are shown in the previous tables, 7.1.3.1.1 and 7.1.3.1.2.)

Based on the re-evaluation, 4 additional patients whose AE caused them to drop out of their respective studies and who were not included in the ISS were identified[3]. Consequently there were a total of 126 dropouts due to AEs. Alkermes also noted that 10 patients, including the 4 patients incorrectly excluded from the ISS, had different disposition statuses recorded on the adverse event and study drug summary sheets of the CRFs.

Alkermes used the information from *iss_ae.xpt* and *iss_subj.xpt* to generate another dataset (*aediscon.xpt)* which listed (by study number) all subjects who discontinued due to AEs. The information in both datasets was reconciled as much as possible, particularly for the 10 cases in which there was a difference in reporting between the adverse event and study drug summary forms of the CRF. After eliminating for duplicates, the new dataset *aediscon.xpt* contained 126 subjects who discontinued because of an AE (the 122 in the original ISS, and the 4 additional patients previously not included in the ISS).

(See the Appendix for a detailed discussion of the discrepancies in the initial disposition dataset and how the Applicant resolved them.)

To identify the specific AEs that led to treatment discontinuation, and to compare these across treatment groups, I joined the *iss_ae_3.xpt* (a modified version of the original ISS adverse event dataset) and *aediscon.xpt* datasets, matching for the unique subject identification. I evaluated the disposition data for all 126 patients. The results were tabulated by study category: 4-6 months' duration vs. greater than 6 months' duration.

3 Patients ALK21-003-202-013, ALK21-003-215-029, ALK21-006-236-014, and ALK21-006-248-017.

7.1.3.2.1 ADVERSE EVENTS ASSOCIATED WITH DROPOUTS – 4 TO 6 MONTH STUDIES

Reviewer's analysis of dropouts due to AEs:

(a) Dropouts due to Adverse Events - Studies of 4-6 months' exposure

I used the information in the joined the *iss_ae_3.xpt* and *aediscon.xpt* datasets (n = 126) to determine the number of and reasons for treatment discontinuations in the 4-6 month trials. I found that there were 92 patients (92/1090, 8.4%) in the 4-6 month of trials who discontinued treatment due to an AE that occurred within the applicable evaluation period. These 92 patients included the 4 who had originally not been included in the ISS. Table 7.1.3.2.1 (next page) shows the frequency of discontinuations due to AEs by treatment group.

Across the 4-6 month trials, slightly more patients (9.3%, 76/811) in the Medisorb Naltrexone groups withdrew due to an AE than patients in the placebo group (6.5%, 14/214). However, when rates of discontinuation were compared across specific dosage groups, the most discontinuations occurred in the 380-mg group (10.4%, 60/576), followed by the 400-mg group (8%, 2/25), and the 190-mg group (6.7%, 14/210). Patients treated with oral naltrexone were least likely to withdraw because of an AE (3.1%, 2/65).

The most common reason reasons for discontinuation among all patients were injection site reactions (2%), alcoholism (i.e. lack of treatment efficacy) (1%), nausea (0.9%), pregnancy (0.6%), abnormal LFTs (0.5%), and suicide-related AEs (0.4%). AEs associated with the 380-mg dose that led to more dropouts than in placebo group included injection site reactions (3% vs. 0.5%), nausea (2% vs. 0%), pregnancy (1% vs. 0%), headache (0.5% vs. 0%), and suicide-related AEs (0.3% vs. 0%)

Overall, there was no difference between the placebo and the combined Medisorb Naltrexone groups with respect to the frequency of discontinuations due to increased LFTs (0.5% each). However, there was a markedly higher number of dropouts due reported LFT elevations in the Medisorb Naltrexone 190-mg group (1.4%) and the oral naltrexone group (1.5%) compared to the placebo group.

Treatment with Medisorb Naltrexone appears to be associated with a slightly higher rate of dropouts due to suicidal behavior compared to treatment with placebo (0.9% vs. 0%, respectively). The risk of discontinuation due to this AE did not appear to be associated with increasing dose: 1% of patients in the 190-mg group vs. 0.4% of the 380-mg group and 0% of the 400-mg group.

The risk of dropout due to depression was also slightly greater in the combined Medisorb Naltrexone groups than in the placebo patients (0.25% vs. 0%). The proportion of patients withdrawing due to depression was greatest in the oral naltrexone group (1.5%).

Of note, considerably more patients in the placebo group (1.9%) discontinued due to worsened alcoholism or alcohol withdrawal (i.e. lack of treatment efficacy) than did patients treated with

Medisorb Naltrexone (0.9%). Among the Medisorb Naltrexone patients, 1.9% of patients in the 190-mg group withdrew due to lack of efficacy, compared to 0.5% in the 380-mg arm, and 0% in the 400-mg arm. The highest rate of withdrawals due to lack of efficacy was in the oral naltrexone group (3% of patients).

Table 7.1.3.2.1.a: Most frequently reported AEs leading to treatment discontinuation – Studies of 4-6 months' duration

SOC	Preferred Term/AE	Placebo		Medisorb Naltrexone						Oral naltrexone	
				190 mg		380mg		400 mg			
		N	%	N	%	N	%	N	%	N	%
General disorders and administration site conditions	*Injection Site Reactions -Total*	*1*	*0.47*	*5*	*2.4*	*16*	*2.77*	*1*	*4*	*0*	*0.0*
	Induration	0	0.00	0	0.00	8	1.39	1	4.00	0	0.00
	Pain	1	0.47	0	0.00	3	0.52	0	0.00	0	0.00
	Edema	0	0.00	1	0.48	2	0.35	0	0.00	0	0.00
	Tenderness	0	0.00	1	0.48	1	0.17	0	0.00	0	0.00
	Bruising	0	0.00	1	0.48	0	0.00	0	0.00	0	0.00
	Burning	0	0.00	1	0.48	0	0.00	0	0.00	0	0.00
	Inflammation	0	0.00	0	0.00	1	0.17	0	0.00	0	0.00
	Necrosis	0	0.00	0	0.00	1	0.17	0	0.00	0	0.00
	Pruritus	0	0.00	1	0.48	0	0.00	0	0.00	0	0.00
Gastrointestinal disorders	*Total*	*0*	*0.0*	*2*	*0.96*	*16*	*2.76*	*0*	*0.0*	*0*	*0.0*
	Nausea	0	0.00	1	0.48	9	1.56	0	0.00	0	0.00
	Gastro-esophageal reflux disease	0	0.00	0	0.00	2	0.35	0	0.00	0	0.00
	Vomiting NOS	0	0.00	1	0.48	1	0.17	0	0.00	0	0.00
	Abdominal pain NOS	0	0.00	0	0.00	1	0.17	0	0.00	0	0.00
	Constipation	0	0.00	0	0.00	1	0.17	0	0.00	0	0.00
	Diarrhea NOS	0	0.00	0	0.00	1	0.17	0	0.00	0	0.00
	Retching	0	0.00	0	0.00	1	0.17	0	0.00	0	0.00
Psychiatric disorders	*Alcoholism -Total*	*4*	*1.87*	*4*	*1.9*	*3*	*0.52*	*0*	*0.0*	*1*	*1.54*

Table 7.1.3.2.1.a: Most frequently reported AEs leading to treatment discontinuation – Studies of 4-6 months' duration (continued)

SOC	Preferred Term/AE	Placebo		Medisorb Naltrexone						Oral naltrexone	
				190 mg		380mg		400 mg			
		N	%	N	%	N	%	N	%	N	%
Psychiatric disorders	*Other – total*	*2*	*0.94*	*2*	*0.96*	*4*	*0.68*	*0*	*0.0*	*0*	*0.0*
	Anxiety NEC	0	0.00	1	0.48	1	0.17	0	0.00	0	0.00
	Panic attack	0	0.00	1	0.48	1	0.17	0	0.00	0	0.00
	Delirium	0	0.00	0	0.00	1	0.17	0	0.00	0	0.00
	Insomnia	0	0.00	0	0.00	1	0.17	0	0.00	0	0.00
	Loss of libido	1	0.47	0	0.00	0	0.00	0	0.00	0	0.00
	Psychotic disorder NOS	1	0.47	0	0.00	0	0.00	0	0.00	0	0.00
Nervous system disorders	*Total*	*1*	*0.47*	*0*	*0.0*	*6*	*1.03*	*0*	*0.0*	*0*	*0.0*
	Headache NOS	0	0.00	0	0.00	3	0.52	0	0.00	0	0.00
	Dizziness	1	0.47	0	0.00	1	0.17	0	0.00	0	0.00
	Ischemic stroke NOS	0	0.00	0	0.00	1	0.17	0	0.00	0	0.00
	Mental impairment NOS	0	0.00	0	0.00	1	0.17	0	0.00	0	0.00
Investigations	*Abnormal LFTs Total*	*1*	*0.47*	*3*	*1.43*	*1*	*0.17*	*0*	*0.0*	*1*	*1.54*
	AST increased	0	0.00	2	0.95	0	0.00	0	0.00	0	0.00
	Liver function tests NOS abnormal	1	0.47	0	0.00	1	0.17	0	0.00	0	0.00
	ALT increased	0	0.00	1	0.48	0	0.00	0	0.00	0	0.00
	Bilirubin increased	0	0.00	0	0.00	0	0.00	0	0.00	1	1.54
Pregnancy, puerperium and perinatal conditions	*Pregnancy NOS*	*0*	*0.00*	*0*	*0.00*	*6*	*1.04*	*0*	*0.00*	*0*	*0.00*
Investigations	*Other -Total*	*1*	*0.47*	*2*	*0.95*	*2*	*0.34*	*0*	*0.0*	*0*	*0.0*
	LDH increased	0	0.00	2	0.95	0	0.00	0	0.00	0	0.00
	CPK increased	1	0.47	0	0.00	0	0.00	0	0.00	0	0.00
	Eosinophils increased	0	0.00	0	0.00	1	0.17	0	0.00	0	0.00
	Weight decreased	0	0.00	0	0.00	1	0.17	0	0.00	0	0.00

Table 7.1.3.2.1.a: Most frequently reported AEs leading to treatment discontinuation – Studies of 4-6 months' duration (continued)

SOC	Preferred Term/AE	Placebo		Medisorb Naltrexone						Oral naltrexone	
				190 mg		380mg		400 mg			
		N	%	N	%	N	%	N	%	N	%
Infections and infestations	*Total*	*1*	*0.47*	*0*	*0.0*	*4*	*0.69*	*0*	*0.0*	*0*	*0.0*
	Hepatitis C	0	0.00	0	0.00	2	0.35	0	0.00	0	0.00
	Interstitial pneumonia	0	0.00	0	0.00	1	0.17	0	0.00	0	0.00
	Pneumonia NOS	1	0.47	0	0.00	1	0.17	0	0.00	0	0.00
Psychiatric disorders	*Suicide-related Total*	*0*	*0.0*	*2*	*0.95*	*2*	*0.34*	*0*	*0.0*	*0*	*0.0*
	Suicidal ideation	0	0.00	2	0.95	1	0.17	0	0.00	0	0.00
	Suicide attempt	0	0.00	0	0.00	1	0.17	0	0.00	0	0.00
Musculoskeletal and connective tissue disorders	*Total*	*2*	*0.94*	*0*	*0.0*	*2*	*0.35*	*0*	*0.0*	*0*	*0.0*
	Arthralgia	1	0.47	0	0.00	2	0.35	0	0.00	0	0.00
	Intervertebral disc herniation	1	0.47	0	0.00	0	0.00	0	0.00	0	0.00
Psychiatric disorders	*Depression*	*0*	*0.00*	*1*	*0.48*	*1*	*0.17*	*0*	*0.00*	*1*	*1.54*
Skin and subcutaneous tissue disorders	*Total*	*0*	*0.0*	*0*	*0.0*	*2*	*0.34*	*1*	*4*	*0*	*0.0*
	Angioneurotic edema	0	0.00	0	0.00	0	0.00	1	4.00	0	0.00
	Hypotrichosis	0	0.00	0	0.00	1	0.17	0	0.00	0	0.00
	Night sweats	0	0.00	0	0.00	1	0.17	0	0.00	0	0.00
Cardiac disorders	*Total*	*0*	*0.0*	*0*	*0.0*	*2*	*0.34*	*0*	*0.0*	*0*	*0.0*
	Lightheadedness	0	0.00	0	0.00	1	0.17	0	0.00	0	0.00
	Myocardial infarction	0	0.00	0	0.00	1	0.17	0	0.00	0	0.00

Table 7.1.3.2.1.a: Most frequently reported AEs leading to treatment discontinuation – Studies of 4-6 months' duration (continued)

SOC	Preferred Term/AE	Placebo		Medisorb Naltrexone						Oral naltrexone	
				190 mg		380mg		400 mg			
		N	N	N	%	N	%	N	%	N	%
General disorders and administration site conditions	*Total*	*0*	*0.0*	*0*	*0.0*	*2*	*0.34*	*0*	*0.0*	*0*	*0.0*
	Fatigue	0	0.00	0	0.00	1	0.17	0	0.00	0	0.00
	Feeling abnormal	0	0.00	0	0.00	1	0.17	0	0.00	0	0.00
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	*Total*	*1*	*0.47*	*1*	*0.48*	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
	Inflammatory carcinoma of the breast	1	0.47	0	0.00	0	0.00	0	0.00	0	0.00
	Laryngeal cancer NOS	0	0.00	1	0.48	0	0.00	0	0.00	0	0.00
Renal and urinary disorders	*Total*	*2*	*0.94*	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
	Micturition disorder	1	0.47	0	0.00	0	0.00	0	0.00	0	0.00
	Micturition urgency	1	0.47	0	0.00	0	0.00	0	0.00	0	0.00
Respiratory, thoracic and mediastinal disorders	*Total*	*0*	*0.0*	*0*	*0.0*	*2*	*0.34*	*0*	*0.0*	*0*	*0.0*
	Dyspnoea NOS	0	0.00	0	0.00	1	0.17	0	0.00	0	0.00
	Eosinophilic pneumonia acute	0	0.00	0	0.00	1	0.17	0	0.00	0	0.00
Vascular disorders	*Hypertension NOS*	*0*	*0.00*	*0*	*0.00*	*1*	*0.17*	*0*	*0.00*	*0*	*0.00*
Blood and lymphatic system disorders	*Bone marrow depression NOS*	*0*	*0.00*	*0*	*0.00*	*1*	*0.17*	*0*	*0.00*	*0*	*0.00*
Injury, poisoning and procedural complications	*Head injury*	*0*	*0.00*	*1*	*0.48*	*0*	*0.00*	*0*	*0.00*	*0*	*0.00*

(b)Dropouts due to Adverse Events - Studies of > 6 months' exposure

I found that both the *iss_ae_3.xpt* and the *aediscon.xpt* datasets listed 34 participants in the studies of greater than 6 months' exposure who discontinued due to adverse events. However, combining these two datasets found that 2 patients in the *aediscon.xpt* dataset were not included in the *iss_ae_3.xpt* dataset[4]. Also, 2 patients in the *iss_ae_3.xpt* dataset were not listed in the *aediscon.xpt* dataset[5]. Finally, 1 patient (subject ALK21003-230-012, elevated CPK) was included in the *iss_ae_3.xpt* dataset even though this patient withdrew from study ALK21-003 after only one dose of study drug. Thus, there were a total of 35 discontinuants due to AEs in the trials of greater than 6 months' exposure.

The table that follows shows the frequency of discontinuations by type of AE, for each treatment group. Patient's treated with Medisorb Naltrexone 380-mg had the highest incidence of discontinuations due to adverse events (9.5%, 36/379), compared to the 190-mg patients (4.5%, 7/157) and the oral naltrexone patients (2.8%, 1/36).

In terms of specific AEs, injection site reactions (ISRs) were the most commonly occurring AE leading to study withdrawal (1.2%, 7/572). ISRs led to discontinuation almost twice as frequently in the Medisorb Naltrexone 380-mg group (1.6%) compared to the 190-mg patients (0.6%).

Nausea was the next most frequent reason for treatment discontinuation (0.7%, 4/572), and rates were somewhat similar across treatment groups: 0.8% of the 380-mg group, 0.6% of the 190-mg group, and 0% of the oral naltrexone patients withdrew due to nausea.

There were two patients in total (0.3%, 2/572) who discontinued to LFT abnormalities, both of whom were treated with Medisorb Naltrexone 380-mg. One patient (0.2%, 1/572), administered Medisorb Naltrexone 380-mg, ceased treatment with study drug due to elevated CPK levels.

Otherwise, there were 1 (0.2%, 1/572) to 2 (0.3%, 2/572) patients in total who withdrew due to the other specific types of AEs.

4 Patients ALK21003-217-026 (insomnia, feeling jittery) and ALK21006-241-008 (memory impairment).
5 Patients ALK21003-214-003 (exacerbation of alcohol dependence) and ALK21003-230-012 (elevated CPK)

Table 7.1.3.2.1.b: AEs leading to treatment discontinuation – Studies of > 6 months' exposure

SOC	HLT	PT	N Total	190-mg, N = 157		380-mg, N = 379		Oral, N = 36	
				N	%	N	%	N	%
General disorders and administration site conditions	*Total*		*12*	*3*	*1.92*	*9*	*2.37*	*0*	*0.0*
	Injection site reactions	*Total*	7	1	0.64	6	1.58	0	0.0
		Induration	3	0	0.00	3	0.79	0	0.00
		Pain	2	0	0.00	2	0.53	0	0.00
		Anesthesia	1	0	0.00	1	0.26	0	0.00
		Urticaria	1	1	0.64	0	0.00	0	0.00
	Febrile disorders	Pyrexia	2	0	0.00	2	0.53	0	0.00
	Asthenic conditions	Fatigue	1	1	0.64	0	0.00	0	0.00
	General signs and symptoms NEC	Influenza like illness	1	1	0.64	0	0.00	0	0.00
	Pains NEC	Pain NOS	1	0	0.00	1	0.26	0	0.00
Psychiatric disorders	*Total*		*7*	*1*	*0.64*	*6*	*1.56*	*0*	*0.0*
	Psychiatric symptoms NEC	Alcoholism	2	1	0.64	1	0.26	0	0.00
	Anxiety symptoms	Agitation	1	0	0.00	1	0.26	0	0.00
	Anxiety symptoms	Nervousness	1	0	0.00	1	0.26	0	0.00
	Emotional and mood disturbances NEC	Emotional disturbance NOS	1	0	0.00	1	0.26	0	0.00
	Parasomnias	Nightmare	1	0	0.00	1	0.26	0	0.00
	Insomnia	Insomnia	1	0	0.00	1	0.26	0	0.00

Table 7.1.3.2.1.b: AEs leading to treatment discontinuation – Studies of > 6 months' exposure (continued)

SOC	HLT	PT	N Total	190-mg, N = 157		380-mg, N = 379		Oral, N = 36	
				N	%	N	%	N	%
Gastrointestinal disorders	*Total*		*6*	*1*	*0.64*	*5*	*1.31*	*0*	*0.0*
	Nausea and vomiting symptoms	Nausea	4	1	0.64	3	0.79	0	0.00
	Gastritis (excl infective)	Gastritis NOS	1	0	0.00	1	0.26	0	0.00
	Gastrointestinal and abdominal pains (excl oral and throat)	Abdominal pain upper	1	0	0.00	1	0.26	0	0.00
Investigations	*Total*		*3*	*0*	*0.0*	*3*	*0.79*	*0*	*0.0*
	Liver function analyses	LFTs NOS abnormal	2	0	0.00	2	0.53	0	0.00
	Skeletal and cardiac muscle analyses	CPK increased	1	0	0.00	1	0.26	0	0.00
Musculoskeletal and connective tissue disorders	*Total*		*3*	*0*	*0.0*	*3*	*0.78*	*0*	*0.0*
	Intervertebral disc disorders NEC	Intervertebral disc degeneration NOS	1	0	0.00	1	0.26	0	0.00
	Muscle pains	Myalgia	1	0	0.00	1	0.26	0	0.00
	Musculoskeletal and connective tissue signs and symptoms NEC	Pain in limb	1	0	0.00	1	0.26	0	0.00

Table 7.1.3.2.1.b: AEs leading to treatment discontinuation – Studies of > 6 months' exposure (continued)

SOC	HLT	PT	N Total	190-mg, N = 157		380-mg, N = 379		Oral, N = 36	
				N	%	N	%	N	%
Nervous system disorders	*Total*		*3*	*0*	*0.0*	*3*	*0.78*	*0*	*0.0*
	Headaches NEC	Headache NOS	1	0	0.00	1	0.26	0	0.00
		Feeling jittery	1	0	0.00	1	0.26	0	0.00
	Memory loss (excl. dementia)	Memory impairment	1	0	0.00	1	0.26	0	0.00
Blood and lymphatic system disorders	*Leukocytoses NEC*	*Eosinophilia*	*2*	*0*	*0.00*	*2*	*0.53*	*0*	*0.00*
Cardiac disorders	*Total*		*2*	*0*	*0.0*	*2*	*0.52*	*0*	*0.0*
	Coronary artery disorders NEC	Coronary artery atherosclerosis	1	0	0.00	1	0.26	0	0.00
	Heart failures NEC (excl ventricular failure)	Cardiac failure congestive	1	0	0.00	1	0.26	0	0.00
Hepatobiliary disorders	Hepatocellular damage and hepatitis NEC	Hepatitis acute	1	1	0.64	0	0.00	0	0.00
Injury, poisoning and procedural complications	Overdoses	Overdose NOS	1	0	0.00	0	0.00	1	2.78
Metabolism and nutrition disorders	Appetite decreased	Appetite decreased NOS	1	0	0.00	1	0.26	0	0.00

Table 7.1.3.2.1.b: AEs leading to treatment discontinuation – Studies of > 6 months' exposure (continued)

SOC	HLT	PT	N Total	190-mg, N = 157		380-mg, N = 379		Oral, N = 36	
				N	%	N	%	N	%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Pancreatic neoplasms malignant (excl islet cell and carcinoid)	Pancreatic carcinoma NOS	1	0	0.00	1	0.26	0	0.00
Pregnancy, puerperium and perinatal conditions	Normal pregnancy, labor and delivery	Pregnancy NOS	1	0	0.00	1	0.26	0	0.00
Skin and subcutaneous tissue disorders	Urticarias	Urticaria NOS	1	1	0.64	0	0.00	0	0.00