FDA PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE MEETING

VIVITROL® (naltrexone for extended-release injectable suspension)

NDA 21-897

16 September 2010

Briefing Document/Background Package

ADVISORY COMMITTEE BRIEFING MATERIALS:
AVAILABLE FOR PUBLIC RELEASE

Alkermes, Inc.
852 Winter Street
Waltham, MA 02451

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ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
ANOVA	analysis of variance
ASI	Addiction Severity Index
AST	aspartate aminotransferase
AUC	area under the curve
BDI	Beck Depression Inventory
BMI	body mass index
CFR	Code of Federal Regulations
CGI	clinical global improvement
C_{max}	maximum plasma concentration
CNS	central nervous system
CSAT	Center for Substance Abuse Treatment
CSR	clinical study report
CYP 450	Cytochrome P450
DAWN	Drug Abuse Warning Network
DHHS	Department of Health and Human Services
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Health Disorders, 4th Edition—Text Revision
ECG	electrocardiogram
EQ-5D	Euro-QOL Health Questionnaire—5 Domains
FAS	full analysis set
FDA	Food and Drug Administration
GCP	good clinical practice(s)
GGT	gamma-glutamyl transferase
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IDC	Individual Drug Counseling
IM	intramuscular(ly)
ISR	injection site reaction
IV	intravenous(ly)
IVRS	interactive voice response system
LAAM	levo-alpha-acetylmethadol

Term	Definition
LFT	liver function test
LOCF	last observation carried forward
MADRS	Montgomery-Asberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NSDUH	National Survey on Drug Use and Health
NTX	naltrexone
PI	principal investigator
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PLG	polylactide-co-glycolide
PSUR	Periodic Safety Update Report
QOL	quality of life
QT [interval]	the time between the beginning of the QRS complex and the end of the T-wave
RAB	Risk Assessment Battery
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAMHSA	Substance Abuse and Mental Health Services Administration
SAP	statistical analysis plan
SD	standard deviation
sNDA	supplemental New Drug Application
SOC	system order class
$t_{½}$	half-life
TEAE	treatment-emergent adverse event
TLFB	Timeline FollowBack
ULN	upper limit of normal
US	United States
VAS	visual analog scale
WHO	World Health Organization

1. EXECUTIVE OVERVIEW

VIVITROL was approved in 2006 by the FDA as an extended-release formulation of naltrexone for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment. VIVITROL is administered by intramuscular (IM) injection once per month. A copy of the current approved VIVITROL package insert is provided in Appendix Section 10.1.

VIVITROL was approved by FDA as a Section 505(b)(2) NDA, meaning that it was approved on the basis of:

- the submitted VIVITROL clinical trial data;
- the published literature related to the safety and efficacy of oral naltrexone; and
- the prior determination of safety and effectiveness of oral naltrexone as evidenced by the approved NDA for oral naltrexone.

The purpose of the supplemental NDA (sNDA) under review is to obtain an additional indication—the treatment of opioid dependence (ie, an Efficacy Supplement). As with the original NDA for VIVITROL for the alcohol dependence indication, this sNDA was submitted pursuant to Section 505(b)(2) by which Alkermes is relying on the clinical studies described in the supplemental application (ALK21-013, ALK21-006, ALK21-006-EXT, ALK21-004, and preliminary data from the ongoing ALK21-021 study) as well the previous FDA determination of safety and effectiveness of oral naltrexone and published literature for the opioid indication.

This document summarizes the safety and efficacy data that support the pending Efficacy Supplement. Section 2 includes some background information on opioid dependence, and a description of the medical need for a new treatment option. Section 3 provides a description of the VIVITROL microsphere and a brief discussion of its mechanism of action, clinical pharmacology, pharmacokinetics (PK), pharmacodynamics (PD), and dose justification. An overview of the VIVITROL clinical development program is provided in Section 4. A detailed description of the pivotal efficacy study design is provided in Section 5. In Section 6 there is a discussion of the efficacy results from study ALK21-013, supportive data from US studies ALK21-006 and its extension (ALK21-006-EXT), and preliminary data from ongoing studies (ALK21-021 and Part B of the ALK21-013 study). Safety is covered in Section 7, and a discussion of the generalizability of VIVITROL program to the US population is in Section 8. A description of the VIVITROL risk/benefit profile in the opioid-dependent population is provided in Section 9.

Opioid addiction is a serious and growing problem associated with rising mortality. A recent publication from SAMHSA indicates the rate of opioid addiction continues to rise at an alarming rate [Substance Abuse and Mental Health (SAMHSA) Data Archive 2009]. Alkermes is continuing to develop medications to treat this and other addiction disorders.

While some patients are being treated for opioid dependence with the currently available products, many patients remain untreated. Two current therapies, methadone (a μ-opioid agonist) and buprenorphine (a partial μ-opioid agonist), produce physical dependence themselves. While effective, they are controlled substances with limited distribution and are

subject to abuse and diversion as well as posing risks for respiratory and CNS depression. The third available option, oral naltrexone, is an opioid antagonist and is effective, although compliance with daily administration in this population is a well described issue.

As many patients in the US with opioid dependence do not receive treatment, additional options are needed. A safe and effective long-acting opioid antagonist may represent an important alternative with meaningful public health impact. Naltrexone for extended-release injectable suspension (VIVITROL) was designed to deliver therapeutic levels of naltrexone for one month. This aspect offers significant advantages over existing therapies. Indeed, the FDA designated the VIVITROL sNDA for "priority review," the criteria for which is: "The drug product, if approved, would be a significant improvement compared to marketed products."

VIVITROL is a non-scheduled, non-narcotic, non-addictive medication administered by health care professionals via a once-per-month long-acting IM injection. Abuse and diversion are not issues as it provides no euphoria, its effects cannot be boosted and it has no street value. VIVITROL poses no risk for CNS or respiratory depression and is not associated with withdrawal symptoms when discontinued.

The IM delivery route ensures that the patient has received the medication. This provides direct assurance of treatment adherence for the patient, the patient's family members, and the health care providers.

The mechanism of action makes it suitable for patients who have medical contraindications or are philosophically opposed to agonist therapy, are strongly motivated to become abstinent or have not had sufficient duration or severity of opioid dependence to meet criteria for agonist maintenance therapy. VIVITROL is also uniquely suitable for patients whose employment or professional license prohibits agonist treatment eg, health care professionals, transportation workers, public safety officials, and military personnel.

Alkermes has conducted several VIVITROL clinical trials (see Section 4) including a large 250-patient placebo-controlled clinical study in opioid dependence (ALK21-013). The ALK21-013 study results are compelling and robust and demonstrate a consistent pattern of clinical efficacy for maintaining opioid abstinence, increasing retention in treatment, reduction in craving for opioids, and protecting against re-establishment of opioid physical dependence. This study, taken with the results and experience accumulated throughout the entire VIVITROL development program and many years of experience with oral naltrexone, demonstrates the safety and effectiveness of this product for the treatment of opioid addiction.

As noted above, the subject of the September 16th Advisory Committee meeting is the sNDA that has been submitted by Alkermes to revise the labeling of VIVITROL to include an indication to treat patients with opioid dependence. Specifically, we understand that the Division is seeking advice from the Advisory Committee concerning the results of the pivotal clinical study submitted by Alkermes (ALK21-013) and whether it provides substantial clinical evidence of safety and effectiveness. The review Division asked Alkermes to comment on the following two points in this briefing package:

- Does the single pivotal clinical study (ALK21-013) have the ability to provide substantial clinical evidence of safety and efficacy?

- Can the clinical data from the ALK21-013 study conducted in Russia be extrapolated to the intended US population?

We believe that the answers to the above two questions are yes.

Substantial Evidence

ALK21-013 is an 18-month randomized, multi-center, study conducted in 2 parts: a 6-month parallel group, placebo-controlled efficacy evaluation (Part A) followed by a 12-month open-label safety extension (Part B). The ALK21-013 clinical study enrolled patients with opioid dependence identified by DSM-IV-TR criteria — see Section 5 for more details.

The lead investigator, Dr. Evgeny Krupitsky, is an established expert in the field of opioid dependence research and treatment (see Section 5 for more details). The clinical sites where study ALK21-013 was conducted were qualified and experienced. The staffs at those sites received training and ongoing supervision and monitoring with regard to the study protocol. The protocol employed at these sites is similar to that which would be employed in the US in terms of design, diagnostic and measurement tools, psychosocial therapy, endpoints, and data analyses. The study protocol and Statistical Analysis Plan were reviewed with and found acceptable by FDA.

The study was rigorously conducted and independently monitored. Study ALK21-013, as all Alkermes clinical trials, was conducted according to the principles of Good Clinical Practice, the Declaration of Helsinki and Consolidated Guidelines approved by ICH. The study complied with FDA and ICH rules governing 'informed consent' and 'institutional (ethics committee) review.' The study was monitored by a Contract Research Organization and independently audited by Alkermes. The study was inspected by FDA investigators who found no deficiencies in the conduct of the study.

The results of the study are robust. The primary endpoint—opioid-free week response profile—was statistically and clinically significant (p=0.0002)—see Section 6. All pre-specified key-secondary and secondary endpoints—retention in treatment (p=0.0042), opioid craving (p<0.0002), positive naloxone challenge test (p=0.0154), and self-reported opioid use (p=0.0004), were statistically and clinically significant (see Table 1).

Table 1: Summary of Efficacy: ALK21-013 Study

Endpoint	**P-Value (VIVITROL vs Placebo)**
Primary Endpoint	
Rate of opioid-free weeks during the last 20 weeks of Part A	P = 0.0002
Secondary Endpoints	
Key Secondary: Retention in treatment	P = 0.0042
Key Secondary: Opioid craving score	P < 0.0002
Positive naloxone challenge test	P = 0.0154
Self-reported opioid use	P = 0.0004

The primary and secondary endpoint results are further supported by the analysis of exploratory endpoints that provide further perspective of the impact, clinical significance and consequence of treatment with VIVITROL—see Section 6.1.3.4.

According to the FDA Guidance, *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Product* (Appendix Section 10.3), the ALK21-013 clinical study possesses the characteristics that provide adequate support for an effectiveness claim:

- It is a large, multi-center trial
  - No single center provided a disproportionately large fraction of patients.
  - No single investigator or site was disproportionately responsible for the favorable effect.
- Analysis of the results reveals consistency across key patient subsets.
- Significant results across multiple endpoints involving different events were:
  - The ALK21-013 study included several important, prospectively identified primary and secondary endpoints some of which represent a beneficial but different effect. According to the guidance, "Where a study shows statistically persuasive evidence of an effect on more than one endpoint, the internal weight of evidence of the study is enhanced."
- Statistically persuasive findings were seen:
  - The low p-values obtained across all primary and secondary endpoints indicate that the results are inconsistent with the null hypothesis of no treatment effect.

The validity of the results of ALK21-013 is supported by the known and established mechanism of action of naltrexone as a μ-opioid receptor antagonist. Based on the pathophysiology of the disease and the known mechanism of action of naltrexone in interrupting that pathophysiology, it is very reasonable to accept the results of study ALK21-013 as demonstrating substantial evidence of effectiveness. In addition, there is extensive evidence of the safety and efficacy of oral naltrexone for the treatment of opioid dependence, although it is well known that compliance is an issue. It has been accepted by the addiction community that "naltrexone works, if you can get the patient to take it"—see Section 6.1.5.

The results of study ALK21-013 are supported by the results of two open-label studies ALK21-006/EXT, a long term, Phase 3 study in alcohol-, opioid- and mixed alcohol- opioid-dependent patients and ALK21-021, a 2 year, Phase 3 study in health care professionals. These studies are supportive based on the observed retention in treatment (see Section 6.2). Retention in treatment is an important indicator of successful treatment of opioid-dependence. The longer a patient remains in therapy the better the chances of prolonged recovery. ALK21-006 enrolled N=121 patients with opioid dependence and mixed opioid- and alcohol dependence. Over 50% remained on treatment with VIVITROL at 6 months, and >30% remained at 12 months. ALK21-021 enrolled N=38 patients; emerging data suggest similar good retention in treatment.

Extrapolation to the Treatment of Opioid Dependence in the United States

There is significant evidence to indicate that the existing body of data with VIVITROL can be extrapolated to clinical treatment of opioid dependence in the US –see Section 8 for further details.

Based on the ICH E5 Guidance, the following properties of VIVITROL make it less likely exposure is influence by ethnic factors:

- dose-linear pharmacokinetics
- naltrexone is not metabolized by the CYP enzyme system.

In addition, the following factors indicate that the results of the VIVITROL opioid program can indeed be generalized to the treatment of opioid dependence in the US:

- The underlying neuropharmacologic mechanism of opioid dependence and the mechanism of action of naltrexone – competitive μ-opioid blockade – are well characterized and operative irrespective of region, country, culture, or treatment context.
- The patient population studied in the VIVITROL program is directly relevant to the treatment of opioid dependence in the US. All patients studied met DSM-IV-TR criteria for opioid dependence. Importantly, there are strong parallels in the underlying motivation and external support between the 013 study population and the anticipated VIVITROL treated patient in the US.
- Treatment of opioid dependence in the US occurs in a wide variety of clinical settings. The clinical sites in the VIVITROL opioid program and specifically the ALK21-013 study are highly reflective of centers that actually use VIVITROL in clinical practice in the US health care system.

Safety experience in the US should adequately address safety in the US treatment population. There exists a significant amount of safety experience with VIVITROL in the treatment of opioid dependence in the US through previously conducted (ALK21-006, ALK21-006-EXT) and ongoing (ALK21-021) studies. In addition, the opioid submission also includes several years of post market safety surveillance data of VIVITROL in the US.

2. OPIOID DEPENDENCE—AN OVERVIEW

Opioids are a class of analgesic medications that are prescribed for treating acute or chronic pain, or relieving coughs or diarrhea. Examples of some common opioid pain medications include morphine, hydrocodone (eg, Vicodin®), and oxycodone (eg, OxyContin®). Heroin, which is synthesized from morphine, is an illegal, rapidly acting, addictive opioid.

Prescription opioids are one of the most prescribed classes of drugs in the United States, with a steep increase in use over the past 15 years. While most people use these prescription opioids responsibly, the nonmedical or illicit use of these medications has more than doubled over the past decade, and dependence on prescription opioids is now as common as dependence on any other illicit drug except marijuana [Substance Abuse and Mental Health (SAMHSA) Data Archive 2009].

According to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth edition, text revision (DSM-IV-TR), **opioid dependence** is defined as a maladaptive pattern of opioid use leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period [American Psychiatric Association 2000]:

1. Tolerance, as defined by either of the following:
   a. A need for markedly increased amount of the substance to achieve intoxication or desired effect
   b. Markedly diminished effect with continued use of the same amount of substance
2. Withdrawal, as manifested by either of the following:
   a. The characteristic withdrawal syndrome for the substance
   b. The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms
3. The substance is often taken in larger amounts or over a longer period than was intended
4. There is a persistent desire or unsuccessful efforts to cut down or control substance use
5. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects
6. Important social, occupational, or recreational activities are given up or reduced because of substance use
7. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance

A diagnosis of opioid dependence is based not merely on physical dependence on opioids, but also entails compulsive use despite harm.

The DSM-IV-TR criteria were used as the diagnostic standard in all Alkermes VIVITROL clinical trials in this population. Specifically, patients were required to have an active diagnosis

of opioid dependence, based on DSM-IV-TR criteria, to be considered eligible for study participation; patients who did not meet these criteria were excluded.

2.1. Prevalence

More than 2 million adults start abusing prescription pain medication each year, and according to the 2008 National Survey on Drug Use and Health (NSDUH), 200,000 people reported using heroin each month [Substance Abuse and Mental Health (SAMHSA) Data Archive 2009].

Unfortunately, use of opioids often progresses to abuse and ultimately dependence. As shown in Figure 1, the rate of opioid dependence among adults 18 years of age and older is increasing, with 1.3 million dependent adults reported in 2008 [Substance Abuse and Mental Health (SAMHSA) Data Archive 2009].

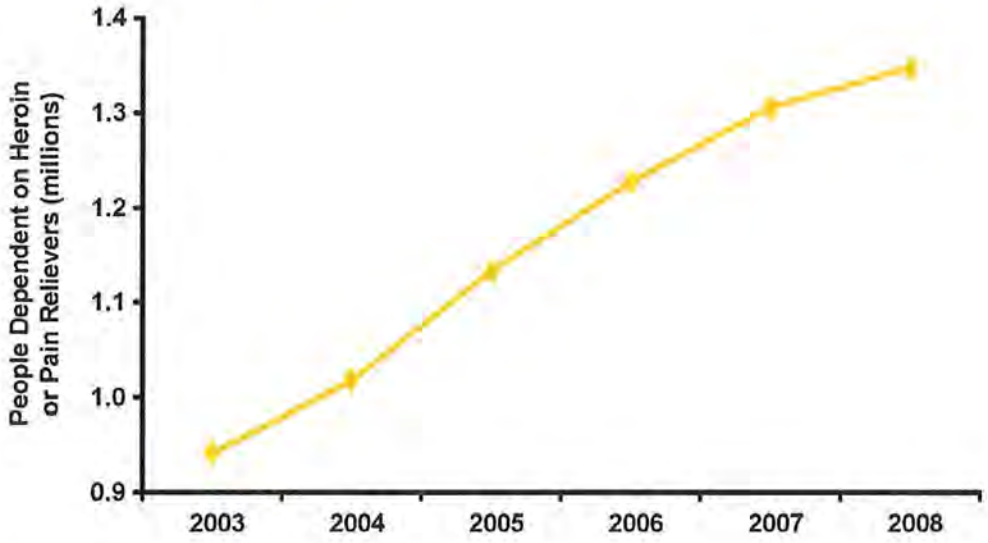


Figure 1: Prevalence of Opioid Dependence in the United States, 2002–2008

2.2. Mortality and Societal Impact

Dependence on opioids, regardless of whether they are prescription opioids or heroin, may negatively affect health, personal relationships, financial stability, and work performance, and may increase an individual's probability of committing a crime. The impact is felt not only by the dependent individual, but by family and friends, as well as by society as a whole.

Opioid dependence is associated with significant morbidity and mortality. As illustrated in Figure 2, from 1999 through 2006, the number of fatal poisonings involving opioid analgesics more than tripled from approximately 4,000 to 13,800 deaths [Warner, 2009].

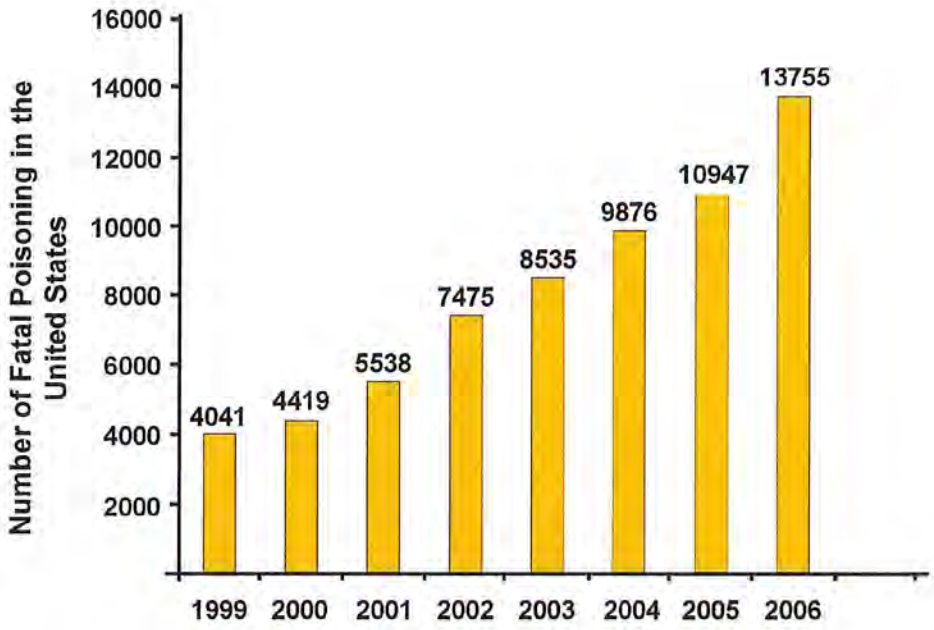


Figure 2: Poisoning Deaths due to Opioid Analgesics; United States 1999—2006

Addiction-related deaths, including accidental overdose, drug-related accidents, and many illnesses directly attributable to chronic drug dependence, are responsible for one-fourth to one-third of deaths in the opioid-addicted population [Stinson, 2005]. Annual estimates of US emergency department visits for non-medical use of opioids more than doubled from about 145,000 in 2004 to about 306,000 in 2008 [Drug Abuse Warning Network (DAWN) 2010].

Among heroin addicts, it is estimated that more than 18 years of potential life are lost before the age of 65, with the leading causes of death being overdose, chronic liver disease, and accidents [Smyth, 2007]. Direct health care cost (eg, hospital inpatient, physician office visit, prescription drug claims, etc.) incurred by self-insured employers on behalf of their employees were found to be on average 8 times higher for opioid abusers than for nonabusers [White, 2005].

The cost of heroin dependence in the US was estimated at $21 billion in 2000 [Jones, 2009], and the cost of prescription opioid abuse at over $9.5 billion in 2005 [Birnbaum, 2006].

2.3. Current Opioid Dependence Treatment: Options and Needs

In the US, available approved pharmacotherapy for opioid dependence includes 3 main drug classes of oral medication: opioid receptor agonist (methadone), opioid receptor partial agonist (buprenorphine), and opioid receptor antagonist (oral naltrexone).

Methadone and buprenorphine are effective agents for the treatment of opioid dependence; however, agonist pharmacotherapy does entail a variety of important concerns. These include the perpetuation of physical dependence, induction of tolerance, potential respiratory depression, central nervous system depression, and the risk of overdose if combined with other opioids, alcohol, or other depressants [Reckitt Benckiser Pharmaceuticals Inc. 2002;Roxane Laboratories,

Inc. 2002]. Methadone is contraindicated in patients who have co-occurring alcohol dependence with certain pre-existing medical conditions, such as QT prolongation [Roxane Laboratories, Inc. 2002]. Antagonist pharmacotherapy is also unlikely to become subject to diversion and abuse – which is an emerging problem in the US for agonist therapy [Substance Abuse and Mental Health Services Administration (SAMHSA) and JBS International Inc. 2006].

Oral naltrexone, the third pharmacotherapy option, was approved on November 20, 1984 for the blockade of the effects of exogenously administered opioids. The package insert for REVIA (oral naltrexone) [DURAMED 1984] provides information on use in opioid-dependent patients as follows:

- "REVIA (naltrexone) has been shown to produce complete blockade of the euphoric effects of opioids in both volunteer and addict populations…."
- There are no data that demonstrate an unequivocally beneficial effect of REVIA on rates of recidivism among detoxified, formerly opioid-dependent individuals who self-administer the drug. The failure of the drug in this setting appears to be due to poor medication compliance.
- The drug is reported to be of greatest use in good-prognosis opioid addicts who take the drug as part of a comprehensive occupational rehabilitative program, behavioral contract, or other compliance-enhancing protocol. REVIA, unlike methadone or LAAM (levo-alpha-acetylmethadol), does not reinforce medication compliance and is expected to have a therapeutic effect only when given under external conditions that support continued use of the medication.

Despite its clear pharmacologic effects of blocking opioid receptors (see Section 3.2.2), its clinical effectiveness has been limited with heterogeneity reported in treatment response. Multiple clinical trials have identified poor patient compliance as being responsible for this heterogeneity [Johansson, 2006]. This stands to reason, as oral naltrexone requires consistent daily dosing in a patient population prone to relapse.

More than half of the 1.5 million Americans now suffering from opioid dependence remain untreated. Stigma is a great obstacle to treatment of opioid dependence [Joseph, 2000], and may possibly be alleviated by the type and setting of care. The social desirability of an abstinence model [O'Connor 2005];[Narcotics Anonymous World Services Inc. 2007] that is based upon a non-reinforcing "blocker" may make it easier for more addicts to accept becoming patients. Also, treatment in a medical setting, administered by a physician or nurse, may confer less burden of stigma and deterrence to seeking treatment [Obama 2010].

In 1975, the National Institute on Drug Abuse began calling for, and repeated the call for, a sustained-release antagonist preparation [National Institute on Drug Abuse (NIDA) 1976]. The long-acting injectable preparation was proposed as a means of overcoming the obstacle of day-to-day noncompliance with oral naltrexone, which limits its utility.

An extended-release antagonist potentially offers a number of specific advantages from the perspective of patients, providers and society:

- Patients who have not had sufficient duration or severity of opioid dependence to meet criteria for agonist treatment will have a useful option for maintenance pharmacotherapy.

- Patients can return to work. The mechanism of action makes it suitable for patients whose employment or professional license prohibits agonist treatment eg, health care professionals, transportation workers (airline pilots, interstate truck drivers), public safety officials (police, fire, rescues workers), and military personnel.
- The extended-release formulation assures month-long continuity of effect, overcoming the high risk of non-adherence that has been common with the daily oral regimen. This provides direct assurance of treatment adherence for the patient, the patient's family members, and the health care providers The formulation also dispenses with any need for daily supervised administration.
- The absence of physical dependence means that the agent has no potential for producing withdrawal symptoms upon discontinuation. A concern about withdrawal symptoms is understood to intimidate opioid-dependent patients and keep them from considering starting or restarting maintenance pharmacotherapies.

Consistent with the NIDA research goal, and with initial funding from NIDA, VIVITROL was developed to circumvent the requirement for compliance with a daily dosing regimen that is necessitated by oral naltrexone (Table 2).

Table 2: NIDA Goals for Narcotic Agonist Development

NIDA Monograph (1976)*: Stated Goals	VIVITROL Characteristics
"It was felt from the outset that a most desirable component of antagonist therapy would be a long-acting drug, so that the need for an addict to decide to take his medication would be minimized."	VIVITROL (naltrexone for extended-release injectable suspension) is a long-acting antagonist therapy
"It was recognized very early that in order to achieve the desired one week, one month or longer duration between dosages, it would be necessary to develop a long-acting drug delivery system or a sustained-release preparation of an acceptable but short-acting antagonist."	A single intramuscular injection of VIVITROL provides therapeutic concentrations of naltrexone for 1 month
"A 'drug-delivery system' is the unwieldy but currently favored expression describing any pharmaceutical preparation capable of providing a sustained or long-acting antagonistic effect.... Distinct from the problem not considered here, of finding an optimum antagonist, is the problem of inventing suitable carriers for the antagonist, carriers that will deliver the antagonist, releasing it uniformly bit by bit over a period of time."	VIVITROL uses the Medisorb drug delivery system in which naltrexone is gradually released from polymer microspheres

*Source: [National Institute on Drug Abuse (NIDA) 1976]

3. DESCRIPTION OF VIVITROL

VIVITROL is a microsphere formulation of naltrexone for suspension, to be administered by IM gluteal injection. In this microsphere-based formulation, naltrexone is incorporated into a biodegradable matrix of polylactide-co-glycolide (PLG). PLG is a common, biodegradable medical polymer with a history of safe human usage in sutures, bone fixation devices, abdominal mesh, and extended-release pharmaceuticals including Risperdal® Consta® (risperidone), which is also manufactured by Alkermes.

An illustration of drug release from VIVITROL microspheres is provided in Figure 3. Upon injection, the VIVITROL microspheres begin to absorb water almost immediately, leading to a swelling of the microspheres. This process begins an initial release phase of drug at or near the surface of the microspheres is released. As water absorption continues, the polymer begins to undergo hydrolysis and later, physical erosion of the polymer is observed. Drug diffuses into the surrounding media as the polymer continues to undergo hydrolysis and erosion resulting in a sustained release of drug from the microspheres. The polymer matrix eventually breaks down into lactic acid and glycolic acid, which are completely metabolized locally by the body and eliminated as carbon dioxide and water.

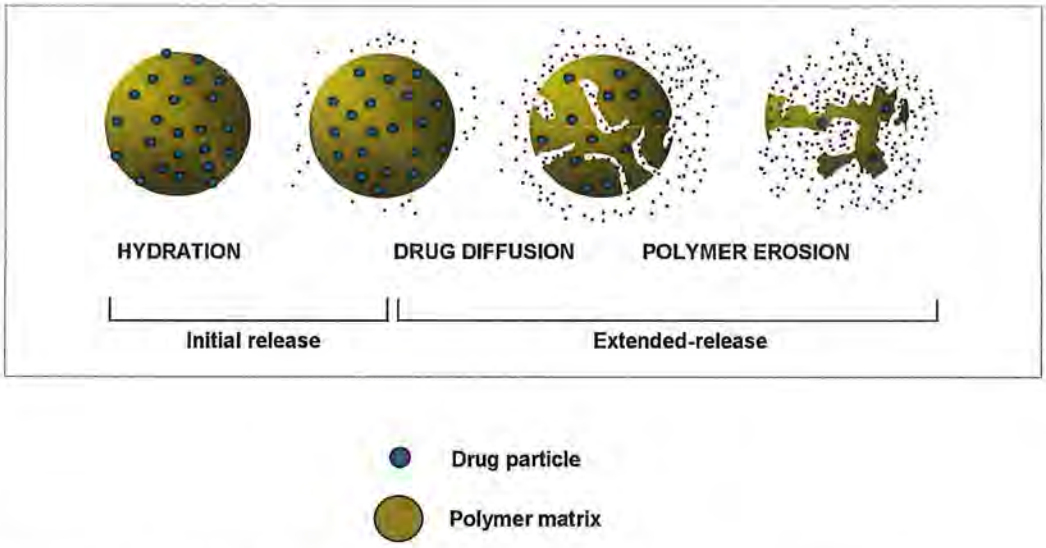


Figure 3: Illustration of Drug Release from VIVITROL Microspheres

3.1. Mechanism of Action

VIVITROL (naltrexone) is an opioid antagonist. As an antagonist, it competitively blocks opioids from binding to the receptor site (in particular, the μ-receptor), thereby shifting the concentration-response curve for any given opioid agonist to the right (Figure 4). This makes VIVITROL different from other approved treatment options (an opioid agonist [methadone] and a partial agonist [buprenorphine]) that activate the μ-opioid receptors. By antagonizing, or

blocking, the μ-opioid receptor, VIVITROL does not cause the same effects as opioid agonist medications, such as euphoria or reinforcing qualities. Furthermore, because VIVITROL blocks opioid receptors rather than activates them, it is not associated with the development of tolerance or dependence.

Figure 4: Competitive Antagonism by Naltrexone Shifts the Concentration-Response Curve of an Opioid Agonist to the Right

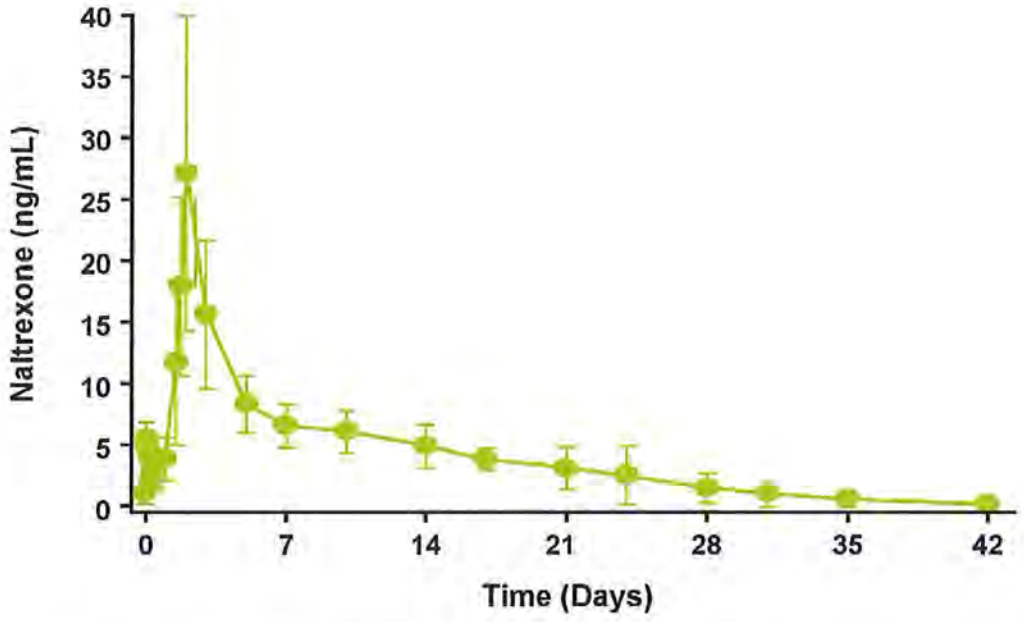
3.2. Clinical Pharmacology

The VIVITROL clinical pharmacology program was designed to characterize those aspects of naltrexone pharmacokinetics or pharmacodynamics that are unique to VIVITROL by virtue of its extended-release features. In addition, information pertaining to the ability of naltrexone to inhibit or induce major drug metabolizing enzymes was generated. A substantial amount of data pertaining to naltrexone pharmacokinetic and pharmacodynamic properties exists in published scientific literature. Data from published literature provides information pertaining to the distribution, metabolism, and elimination of naltrexone in support of VIVITROL for opioid dependence. Further, there is significant literature evidence of the mechanism of action and clinical efficacy of naltrexone for the treatment of opioid dependence.

The clinical studies performed to evaluate VIVITROL pharmacokinetics and pharmacodynamics include three phase 1 studies, one phase 1b study, one phase 2 study, and one phase 3 study. These studies contained the following objectives: 1) characterization of VIVITROL pharmacokinetics (one phase 1 dose-escalation study, one phase 1 multiple dose study); 2) pharmacokinetics of VIVITROL in special populations (one phase 1 study in hepatically impaired patients); 3) population pharmacokinetics (one phase 3 study); 4) demonstration of biologic activity, safety and tolerability (one phase 1b study in alcohol dependent patients; and 5) exploration of the pharmacokinetic/pharmacodynamic relationship pertaining to opiate blockade (one phase 2 study in opioid users).

3.2.1. VIVITROL Pharmacokinetics

Following a single IM injection, VIVITROL provides measurable naltrexone plasma concentrations for >30 days. The concentration-time profile is characterized by a transient initial peak which occurs approximately 2 hours after injection, followed by a second peak observed approximately 2 days later. Beginning approximately 14 days postdose, naltrexone concentrations slowly decline in a log-linear fashion. Naltrexone absorption is mediated by its release from the microspheres, the rate of which is largely dependent on the hydrolysis and erosion of the PLG matrix. The gradual hydrolysis of the polymer, particularly 2–4 weeks after injection, results in prolonged absorption of naltrexone into the systemic circulation. The observed elimination $t_{½}$ of naltrexone following VIVITROL injection (~5–10 days) reflects the slow absorption rate of naltrexone into the systemic circulation (ie, characteristic of "flip-flop" pharmacokinetics). The concentration-time profile of naltrexone following repeat administration (steady state) of VIVITROL is shown in Figure 5.



Source: [Dunbar, 2007;Dunbar, 2006]

Figure 5: Naltrexone Plasma Concentrations at Steady State following 380 mg IM VIVITROL Administration (Dose 4 of 4; Mean ±SD; N=10 ALK21-005)

Exposure (AUC) to naltrexone is linear over the dose range 141 to 530 mg, a range that includes the proposed clinical dose (380 mg). Repeat dosing of 380 mg at 28-day intervals results in minimal accumulation of naltrexone (13%) and the major metabolite, 6β-naltrexol (11%). The pharmacokinetics of naltrexone and 6β-naltrexol were not time-dependent.

Naltrexone is subject to extensive first pass metabolism following oral dosing. Intramuscular administration of VIVITROL circumvents delivery of naltrexone directly to the liver, thereby

avoiding direct hepatic biotransformation. Consistent with a reduction in first pass metabolism, VIVITROL administration results in less 6β-naltrexol production compared with oral administration. In a phase 1 study conducted in healthy subjects (ALK21-005), naltrexone exposure (C_{max} and AUC) over a 28-day period following VIVITROL administration (380 mg) exceeded by 2- to 4-fold naltrexone exposure following oral administration (based on predicted oral naltrexone exposure of a 50 mg/day dose for 28 days; see Table 3) with a 3.6-fold reduction in total dose (380 mg VIVITROL vs 1400 mg oral naltrexone). Over the same period, 6β-naltrexol exposure ($AUC_{0\text{-}28d}$) exceeded that of naltrexone by more than 20-fold following oral dosing (50 mg/day; 1400 mg/month). In contrast, following VIVITROL administration (380 mg), 6β-naltrexol $AUC_{0\text{-}28d}$ was approximately only 2-fold higher than naltrexone $AUC_{0\text{-}28d}$. The steady state pharmacokinetic parameters of naltrexone and 6β-naltrexol following VIVITROL and oral naltrexone administration, generated in a cross-over study, are listed in Table 3.

Table 3: Steady State Pharmacokinetic Parameters of Naltrexone and 6β-naltrexol following VIVITROL (380 mg) and Oral Naltrexone (50 mg) Administration

		VIVITROL	Oral Naltrexone
Dose / # of Subjects		**380 mg every 28 days; Dose 4 of 4 / n=10**	**50 mg daily[a]; Dose 5 of 5 /n=14**
Naltrexone	C_{max} (ng/mL)	28.0 (12.2)	13.7 (10.6)
	$AUC_{0\text{-}28}$ (ng•day/mL)	160 (24.2)	41.2[b]
	$t_{½}$ (days)	4.7 (1.3)	0.17 (0.07)
6β-naltrexol	C_{max} (ng/mL)	34.2 (12.9)	139 (36.0)
	$AUC_{0\text{-}28}$ (ng•day/mL)	294 (70.4)	1002[c]
	$t_{½}$ (days)	5.1 (1.1)	0.57 (0.08)

[a] 50 mg/day ×28 days = 1400 mg total equivalent monthly dose
[b] Calculated as ($AUC_{0\text{-}1}$ * 28), where AUC0-1 = 1.47 ng*day/mL following the 5th oral dose
[c] Calculated as ($AUC_{0\text{-}1}$ * 28), where AUC0-1 = 35.8 ng*day/mL following the 5th oral dose

Mild or moderate hepatic impairment has no effect on the pharmacokinetics of naltrexone or 6β-naltrexol. Results of a phase 1 clinical study (ALK21-009) demonstrated that patients with moderate hepatic impairment had sufficient hepatic capacity to metabolize naltrexone following VIVITROL administration to the same extent as healthy subjects. The effect of severe hepatic impairment was not evaluated.

Population pharmacokinetic methods were used to evaluate the influence of additional intrinsic and extrinsic factors on VIVITROL pharmacokinetics. Patients with alcohol dependence, opioid dependence, or both were found to have increased apparent naltrexone clearance (24%),

increased apparent volume for naltrexone (35%) and increased apparent 6β-naltrexol clearance (30%) relative to healthy subjects. Increasing weight was correlated with increases in apparent naltrexone clearance and apparent volume of naltrexone, while decreasing creatinine clearance was correlated with a decrease in apparent 6β-naltrexol clearance. However, the magnitude of these influences is unlikely to be clinically meaningful. No significant effect of gender, age and race on VIVITROL pharmacokinetics was identified. There are no recommended dose adjustments of VIVITROL based on demographic parameters in the VIVITROL label for alcohol dependence.

The potential for drug interactions resulting from VIVITROL administration was evaluated using data obtained from nonclinical and clinical studies conducted with naltrexone. Naltrexone is extensively metabolized to 6β-naltrexol by cytosolic aldoketo reductase enzymes (previously identified as dihydrodiol dehydrogenases). Naltrexone and 6β-naltrexol are also subject to glucuronide conjugation. Cytochrome P450 (CYP 450) enzymes are not involved in naltrexone metabolism, therefore in vivo drug interaction studies were not conducted with VIVITROL. In vitro data suggest drug interactions based on metabolic or protein binding interactions are not likely to occur. In vitro studies determined that naltrexone does not induce CYP P450 enzymes 3A4 or 1A2. The lack of clinically significant pharmacokinetic drug interactions reported with nearly a quarter century of use of oral naltrexone supports this conclusion.

3.2.2. VIVITROL Pharmacodynamics

Naltrexone blocks opioids by binding competitively at the μ-opioid receptor. Oral naltrexone was approved by the FDA for use in the treatment of opioid blockade in 1984. A number of clinical investigations confirming naltrexone blockade of opioid agonists have been conducted, and indeed it was predominantly these empirical studies that formed the basis of FDA approval [Korvick 2008;National Institute on Drug Abuse (NIDA) 1976]. For the purpose of supporting the efficacy of VIVITROL in opioid dependence, a brief summary of clinical studies of oral naltrexone is provided. Additionally, the FDA currently recommends the use of oral naltrexone for the purposes of opioid blockade during development of bioequivalent generic opioid agonists. In combination with recognized pharmacokinetic exposure of naltrexone, these data in total provide a strong basis of support for the pharmacodynamic blockade by naltrexone.

A confirmatory clinical investigation of direct pharmacodynamic blockade provided by VIVITROL has also been conducted (ALK21-004, described below).

A thorough review by Gonzalez and Brogden [Gonzalez and Brogden 1988] of the pharmacodynamic and pharmacokinetic properties of naltrexone in opioid dependence summarizes much of the clinical evidence utilized by the FDA for approval of opioid blockade. Briefly, doses of naltrexone ranging from 20 to 200 mg daily attenuated the response to opioid challenge between 24 and 72 hours after naltrexone administration. A 50 mg dose of naltrexone was shown to block morphine (30 mg, subcutaneously) [Martin, 1973] and heroin (25 mg, IV) [Resnick, 1974] agonism for 24 hours, while a dose of 100 mg naltrexone provided nearly complete blockade of heroin (25 mg, IV) for 48 hours [Verebey, 1976]. In another study, the subjective effects of IV heroin were reduced to 14% of control values 48 hours after patients received an oral naltrexone dose of 40–200 mg [Volavka, 1976]. In a study of naltrexone (120–200 mg) blockade of hydromorphone, O'Brien et al [O'Brien, 1975] reported a loss of the reinforcing aspects of the agonist and reduced craving. A more recent study has demonstrated

blockade of buprenorphine (2–16 mg) effects by naltrexone (100–150 mg) [McAleer, 2003]. Multiple studies of oral naltrexone for opioid dependence indicated positive outcomes for reduction in craving as well as for retention in treatment compared to placebo [Gonzalez and Brogden 1988]. Evidence from multiple studies identified a strong concentration-effect relationship whereby even low levels of naltrexone observed at 24- and 48-hours postdose conferred a high level of opioid blockade [Resnick, 1974;Verebey, 1976] VIVITROL provides naltrexone levels (Table 3) over the period of one month that are equal to or above those following oral naltrexone administration across the dose ranges described in the literature.

Further substantiating the clinical utility of opioid blockade provided by naltrexone, the use of naltrexone is recommended by the FDA to provide blockade during the development of bioequivalent formulations of potent opioid agonists (eg, fentanyl, morphine sulfate) in healthy volunteers. In these studies, it is recommended that naltrexone (50 mg) be administered prior to, at the time of, and following opioid agonist administration, thus providing blanket opioid blockade. Naltrexone was also utilized to provide blockade of opioid agonism by hydromorphone during the clinical development of Exalgo® (extended release hydromorphone) [NDA 21-217, 2009]. Based on the collective pharmacokinetic and pharmacodynamic data, the monthly exposure of naltrexone following VIVITROL 380 mg administration provides a comparable level of blockade to oral naltrexone.

The pharmacodynamic activity of VIVITROL was demonstrated by its ability to block the pupil constriction and euphoric feelings of exogenously administered hydromorphone. Study ALK21-004, was a Phase 2, double-blind, parallel-group, pilot study in experienced opioid users conducted to assess the degree of opiate blockade conferred by VIVITROL. Non-dependent, opiate-using patients received a single IM injection of VIVITROL 75 mg (n=9), 150 mg (n=8), or 300 mg (n=10). Prior to, and at weekly intervals following VIVITROL administration, patients received increasing doses of intramuscular hydromorphone (0, 3, 4.5 and 6 mg). Subjective and objective responses were collected following each hydromorphone dose in order to assess the degree of opiate blockade. Blood samples for the determination of naltrexone and 6β-naltrexol concentrations were collected at weekly intervals.

Pharmacological activity at opioid receptors was confirmed by the finding that VIVITROL blunted the pupil constriction and euphoric feelings typically associated with hydromorphone administration. Assessed by the objective measure of pupil size, doses of 150 mg and 300 mg produced complete opiate blockade for >28 days; a lower dose of 75 mg produced partial blockade for a shorter period (14 days). Plasma naltrexone and 6β-naltrexol concentrations following VIVITROL administration were dose-related. In addition, the following pharmacokinetic/pharmacodynamic relationship was observed: as naltrexone concentrations increased, opiate blockade was strengthened, extending blockade beyond 1 month post-injection.

3.3. Dose Justification

VIVITROL is currently marketed in the US for use in adults with alcohol dependence. It was administered in this study at the currently marketed dose (380 mg).

The dose of 380 mg was selected after evaluation of VIVITROL 150 mg and 300 mg in an opioid blockade study, with both doses demonstrating complete blockade of exogenous opioids for greater than 28 days, and after evaluation of VIVITROL 190 mg and 380 mg in a phase 3 clinical study conducted in patients with a diagnosis of DSM-IV alcohol dependence. In that

phase 3 study, doses of 190 mg and 380 mg were selected in order to provide systemic exposure of naltrexone on the same order of magnitude as is observed following oral dosing. In fact, naltrexone exposure over a 28-day period with VIVITROL 380 mg was 3.9-fold greater than exposure following oral dosing of 50 mg per day for 28 days due to the absence of first pass metabolism, 6β-naltrexol exposure with VIVITROL 380 mg was 3.4-fold lower than following oral dosing.

A placebo-controlled phase 3 clinical trial for the treatment of alcohol dependence evaluated 190 mg and 380 mg VIVITROL. The greatest efficacy was observed following administration of VIVITROL 380 mg, leading to the selection of VIVITROL 380 mg for marketing.

For the treatment of opioid dependence, the goal is to provide a sufficient amount of naltrexone to block the variety of doses of opioids that people take as part of their addiction—the higher the dose, the greater the level of competitive blockade that would be established. In view of the extensive postmarketing experience with VIVITROL 380 mg, and considering the desire to provide the highest degree of opioid blockade, this study was conducted with VIVITROL 380 mg.

4. VIVITROL OPIOID DEPENDENCE DEVELOPMENT PROGRAM

VIVITROL (naltrexone for extended-release injectable suspension) was approved in the United States (US) for the treatment of alcohol dependence in April 2006, and was first marketed in June 2006. VIVITROL was approved by FDA as a Section 505(b)(2) NDA, meaning that it was approved on the basis of:

- the submitted VIVITROL clinical trial data;
- the published literature related to the safety and efficacy of oral naltrexone; and
- the prior determination of safety and effectiveness of oral naltrexone as evidenced by the approved NDA for oral naltrexone.

In addition to the literature describing the safety and effectiveness of oral naltrexone for alcohol dependence, the original NDA approval for Vivitrol was based on clinical studies conducted by Alkermes with the extended-release formulation that included 1065 patients, most of them alcohol dependent, who participated in 7 primary clinical trials and 3 extension studies of the large phase 3 trials.

The pending supplemental NDA is intended to demonstrate the efficacy and safety of VIVITROL for a new indication—the treatment of opioid dependence. It also is submitted pursuant to Section 505(b)(2) of the Act. Accordingly, Alkermes has conducted and submitted the results of clinical studies in opioid dependent patients with the VIVITROL extended-release formulation, has included safety and effectiveness data by reference to the literature for oral naltrexone treatment of opioid dependence, has included safety and effectiveness data by reference to the Trexan NDA 18-932 (naltrexone) and is relying on FDA's previous determination of the safety and effectiveness of Trexan NDA 18-932.

The clinical trials contributing to the demonstration of efficacy in the opioid-dependent population are summarized in Table 4, specifically, the pivotal ALK21-013 and the supportive ALK21-006, ALK21-006-EXT.

A summary of published clinical trials of oral naltrexone for the treatment of opioid dependence is provided in Table 5.

Clinical safety data are obtained from the following sources:

- Published data on the safety of naltrexone, administered as an oral or injectable formulation to patients with opioid dependence.
- Study ALK21-006, a 1-year, open-label, phase 3 study conducted in adults with alcohol and/or opioid dependence. Of the 436 patients in study ALK21-006, 121 were opioid dependent.
- Study ALK21-006-EXT, a long-term safety extension of study ALK21-006.
- Study ALK21-013, an 18-month phase 3 safety and efficacy study comprising a 6-month double-blind, placebo-controlled evaluation period followed by a 12-month open-label safety extension. This study enrolled 250 opioid-dependent adults.

ALK21-013 is an ongoing study, although all active patients have completed Part A, the double-blind portion of the trial.

- Study ALK21-021, is an ongoing, open-label study of the safety and tolerability of VIVITROL administered for up to 24 months to healthcare professionals participating in an extended outpatient treatment program for opioid dependence. This study was initiated in the first half of 2009. Preliminary interim safety data for the 38 opioid-dependent patients participating in this study are included.
- Postmarketing safety data received from the use of VIVITROL. All postmarketing reports, whether postmarketing use was for the approved indication or for an off-label purpose, are included in the postmarketing safety analysis.

Table 4: Overview of VIVITROL Clinical Trials that Support the Opioid Dependence Indication

Study ID; Location of Study	Type of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients	Healthy Volunteers or Diagnosis of Patients	Duration of Treatment	Results
Safety and Efficacy							
ALK21-013; Russia	Efficacy; Safety & tolerability	Randomized, double-blind Placebo-controlled	VIVITROL 380 mg, every 28 days, IM Placebo, every 28 days, IM	250 (126 VIVITROL, 124 placebo	Opioid dependence	24 weeks	See Section 6 and Section 7
ALK21-006; United States	Long term safety & tolerability	Randomized, open-label Active-controlled	VIVITROL 380 mg, every 28 days, IM Naltrexone, 50 mg, daily, oral	436 (373 VIVITROL, 63 oral naltrexone)	Alcohol and/or opioid dependence	1 year	See Section 6 and Section 7
ALK21-006-EXT; United States	Long term safety & tolerability	Open-label Uncontrolled	VIVITROL 380 mg, every 28 days, IM	108 VIVITROL	Alcohol and/or opioid dependence	3 years	See Section 6 and Section 7

(table continues)

Table 4: Overview of VIVITROL Clinical Trials that Support the Opioid Dependence Indication (continued)

Study ID; Location of Study	Type of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients	Healthy Volunteers or Diagnosis of Patients	Duration of Treatment	Results
			Clinical Pharmacology				
ALK21-005; United States	Pharmaco-kinetics; Safety & tolerability	Randomized, double-blind Placebo-controlled, Active-controlled	Cohort A: Oral naltrexone 50 mg VIVITROL 190 mg, IM VIVITROL 380 mg, IM Placebo, IM Cohort B: Oral naltrexone 50 mg ×5 days; VIVITROL 380 mg every 28 days ×4 months, IM Placebo, IM	42 Cohort A: n=28 oral naltrexone; n=12 VIVITROL 190 mg; n=12 VIVITROL 380 mg; n=4 placebo for VIVITROL Cohort B: n=14 oral naltrexone 50 mg; n=12 VIVITROL 380 mg; n=2 placebo	Healthy volunteers	Cohort A: single dose Cohort B: 4 months	See Section 3.2.1.
ALK21-004; United States	Single-dose opioid challenge	Randomized, double-blind	VIVITROL 75, 150, or 300 mg single-dose, IM	27 (n=9 VIVITROL 75 mg; n=8 VIVITROL 150 mg; n=10 VIVITROL 300 mg)	Non-dependent, experienced opioid users	Single dose	See Section 3.2.2.

Table 5: Published Clinical Studies of Oral Naltrexone for Opioid Dependence

Authors	Subjects (N)	NTX ± Other Drug	Study Design	Endpoints	Results
[Hollister, 1978]	Three opioid dependent subject types: recently detoxified, methadone-maintained and drug-free formerly dependent; outpatient (124)	Titrate NTX up to 150 mg for wk 1 then 50 mg Mon-Fri and 100 mg Sun × 8 wks (350 mg/wk) then 100 mg Mon/Wed and 150 mg Fri × 27 wks (350 mg/wk)	RCT, placebo-controlled, double-blind, multi-site NTX vs placebo	Post-treatment global evaluation, retention rates, urine tests, social/psychological changes, craving	10% opioid-positive urine samples in the NTX group compared to 33% in the placebo following the first positive urine sample (P=0.002); no significant difference in subjects submitting 5 or more urine samples. No overall significant differences in social/psychological changes, retention rates or post-treatment global evaluation. Statistically less craving in NTX group (P=0.024).
[San, 1991]	Heroin dependent, post inpatient heroin detoxification and NTX induction; outpatient maintenance (50)	Not directly stated, but likely NTX 350 mg/wk × 6 months after initial NTX induction	RCT, placebo-controlled, double-blind NTX versus placebo; all received NTX 350 mg/wk × 1 month induction before study, all received psychotherapy	Degree of treatment acceptance, % relapse (urine tests), retention rates, AEs	No significant differences between NTX and placebo in acceptance of treatment, retention rates, opioid and other drug consumption, drug compliance or AEs.
[Lerner, 1992]	Opioid dependent subjects, post-heroin detoxification, living in housing projects; opioid-free for 1-2 wks; outpatient (31)	NTX 12.5, 25 and 50 mg on first, second, third day, respectively then 50 mg/day × 7 days then 100 mg Mon/Wed and 150 mg Fri (350 mg/wk) for 2 months total	RCT, placebo-controlled, double-blind NTX + psychotherapy vs placebo + psychotherapy 12 month follow-up	Urine tests, self-reports of use, craving, investigator assessments, retention rates	No difference between NTX and placebo for abstinence or retention rates (for both the 2 month trial and the 12 month follow-up). NTX decreased craving (P<0.001) compared to placebo but not usage.

Table 5: Published Clinical Studies of Oral Naltrexone for Opioid Dependence (continued)

Authors	Subjects (N)	NTX ± Other Drug	Study Design	Endpoints	Results
[Shufman, 1994]	Heroin dependent, post heroin detoxification; abstinent between 10 days and 12 months; outpatient (32)	NTX 25 mg twice a wk × 2 wks then 50 mg 3 times a wk (150 mg/wk) × 10 wks	RCT, placebo-controlled, double-blind NTX vs placebo; all received psychotherapy	Retention rates, urine tests, duration of abstinence, AEs	NTX compared to placebo had fewer opioid-positive urine samples and greater numbers of drug-free subjects (almost double), but these results were not statistically significant. Improvement in most psychological parameters ($P<0.05$). No differences were found in retention rates or AEs.
[Guo, 2001]	Heroin dependent subjects who completed detoxification and were opioid-free for 5-7 days (49)	NTX 50 mg/day x 6 months	RCT, double-blind, placebo-controlled NTX vs placebo	Abstinence, urine tests, euphoric effects of heroin	Completion rate: 29% NTX group, 7% placebo group. Average abstinence period: 3.34 months NTX group, 2.08 months placebo group ($P<0.05$). % of opioid-positive urines: 24% NTX group, 40% placebo group ($P<0.05$). No euphoric effects of heroin: 68% NTX group, 33% placebo group ($P<0.01$).
[Krupitsky, 2004]	Heroin dependent subjects abstinent from opioids for at least 1 week (52)	Doses and frequency of NTX not specified. 6 month study	RCT, double-blind, placebo-controlled NTX vs placebo	Retention and relapse rates, urine tests	Retention rates: 44% NTX group, 16% placebo group ($P<0.01$). Relapse rates: 30% NTX group, 72% placebo group ($P<0.01$). Opioid-positive urine results were approximately equal for the 2 groups.

Table 5: Published Clinical Studies of Oral Naltrexone for Opioid Dependence (continued)

Authors	Subjects (N)	NTX ± Other Drug	Study Design	Endpoints	Results
[Krupitsky, 2006]	Heroin dependent subjects abstinent from opioids for at least 1 week (280)	NTX 50 mg/day; fluoxetine 20 mg/day. 6 month study	RCT, double-blind, placebo-controlled NTX + fluoxetine (NF) vs NTX + placebo (NP) vs fluoxetine + placebo (FP) vs placebo + placebo (PP). All received counseling with parental or significant other involvement.	Retention and relapse rates, urine tests, reduction in HIV risk, psychiatric symptoms	Retention rates: 43% NF group, 36% NP group, 21% FP group, 10% PP group. 2-3 times increased retention and prevention of relapse in the NTX group compared to placebo (OR = 3.5, P<0.0001), adding fluoxetine did not improve outcomes. Opioid-positive urines: 14% PP group which was significantly greater than those in the other groups, 6% NF, 5% NP, 7% FP.
[Schottenfeld, 2008]	Heroin dependent subjects post 14 day opioid detoxification (126)	NTX Buprenorphine	RCT, double-blind, NTX 100-100-150mg M-W-F, vs buprenorphine up to 24-24-26mg M-W-F, vs placebo for 24 weeks	Days to first heroin use, days to relapse, max days of consecutive abstinence, HIV risk behaviors	For heroin use endpoints, buprenorphine > NTX > placebo. NTX placebo differences were not statistically significant. No group differences in HIV risk behaviors.
[Hulse, 2009]	Heroin dependent subjects post detoxification (70)	Oral NTX NTX implant	RCT, double-blind. Oral NTX 50mg/d NTX implant 2.3g, 6 month study	NTX blood levels, regular heroin use (≥4d/wk), abstinence	Higher NTX blood concentrations were seen in the implant group. More regular heroin use in oral group. Greater abstinence in implant group, but not statistically significant.
[Curran and Savage 1976]	Parolees or probationers (38); opioid dependence not explicitly stated	NTX (doses not specified) Mon-Sun × 2 months then thrice weekly × 7 months	Placebo-controlled, randomization and blinding unclear NTX vs placebo	Duration of treatment, relapse	No difference in successful completion; sharp increase in heroin use when NTX changed from 6 days/wk to thrice weekly.

Table 5: Published Clinical Studies of Oral Naltrexone for Opioid Dependence (continued)

Authors	Subjects (N)	NTX ± Other Drug	Study Design	Endpoints	Results
[Rawson, 1979]	Heroin dependent, post 2-week heroin detoxification (181 assigned, 58 actually completed detox and entered study)	NTX 50 mg/day × 2 wks then 50 mg Mon-Fri and 100 mg Sat (350 mg/wk) × 6 wks then 100 mg Mon/Wed and 150 mg Fri × 16 weeks then 16 week taper off	RCT, blinding unclear NTX alone versus NTX + behavior therapy (BT) vs BT alone; NTX initiated after 2 week detox 12 month follow-up	Urine tests, retention rates	NTX + BT and NTX groups stayed in treatment nearly twice as long as the BT group (P<0.025); both NTX groups had more opiate-free urines than the BT group (P<0.05); no significant difference in urines between the 2 NTX groups.
[Stella, 2005]	Opioid dependent, post opioid detoxification (56)	NTX 50 mg/day; prazepam (a benzodiazepine). 6 month study	RCT, placebo-controlled, only the 2 combination arms were reported as double-blind Placebo vs NTX vs NTX + placebo (NPl) vs NTX + prazepam (NPr); all received psychotherapy	Months to relapse, urine tests, AEs	Placebo group: 10 relapsed within 3 months, 1 within 3-6 months, 3 remained opioid-free; NTX group: 6 relapsed within 3 months, 2 within 3-6 months, 6 remained opioid-free; NPl group: 7 relapsed within 3 months, 1 within 3-6 months, 6 remained opioid-free; NPr group: 1 relapsed within 3 months, 1 within 6 months, 12 remained opioid-free. Significantly lower opioid-positive urines in the NPr group compared to the other groups.

Table 5: Published Clinical Studies of Oral Naltrexone for Opioid Dependence (continued)

Authors	Subjects (N)	NTX ± Other Drug	Study Design	Endpoints	Results
[Ladewig 1990]	Opioid dependent subjects abstinent for at least 10 days; (20); outpatient	NTX 50 mg/day × 3 weeks, then 100 mg Mon/Wed and 150 mg Fri (350 mg/wk); specific study duration not reported (reported duration range: min of 30 days and max of 124 days)	RCT, not blinded NTX + psychotherapy vs psychotherapy	Urine tests, AEs	At 4 weeks, 21% of NTX group had opioid-positive urines vs 75% of the control group. At 6 weeks, 43% of NTX group had opioid-positive urines vs. 100% of the control group ($P<0.05$). Overall % of opioid-positive urines: 29% of NTX group vs. 58% of the control group ($P<0.05$). No difference in rates of AEs.
[Cornish, 1997]	Federal probationers or parolees with history of opioid dependence, (mostly heroin); outpatient (51)	NTX 25 mg/day × 2 days then 50 mg/day x 3 days then 100 mg Tue and 150 mg Fri (250 mg/wk) for 6 months total	RCT, not blinded NTX + probation + brief drug counseling vs. probation + brief drug counseling; all received a monetary reward	Urine tests/breathalyzer tests, study retention, re-incarceration	Significantly lower opioid use in NTX group. Opioid-positive urines: 8% in NTX group versus 30% in control ($P<0.05$). 52% retention in NTX group compared to 33% of controls (not statistically significant). 56% of controls and 26% of NTX group were re-incarcerated ($P<0.05$).

AEs: adverse events; NTX: naltrexone; RCT: randomized controlled trial.

5. DESIGN OF THE ALK21-013 EFFICACY STUDY

5.1. Introduction

Study ALK21-013 is a Phase 3, randomized, multi-center study designed to evaluate the efficacy and safety of VIVITROL in the treatment of N=250 patients with opioid dependence.

The study is comprised of two parts, A and B (Figure 6). Part A was a double-blind, parallel-group, placebo-controlled 24-week assessment of efficacy, QOL, and safety. Part B is an open-label extension to assess long-term safety (up to 1.5 years). Part B of the study is ongoing.

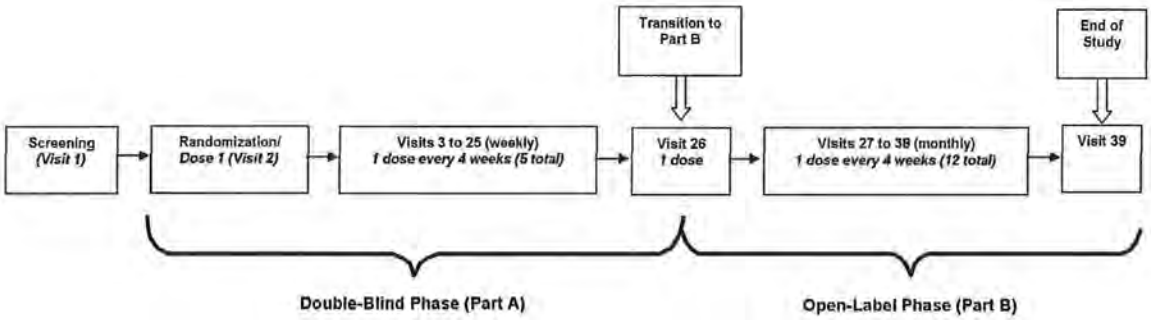


Figure 6: Study Timeline—ALK21-013

All patients, both in the VIVITROL and placebo treatment groups, received Individual Drug Counseling (IDC) throughout the study. IDC is a manual-based standardized method of psychosocial therapy developed by NIDA. Therefore, the therapeutic effect of VIVITROL was assessed in the context of a background of a broader treatment program.

The study was designed in collaboration with the lead investigator, Dr. Evgeny Krupitsky (St. Petersburg, Russia) and experts in the field of opioid addiction treatment in research in the United States (Dr. Walter Ling, UCLA, Dr. Edward Nunes, Columbia).

Dr. Krupitsky is Professor and Chief of the Department of Addictions at St. Petersburg Medical University and an adjunct Professor of Psychiatry at the University of Pennsylvania School of Medicine. As part of his training, Dr. Krupitsky completed a fellowship in addiction psychiatry at Yale University. Dr. Krupitsky has conducted opioid-dependence treatment trials in St. Petersburg in collaboration with Dr. George Woody at the University of Pennsylvania School of Medicine [Krupitsky, 2004;Krupitsky, 2006]. Several of these trials, both completed and ongoing, were reviewed and funded by NIDA.

The study design, including the choice of control groups, was discussed and agreed upon with the Division of Anesthesia, Analgesia, and Rheumatology Products of the Food and Drug Administration (FDA) during an End-of-Phase 2 meeting held on 19 April 2007 and in subsequent correspondences. The final Statistical Analysis Plan (SAP, see Appendix Section 10.4) for this study incorporates the Division's subsequent comments dated 06 May 2009. The analyses of the primary and secondary efficacy endpoints were consistent with the Division's recommendations.

All ALK21-013 study investigators were experienced in the field of opioid addiction research and treatment, and had demonstrated an ability to conduct high quality therapeutic research in the context of pre-study investigator meeting and routine site monitoring visits.

Study sites performed in accordance with the standards of good clinical practice, ensured initial and ongoing review by both a national and (when required) local ethics committee, utilized witnessed informed consent and made their records and facilities available for independent audit.

Two sites were audited by an external Good Clinical Practice (GCP) auditor (in December of 2008) and four sites were audited by an Alkermes GCP auditor (May-June 2009). The Trial Master File was audited prior to the site audits. The site study files, signed informed consent forms for all patients, and subject CRFs and source documents for a random selection of patients were audited. Additionally, test article storage and dispensation records were audited. Each site audit lasted two days.

In July 2010, 4 centers were inspected by the FDA. The inspection was successful with no deficiencies observed (no 483 violations). The FDA investigators stated that a "No Action Indicated" communication would be prepared.

5.2. Patient Selection Criteria

Eligible patients included those with a current diagnosis of opioid dependence who were actively seeking treatment and who were receiving or had recently received inpatient treatment for opioid detoxification. The diagnosis of opioid dependence was based on DSM-IV. Prior to randomization, patients were required to be opioid free for a minimum of 7 days.

Patient selection included criteria to exclude patients with poly-substance abuse. In consultation with the FDA, it was decided to focus the study on patients with opioid dependence. The purpose was to avoid confounding the efficacy signal with treatment effects potentially related to other substances of abuse or dependence.

5.2.1. Inclusion Criteria

For inclusion into the trial, each patient was required to fulfill all of the following criteria:

1. Was capable of understanding and complying with the protocol, and signed the informed consent document
2. Was 18 years of age or older
3. Had a current diagnosis of opioid dependence, based on the criteria of the DSM-IV-TR
4. Was voluntarily seeking treatment for opioid dependence
5. Was completing or had recently completed up to 30 days of inpatient treatment for opioid detoxification, and had been off all opioids (including buprenorphine and methadone) for at least 7 days
6. Had a non-custodial stable residence and a telephone, plus one contact with verifiable address and telephone number
7. Had a significant other (eg, spouse, relative) who would supervise the patient's compliance with the visit schedule and study procedures

8. If female and of childbearing potential, must have agreed to use an acceptable method of contraception for the duration of the study

5.2.2. Exclusion Criteria

For the purpose of assuring patients' safety and minimizing confounding variables, any of the following was regarded as a criterion for exclusion from the trial:

1. Pregnancy (ie, positive urine and/or serum pregnancy test) and/or currently breastfeeding
2. Clinically significant medical condition or observed abnormalities (including: physical examination, ECG, laboratory evaluation, and/or urinalysis findings)
3. Positive naloxone challenge test at randomization (Day 0)
4. Evidence of hepatic failure including: ascites, bilirubin >10% above upper limit of normal (ULN) and/or esophageal variceal disease
5. Past or present history of an AIDS-indicator disease (eg, Pneumocystis carinii pneumonia, tuberculosis, Kaposi's sarcoma) in patients infected with HIV
6. Active hepatitis and/or aspartate aminotransferase (AST), alanine aminotransferase (ALT) >3×ULN
7. Current major depression with suicidal ideation, psychosis, bipolar disorder, or any psychiatric disorder that would compromise the patient's ability to complete the study
8. Recent history (within 6 months prior to screening) of suicidal ideation or suicide attempt
9. Current dependence (within the past year) to any drugs other than prescription opiates or heroin, caffeine, marijuana, or nicotine, based on DSM-IV-TR criteria
10. Active alcohol dependence within the past 6 months
11. Current alcohol use disorder that would, in the investigator's opinion, preclude successful completion of the study procedures
12. Positive urine drug test for cocaine or amphetamines at screening
13. Use of oral naltrexone for 7 consecutive days within 60 days prior to screening
14. Receipt of any approved or investigational depot product administered into the gluteal muscle within 6 months prior to screening
15. Participation in a clinical trial of a pharmacological agent within 6 months prior to screening
16. Use of any excluded medication at screening or anticipated/required use during the study period
17. Receipt of parenteral naltrexone within 6 months prior to screening
18. Known intolerance and/or hypersensitivity to naltrexone, carboxymethylcellulose, or polylactide-co-polymers (PLG)
19. Any finding that in the view of the PI would compromise the patient's ability to fulfill the protocol visit schedule or visit requirements

20. Parole or probation, or those with pending legal proceedings that had the potential for incarceration of the patient during the study period
21. Investigator-site personnel or immediate family of investigator-site personnel working directly on this project
22. Employment by Alkermes (permanent, temporary contract worker, or designee responsible for the conduct of the study) or immediate family of an Alkermes employee

5.3. Study Design

Prior to entering the study, prospective patients were in the process of completing or had recently completed up to 30 days of inpatient treatment for opioid detoxification, and had been off all opioids (including buprenorphine and methadone) for at least 7 days.

After successfully completing screening evaluations, eligible patients were randomized into 1 of 2 possible treatment groups (VIVITROL 380 mg or placebo) in a 1:1 ratio. Placebo for VIVITROL was composed of PLG microspheres without active naltrexone.

The first dose of study medication was administered on the day of or within 1 week after discharge from an inpatient treatment facility for opioid detoxification. Study treatment was administered as an intramuscular (IM) injection every 4 weeks, for a total of 6 injections in Part A.

Treatment allocation was stratified by site and gender, to minimize potential imbalance at each site using blocked, large-scale randomization. Randomization was centralized by an automated interactive voice response system (IVRS)."

During Part B, all patients received VIVITROL (380 mg) every 4 weeks in an open-label fashion for an additional 13 doses. Placebo injections were not administered during Part B.

At the conclusion of both parts of the study, each completed patient had received 19 monthly injections of study drug over approximately 1.5 years.

All patients, regardless of study treatment group, received Individual Drug Counseling (IDC) throughout the study. IDC is a manual-based standardized method of psychosocial therapy that can be adapted to a primary care setting. This method was developed in the United States by NIDA. IDC focuses on the symptoms of drug addiction and related areas of impaired functioning and the content and structure of the patient's ongoing recovery program. IDC gives the patient coping strategies and tools for recovery and promotes 12-step ideology and participation. Sessions typically involve a review of substance use or efforts to achieve or maintain abstinence, overall functioning, adverse effects, support for efforts to reduce substance use or remain abstinent, and advice for the achievement of abstinence.

Throughout the study, opioid use is monitored through urine drug tests and patients' self-reported data, collected via the Timeline FollowBack (TLFB) method. At screening, each prospective patient provided TLFB data, and each patient's urine was tested for opioids (including methadone), cocaine, benzodiazepines, and amphetamines. Thereafter, TLFB data was collected and urine drug testing for opioids (including methadone) was performed for each enrolled patient each week in Part A and every 4 weeks in Part B.

Importantly, IDC sessions and TLFB collection of self-reported opioid use data were performed by different study site personnel in order to avoid any potential bias on the part of the patient or staff member.

5.4. Evaluation Schedule

Following screening and randomization (Visits 1 and 2), visits occurred weekly during Part A, and monthly during Part B. The visit schedule and assessments that were conducted at each visit are summarized in Table 6.

As described above, urine screens for opioids and collection of opioid use by TLFB, evaluations were performed at each visit. Further evaluations included a visual analog scale (VAS) to assess opioid craving; continuous monitoring and assessment of adverse events (AEs), physical examination and electrocardiogram (ECG) findings, vital sign measurements, injection site assessments, and lab test results; and structured interviews and additional questionnaires as noted in Table 6. Outcome measures of efficacy are described in detail in Section 5.5 below.

Table 6: Study ALK21-013 Visit Assessments

Visit	Assessments	
	PART A	
Screening	• Informed consent • Demographics, height • Medical history including documentation of DSM-IV-TR opioid dependence and number of detoxification events in the last 12 months • Concomitant medication use and review of prohibited medications • Physical examination (including waist circumference and hip circumference measurements), vital signs, and weight • Electrocardiogram	• Blood and urine samples for biochemistry, hematology, and urinalysis • HIV antibody test • Urine pregnancy test (as applicable) • Urine drug testing for opioids (including methadone), cocaine, and amphetamines • Opioid craving (visual analog scale) • AE assessment • Self reported opioid use (via TLFB) for the previous 60 days
Randomization & First Dose	• Review of eligibility criteria • Concomitant medication update • Vital signs, weight • Urine pregnancy test (as applicable) • Urine drug testing for opioids (including methadone) and benzodiazepines • Naloxone challenge • Randomization • Individual Drug Counseling • Beck's Depression Inventory (BDI) • Montgomery-Asberg Depression Rating Scale (MADRS) • Addiction Severity Index (ASI)	• Clinical Global Impression (CGI) • Risk Assessment Battery • SF-36v2 • Social Functioning and Healthcare Utilization Questionnaire • Euro-QOL (EQ-5D) • Timeline Follow-Back (TLFB) • Opioid craving (visual analog scale) • AE Assessment • Injection site assessment • Distribution of a Part A emergency treatment card • Receipt of injection

Table continues

Table 6: Study ALK21-013 Visit Assessments (continued)

Visit	Assessments	
Weekly Interim Visits	• Concomitant medication update • Vital signs • Urine drug testing for opioids (including methadone) • Naloxone challenge (if urine drug test is positive for opioids) • IDC (biweekly)	• SF-36v2 questions #5 and #9 only • TLFB • Opioid craving (visual analog scale) • AE assessment • Confirmation patient has a Part A emergency treatment card
Monthly Dosing Visits	• Concomitant medication update • Vital signs, weight • Urine pregnancy test (as applicable) • Blood and urine samples for biochemistry, hematology, and urinalysis • Urine drug testing for opioids (including methadone) • Naloxone challenge (if urine drug test is positive for opioids) • IDC • SF-36v2 (Month 4 only)	• SF-36v2 questions #5 and #9 only (every visit *except* Month 4) • Social Functioning and Healthcare Utilization Questionnaire • TLFB • Opioid craving (visual analog scale) • AE assessment • Injection site assessment • Confirmation patient has a Part A emergency treatment card • Receipt of injection
Transition Visit, End of Part A, or Part A Early Termination	• Concomitant medication update • Physical examination, vital signs, weight • Urine pregnancy test (as applicable) • Blood and urine samples for biochemistry, hematology, and urinalysis • Urine drug testing for opioids (including methadone) • Naloxone challenge • IDC • Addiction Severity Index (ASI) • Clinical Global Impression (CGI)	• Risk Assessment Battery (RAB) • SF-36v2 • Social Functioning and Healthcare Utilization Questionnaire • Euro-QOL (EQ-5D) • TLFB • Opioid craving (visual analog scale) • ECG • AE assessment • Injection site assessment • Collection of Part A emergency treatment card

Table continues

Table 6: Study ALK21-013 Visit Assessments (continued)

Visit	Assessments	
PART B		
Transition Visit, Start of Part B	• Distribution of Part B emergency treatment card	• Receipt of injection
Monthly Dosing Visits	• Concomitant medication update • Vital signs, weight • Physical examination, ECG (Month 12 only) • Blood and urine samples for biochemistry, hematology, and urinalysis (every 3 months) • Urine pregnancy test (as applicable) • Urine drug testing for opioids (including methadone) • Naloxone challenge (if urine drug test is positive for opioids) • IDC • Addiction Severity Index (ASI), Clinical Global Impression (CGI), Risk Assessment Battery (RAB) (Month 12 only)	• SF-36v2 (Months 9, 12, and 16) • SF-36v2 questions #5 and #9 only (every month *except* Months 9, 12, and 16) • Social Functioning and Healthcare Utilization Questionnaire • Euro-QOL (EQ-5D) (Months 9, 12, and 16) • TLFB • Opioid craving (visual analog scale) • AE assessment • Injection site assessment • Confirmation patient has a Part B emergency treatment card • Receipt of injection
Follow-up, End of Study, or Part B Early Termination	• Concomitant medication update • AE assessment • Physical examination, vital signs, weight • ECG • Blood and urine samples for biochemistry, hematology, and urinalysis • Urine pregnancy test (as applicable) • Opioid craving (visual analog scale) • Urine drug testing for opioids (including methadone) • Naloxone challenge • IDC	• Addiction Severity Index (ASI) • Clinical Global Impression (CGI) • Risk Assessment Battery (RAB) • SF-36v2 • Social Functioning and Healthcare Utilization Questionnaire • Euro-QOL (EQ-5D) • TLFB • Injection site assessment • Collection of Part B emergency treatment card

5.5. ALK21-013 Outcome Measures

5.5.1. Primary Outcome Measure – Opioid-Free Response Profile

The prespecified primary analysis of the primary endpoint of study ALK21-013 was the response profile of the rate of opioid-free weeks during weeks 5 to 24 of Part A. The primary outcome analysis was chosen at the suggestion of the FDA and was considered to yield the most unequivocal evidence of treatment success with high face validity and clinical meaningfulness.

The definition of the primary outcome measure and its meaningfulness are described in this section. Although the initial designation "Opioid-Free Urine Response Profile" to describe the primary outcome measure was used, the prespecified criteria encompass treatment dimensions beyond the opioid urine test. Both self-reported opioid use and retention in treatment are reflected in the primary analysis.

Urine opioid screens were performed weekly during Part A of Study ALK21-013. Therefore, each patient had 20 occasions to submit a urine sample during weeks 5 to 24. Urine samples were collected under direct observation by study-site personnel. A patient with 20 opioid-free urine samples was scored with a frequency of 100%. A patient with 19 opioid free urine samples would have a frequency of 95%, etc. For each treatment group, the response profile was generated by calculating the cumulative percent of patients at each observed value of the rate of opioid-free drug tests ($\geq$0%, $\geq$5%, $\geq$10%, $\geq$15%... $\geq$95%, =100%). Response profiles for 2 treatment arms are displayed graphically by plotting cumulative percent of patients at each observed rate on the same plot. Results were statistically compared with a 2-sided Van der Waerden test.

Consistent with prior research and with the agreement of the FDA, Weeks 1 to 4 of Part A were not included in the prespecified analysis. These initial four weeks of the treatment period were designated *a priori* as a "grace period." It was anticipated that during the initial weeks of therapy, patients might challenge the blockade by continuing to abuse opioids. Patients treated with VIVITROL; however, would have the opportunity to undergo behavioral change by learning that the reinforcing effects of the abused opioid had been extinguished by treatment.

The response profiles of each group utilized a highly rigorous definition of opioid-free. In order to be considered opioid-free all three of the following criteria need to be satisfied:

1. Show no detectable opioids in the urine sample. A validated, sensitive assay was employed for urine testing. The urine drug tests used in this study were immunochromatography-based one-step in vitro tests for opiates and methadone. The opiate test detected urine morphine concentration with a sensitivity level of 300 ng/mL, and the methadone test detected urine methadone concentration with a sensitivity level of 300 ng/mL. As indicated by NIDA, when testing heroin use (the drug of choice for the majority of patients in this study), a test with a sensitivity level of 300 ng/mL may detect morphine in the urine for up to 4 days after the last dose of heroin is taken [National Institute on Drug Abuse (NIDA) 1986]. The test sensitivity employed in the study is more stringent than the US Department of Health and Human Services (DHHS) guidance which recommend a cutoff (sensitivity level) of 2000 ng/mL when testing for opiates in the urine [Substance Abuse and Mental Health Services Administration (SAMHSA) 2004],

2. Confirm no opioid use by self-report. Patients who reported opioid use during the TLFB session were not considered opioid free for the week even if urine testing did not detect the presence of opioids.
3. Attend the scheduled clinic visit. Patients who did not attend the weekly clinical visit or who discontinued treatment did not submit an opioid-free urine. As such, missed visits or visits following treatment discontinuation were scored as non opioid-free. The prespecified analysis of the primary endpoint thereby accounts for clinic attendance and retention in treatment. This criterion added further meaningfulness to the primary endpoint. According to DHHS, retention in a treatment program may be the single most important indicator of medication-assisted treatment outcomes [Center for Substance Abuse Treatment (CSAT) 2005]. In studies that have examined patients who left methadone maintenance treatment prematurely, length of retention was the most significant indicator of treatment effect [Center for Substance Abuse Treatment (CSAT) 2004].

The primary endpoint was selected as it was considered to be both objective and highly clinically meaningful. Urine opioid drug testing has frequently been used as a primary or secondary endpoint in clinical studies of opioid dependence treatment. A key feature of opioid-dependence is inappropriate self-administration of exogenous opioids; detected opioid use is a direct reflection an active disease manifestation and thus has high face validity. In contrast to subjective reporting, urine opioid tests provide an objective measure of opioid use, hence avoiding potential patient underreporting of use. Finally, as noted above, the endpoint incorporates the important dimension, treatment retention, in the definition of opioid-free.

Using response profiles to display opioid use provided more information than the usual method of reporting either total abstinence or average use per treatment group, as these profiles provide an entire range of data from no treatment response to total abstinence. This additional information could aid prescribing physicians to make more informed decisions based on their goals for individual patients. The response profile approach has been used as the basis of recent FDA approvals of medications for the treatment of neuropathic pain and fibromyalgia.

5.5.2. Sample Size Considerations for the Primary Endpoint

The sample size (N=250) was expected to provide 85% and 96% power to detect an effect size of Cohen's d=0.4 and 0.5, respectively, by a Wilcoxon rank-sum test at a 0.05 two-sided significance level. Further detail is provided in the Statistical Analysis Plan (SAP) for study ALK21-013 (see Appendix Section 10.4).

5.5.3. Secondary Outcome Measures

The ALK21-013 protocol and SAP specified 2 key secondary and 2 additional secondary endpoints to further evaluate the robustness and meaningfulness of treatment effects assessed by the primary endpoint. The key secondary endpoints were (1) retention in study treatment and (2) opioid craving. To account for potential multiplicity, the 2 key secondary endpoints were analyzed in hierarchical order following the analysis of the primary endpoint. There were 2 additional secondary endpoints: (1) self-reported opioid use and (2) occurrence of positive naloxone challenge test. The secondary endpoints are described below. Further details regarding the analysis are provided in the SAP (see Appendix Section 10.4).

5.5.3.1. Key Secondary Endpoint: Retention in Treatment

Treatment retention is a particularly important outcome measure. As noted above, according the DHHS, retention in a treatment program may be the most important indicator of medication-assisted treatment outcomes [Center for Substance Abuse Treatment (CSAT) 2005]. In studies that have examined patients who left methadone maintenance treatment prematurely, length of retention in treatment was the most significant indicator of treatment effect [Center for Substance Abuse Treatment (CSAT) 2004].

Retention in treatment is considered to be of such high importance that in order for opioid treatment programs to be certified by the DHHS those programs need to conduct annual reviews of retention, and federally licensed programs must demonstrate regular monitoring of retention in treatment [Substance Abuse and Mental Health (SAMHSA) Data Archive 2007].

Treatment retention was analyzed as the time from randomization to the final study visit displayed on a Kaplan-Meier plot. In contrast to the primary endpoint, in this context efficacy is defined as continued attendance in scheduled clinic visits irrespective of urine opioid screen results or self-reported use of opioids.

5.5.3.2. Key Secondary Endpoint: Opioid Craving

Another important outcome domain in the treatment of opioid dependence is drug craving. Drug craving is a compelling desire for previously experienced effects of a reinforcing substance that can emerge in the presence of both internal and external cues, and to a greater extent, with perceived availability of the substance, often leading to relapse. Craving early during protracted abstinence in the absence of cues has also been characterized, often as an internal stress response, and has been documented in drug dependent individuals for weeks after acute withdrawal [Koob 2008].

Naltrexone's blockade of opioid receptors is thought to block the rewarding effect of opioids and thereby lead to reduced craving; however, oral naltrexone has not necessarily been associated with craving decreases [Dijkstra, 2007]. In human laboratory research, both drug-cue-related imagery and stress significantly increase opioid craving. Oral naltrexone has been found to reduce drug cue-induced craving but not stress-induced craving, and stress-related arousal responses are thought to contribute to high rates of noncompliance and relapse [Hyman, 2007]. Another factor is that craving is thought to be influenced by the patients' environment, increasing with perceived availability of the substance [Koob 2008]. With unsupervised oral naltrexone self-administration, failure to self-administer creates a perceived (and pharmacologically real) opportunity for obtaining drug effects on a daily basis.

Methods of measurement vary; however, the most common and basic assessment tool is a simple visual analog scale (VAS) measuring how much craving or urge to use the patient is experiencing. Craving was therefore assessed by VAS in the ALK21-013 study.

5.5.3.3. Secondary Endpoint: Self-Reported Opioid Use

The primary endpoint of the study was based on objective assessment – urine drug screen. Subjective self reports of opioid use were included as a secondary endpoint in the study to complement and substantiate the objective assessments with subjective reports from the study

patients. Self reports of opioid use were collected using a validated methodology, the TLFB method [Sobell and Sobell 1992].

In addition to its role as a secondary endpoint, the TLFB report was used as an additional criterion for opioid free. As described above, in order for a patient to be considered opioid free for a study week, the patients TLFB response had to confirm that no opioids had been used.

5.5.3.4. Secondary Endpoint: Positive Naloxone Challenge Test

If a patient had a positive urine drug screen during the study, a naloxone challenge test was performed. The naloxone challenge test entails administration of a small sub-cutaneous injection of a short acting opioid antagonist, naloxone. The test was deemed positive if the injection elicited signs and symptoms of opioid withdrawal.

Opioid withdrawal symptoms elicited by the naloxone challenge test performed during the study provided evidence that a patient has been using opioids to a sufficient degree that physical dependence has been re-established. The rate of positive naloxone challenge tests was compared between treatment groups.

5.5.4. Exploratory Outcome Measures

The ALK21-013 study included a battery of exploratory outcome measures including of health outcomes and quality of life (QOL) assessments. Exploratory endpoints included responses to the Addiction Severity Index (ASI), the Short Form Health Survey (SF-36v2), the Euro-QOL health outcome survey (EQ-5D), the Clinical Global Impression (CGI) scale, and the Risk Assessment Battery (RAB). The purpose of the exploratory measures was to provide further perspective on the impact, meaningfulness, and consequence of the reduction in opioid usage and retention in treatment, as captured by the primary and secondary endpoint analyses.

6. STUDY ALK21-013 EFFICACY RESULTS

In an adequate and well-controlled study (ALK21-013) with a 6-month pivotal efficacy evaluation, VIVITROL 380 mg, compared to placebo, demonstrated substantial evidence of efficacy in the treatment of opioid dependence. The finding is based on demonstration of clinically meaningful and statistically significant improvement in the primary prespecified efficacy endpoint. In addition, all prespecified key secondary, and other secondary efficacy endpoints demonstrated significantly greater improvement with VIVITROL versus placebo. Specific findings in the VIVITROL group (versus placebo) included the following:

- **Higher rate of confirmed opioid abstinence:** The results of the primary prespecified analysis of the primary endpoint indicated patients in the VIVITROL group had a statistically and clinically significantly greater proportion of confirmed opioid-free weeks (P=0.0002). A secondary analysis of self-reported opioid use demonstrated a similar significant treatment effect with VIVITROL compared to placebo (P=0.0004).
- **Longer retention in treatment:** Retention in treatment was statistically significantly longer for patients in the VIVITROL group versus the placebo group (P=0.0042). Median days on treatment for VIVITROL group was >168 compared to 96 in placebo group.
- **Reduced opioid craving:** Patients treated with VIVITROL demonstrated a significant reduction in opioid craving compared to placebo (P<0.0002). This statistically and clinically significant treatment difference was evident by Week 8 and persisted through the end of Part A.
- **Reduced incidence of physiologic dependence:** A significantly greater proportion of patients in the placebo group relapsed to physiologic dependence (defined as a positive naloxone challenge) as compared to patients in the VIVITROL group (P=0.0154).

Exploratory analyses provide further corroboration of efficacy and the clinical relevance of these findings, including significant improvements in health-related quality of life (QOL), decrease in risky behavior, and improvement in global health assessments and mental health related quality of life as assessed by the SF-36v2.

Evidence from Part B of study ALK21-013 which is ongoing, suggests that the benefits observed with VIVITROL therapy during the initial 6 months of treatment are durable.

The results of two long-term, open label studies ALK21-006 and ALK21-021 (ongoing study in opioid-dependent health care professionals) show good retention and thus provide further supportive evidence of efficacy.

6.1. ALK21-013: Efficacy Study Results

6.1.1. Disposition of Patients

For a 6-month study of patients with opioid dependence, retention in the ALK21-013 study was excellent. Retention in patients treated with VIVITROL was significantly higher than in patients receiving placebo treatment. There were no discontinuations due to AEs among patients treated with VIVITROL.

A total of 335 patients were screened and 250 patients enrolled. Of the enrolled patients, 124 were randomized to receive placebo and 126 were randomized to receive VIVITROL 380 mg. A total of 136 (54.4%) patients discontinued during Part A: 77 (62.1%) were in the placebo group and 59 (46.8%) were in the VIVITROL group. Additionally, 2 (1.6%) patients in the placebo group discontinued due to AEs while none of the patients treated with VIVITROL withdrew due to an AE.

Patients treated with placebo were more likely to discontinue treatment due to relapse to opioid dependence. A positive naloxone test was observed in 17 (13.7%) patients in the placebo group compared to just 1 (0.8%) patient in the VIVITROL group (the positive naloxone challenge test in this patient occurred 2 months after his last injection). The naloxone challenge tests were performed in response to a positive urine opioid screen. Positive naloxone challenge tests indicated that the patients had re-initiated abuse of opioids to an extent that physical dependence had been re-established.

A total of 47 (37.9%) of the placebo-treated patients and 67 (53.2%) of the VIVITROL-treated patients entered the open-label safety extension of the study (Part B). Part B is ongoing at the time of this submission.

A summary of patient disposition including reasons for discontinuation (based on blinded data) are presented in Table 7 below. Note that N=12 patients in the placebo group and N=18 patients in the VIVITROL group were categorized as having "withdrawn consent." The category reflects patients who voluntarily elected to not return for further treatment. In most cases, this reason for discontinuation was confirmed by a family member. Since the patient's decision to discontinue therapy was confirmed by a family member, these patients were not considered "lost to follow-up." Importantly, patients assigned to the category of 'withdrew consent" did not actually undergo a formal written withdrawal of consent process.

Table 7: Patient Disposition—ALK21-013

	Placebo	VIVITROL
Patients randomized, N	124	126
Patients dosed (used for Full Analysis Set), N	124	126
Completed[2] double-blind phase Part A (N, %)[1]	47 (37.9)	67 (53.2)
Discontinued during Part A (N,%)[1]	77 (62.1)	59 (46.8)
Reason for discontinuation during Part A (N,%)[1]		
Lack of efficacy	34 (27.4)	22 (17.5)
Patient withdrew consent	12 (9.7)	18 (14.3)
Positive naloxone challenge	17 (13.7)	1 (0.8)
Lost to follow-up	6 (4.8)	6 (4.8)
Investigator judgment	4 (3.2)	8 (6.3)
Major protocol violation	2 (1.6)	1 (0.8)
Adverse event	2 (1.6)	0
Incarceration	0	2 (1.6)
Patient relocated	0	1 (0.8)
Treatment goal met	0	0
Lost Motivation	0	0
On-going at the database lock for Part A analysis	40 (32.3)	49 (38.9)

Source: ALK21-013 CSR Tables 14.1.1 and 14.1.1.1

[1] Percentages are of the number of patients in the Full Analysis Set (FAS)

[2] Patients who continued to open label phase (received at least one open-label injection) were counted as completed Part A

6.1.2. Study Population

The ALK21-013 study enrolled patients with clear evidence of opioid dependence that is generalizable to the opioid-dependent treatment population at large, including opioid-dependent individuals in the US. Baseline characteristics are summarized in Table 8.

All patients met DSM-IV-TR criteria for opioid dependence, and had an average of 9 to 10 years of opioid use.

The population studied included predominantly patients abusing heroin, although patients who abused orally administered opioids were also enrolled. In the 30 days prior to the receipt of the first dose, 221 (88.4%) patients reported use of heroin, 29 (11.6%) reported use of methadone, and 33 (13.2%) reported use of other opioids/analgesics.

Consistent with the population using heroin, the study enrolled patients with a high incidence of viral hepatitis and HIV sero-positivity. The majority of patients had a baseline history of hepatitis C (88.8%), and many (41%) were HIV positive.

Patients in study ALK21-013 study were primarily male (88%) and white (99%).

From the perspective of treatment group comparison, patients in both treatment groups (placebo and VIVITROL) were similar in terms of all demographics and baseline characteristics.

Summary statistics for patient demographics and baseline characteristics are presented in Table 8.

Table 8: Demographics and Baseline Characteristics—ALK21-013

Variable/ Category	Placebo, n=124	VIVITROL, n=126
Age (years)		
Mean (SD)	29.7 (3.6)	29.4 (4.8)
Range	21 – 43	21 – 52
Sex – n (%)		
Male	107 (86.3)	113 (89.7)
Female	17 (13.7)	13 (10.3)
Race – n (%)		
White	124 (100.0)	124 (98.4)
Asian	0 (0.0)	2 (1.6)
Baseline BMI (kg/m^2)		
Mean (SD)	23.20 (2.71)	23.25 (2.66)
Range	17.3 – 30.9	18.2 – 32.5
Duration of Opioid Dependence (years)		
Mean (SD)	10.0 (3.9)	9.1 (4.5)
Range	1 – 21	1 – 26
Reported Opioid Use in Past 30 Days – n (%)		
Heroin	110 (88.7)	111 (88.1)
Methadone	18 (14.6)	11 (8.7)
Other Opioids/Analgesics	12 (9.8)	21 (16.8)
Baseline Hepatitis C or HIV-positive Status – n (%)		
Hepatitis C	114 (91.9)	108 (85.7)
HIV	52 (41.9)	51 (40.5)
Self-Reported Opioid-Negative Days in the 30 Days Prior to Hospitalization for Detoxification		
Mean (SD)	9.17 (16.43)	12.04 (21.41)
Median	0	0

(table continues)

Table 8: Demographics and Baseline Characteristics—ALK21-013 (continued)

Beck Depression Inventory (BDI) total score		
Mean (SD)	12.2 (7.8)	11.8 (7.1)
Median	11.0	11.0
Severity of depression as categorized by BDI total score		
0: No depression	1 (0.8)	2 (1.6)
1 - 10: Normal ups and downs	57 (46.0)	58 (46.0)
11 - 16: Mild mood disturbance	34 (27.4)	41 (32.5)
17 - 20: Borderline clinical depression	14 (11.3)	13 (10.3)
21 - 30: Moderate depression	15 (12.1)	9 (7.1)
31 - 40: Severe depression	3 (2.4)	3 (2.4)
over 40: Extreme depression	0	0

Source: ALK21-013 CSR Tables 14.1.2.1, 14.1.3
Note: SD = standard deviation; BMI = body mass index

6.1.3. ALK21-013 Primary, Secondary and Exploratory Efficacy Results (Part A)

A description of the outcome measures used in the ALK21-013 study is provided in Section 5.5.

6.1.3.1. Primary Analysis of the Primary Endpoint

VIVITROL demonstrated statistically significant and clinically meaningful efficacy in the treatment of opioid dependence as assessed by the primary prespecified analysis of the primary endpoint.

The primary analysis of the primary endpoint was a response profile based on the rate of confirmed opioid-free weeks during Weeks 5 to 24 of Part A. Figure 7 shows the response profiles for each treatment arm (VIVITROL or placebo) based on patients' individual rates of opioid-negative urine tests and self-reported opioid use. Response profiles indicated that patients in the VIVITROL group had a statistically significantly greater proportion of opioid-free weeks compared to patients in the placebo group (P=0.0002). The data used to generate Figure 7 are summarized in Appendix Section 10.4, Table 18.

The median patient treated with VIVITROL had an opioid-free rate of 90% compared to 35% with placebo Table 9.

Total abstinence (100% opioid-free weeks) during Weeks 5 through 24 was reported in 45 (35.7%) patients in the VIVITROL group versus 28 (22.6%) patients in placebo group (P=0.0224).

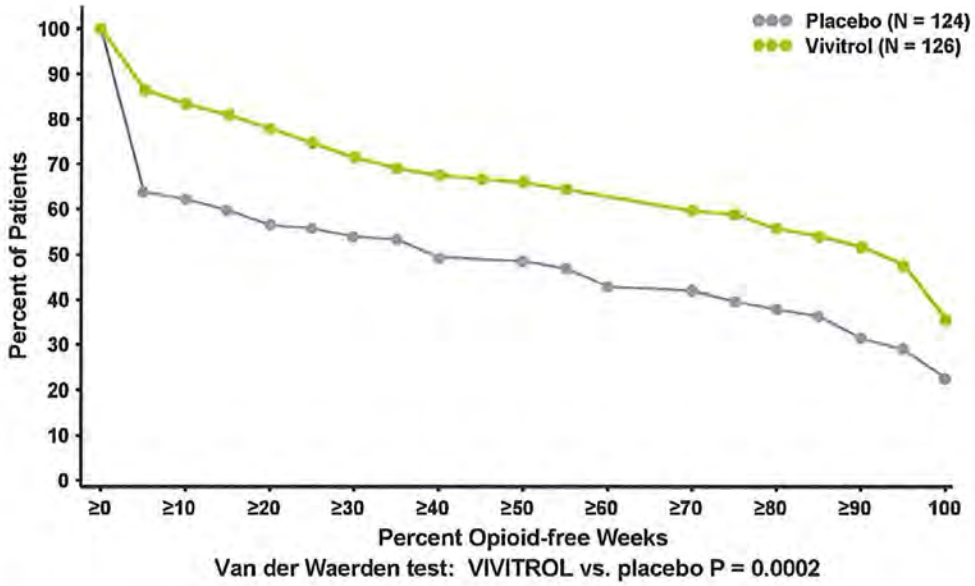
As described in Section 5.5.1, although the name "Opioid-Free Urine Response Profile" was originally used, the prespecified criteria for the primary outcome measure encompass treatment dimensions beyond the opioid urine test. Both self-reported opioid use and retention in treatment are reflected in the primary analysis. The criteria for opioid-free include:

1. Show no detectable opioids in the urine sample using a sensitive immunochromatography-based assay.

2. Confirm no opioid use by self-report. Patients who reported opioid use during the TLFB session were not considered opioid free for the week even if urine testing did not detect the presence of opioids
3. Attend the scheduled clinic visit. Patients who did not attend the weekly clinical visit or who discontinued treatment did not submit an opioid-free urine and thus were scored as non opioid-free in the analysis.

Review of the data revealed that the large majority of "non opioid-free" data points occurred due to discontinuation in treatment or missed clinic visits. As discussed in Sections 6.1.1 and 6.1.3.3, retention in treatment was higher with VIVITROL-treated patients compared to placebo. Patients treated with placebo were more likely to relapse to opioid dependence compared to VIVITROL treated patients; whereas patients in the VIVITROL arm, if they 'slipped' (used opioids but did not become physiologically dependent) were able to remain in the study.

There were 53 occasions (1.24% of data points) on which patients reported using opioids via TLFB but had opioid-free urine drug tests. Per the definition used for the analysis, these data points were scored as non opioid-free.



Source: ALK21-013 CSR Table 14.2.1.1

Figure 7: Study ALK21-013 Primary Analysis: Opioid-Free Weeks Response Profile, Weeks 5–24

Table 9: Opioid-Free Weeks Response Profile: Weeks 5–24

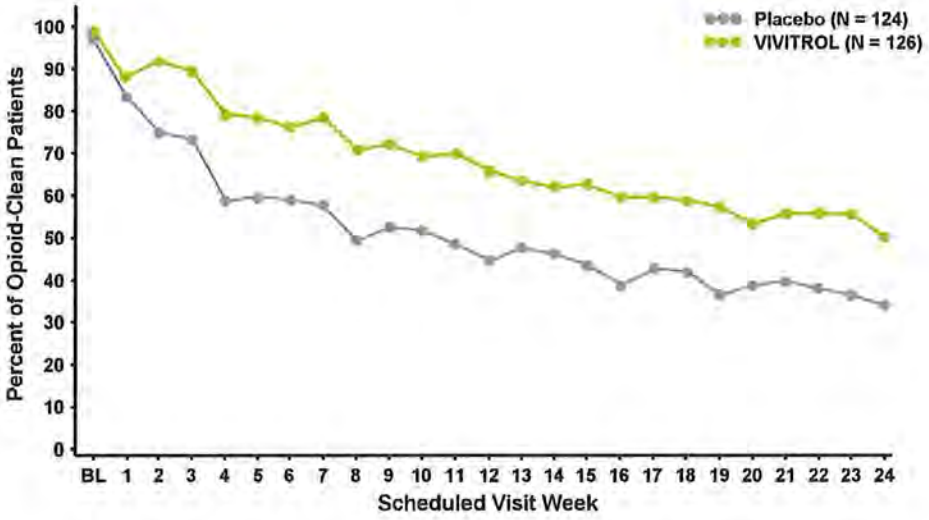
	Opioid-Free Weeks Response Profile (%)	
	Placebo	**VIVITROL**
N	124	126
Mean (SD)	46.0 (43.3)	64.5 (40.1)
Median	35	90
Range	0–100	0–100

Source: ALK21-013 CSR Table 14.2.1.3

6.1.3.2. Additional Analyses of the Primary Endpoint

The finding of efficacy with the primary analysis of the primary endpoint was supported by additional analyses of the primary endpoint.

The percent of opioid-free patients at each visit is displayed in Figure 8. By Week 2 there was a greater proportion of opioid-free patients in the VIVITROL group versus the placebo group, and this separation from the placebo trend persisted for the last 20 weeks of the double-blind phase of the study.



Source: ALK21-013 CSR Figure 4

Figure 8: Study ALK21-013—Percent of Opioid-Free Patients, by Week (Full Analysis Set)

6.1.3.3. Analyses of the Secondary Endpoints

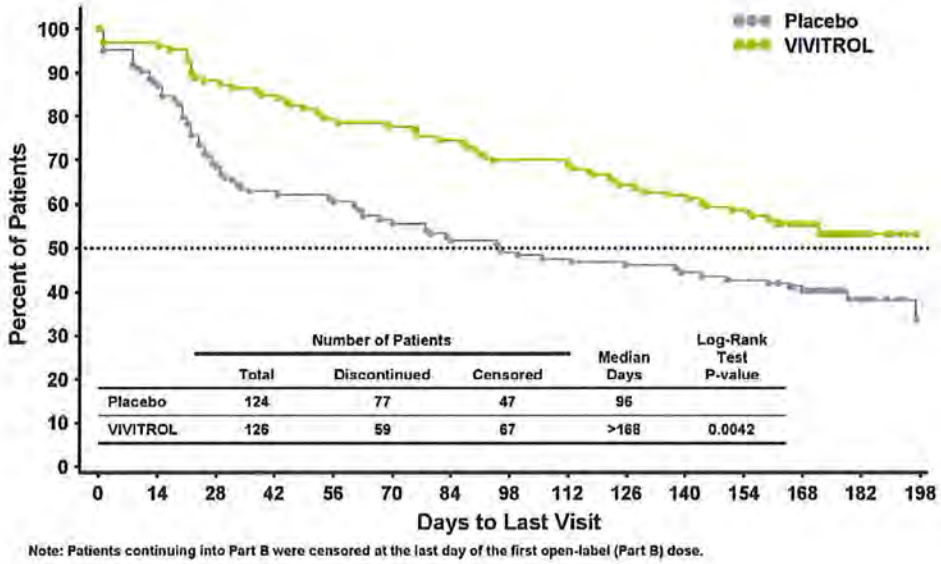
The robustness and clinical meaningfulness of the finding with the primary endpoint were further confirmed by analyses of secondary endpoints. VIVITROL, in comparison to placebo, demonstrated statistically significant and clinically meaningful efficacy in all predefined secondary endpoints including the key secondary endpoints treatment retention ($p=0.0042$), opioid craving ($p<0.0002$), as well as self-reported opioid use ($p=0.0031$), and positive naloxone challenge test ($p=0.0154$).

Key Secondary Endpoint Result: Treatment Retention

Treatment retention has been considered to be the single most important indicator of medication-assisted treatment outcomes [Center for Substance Abuse Treatment (CSAT) 2005]. The longer patients remain engaged in therapy, the greater the opportunity to stabilize abstinence, engage in counseling, organize chaotic lifestyles, and improve family and social relationships that can be supportive of recovery.

Figure 9 demonstrates that patients in the VIVITROL group stayed in the study longer than patients in the placebo group ($P=0.0042$, adjusted for multiplicity). Median days on treatment for patients in the VIVITROL group was >168 days compared to 96 days for patients in placebo group.

A total of 47 (37.9%) of the placebo-treated patients and 67 (53.2%) of the VIVITROL-treated patients completed Part A and entered the open-label safety extension of the study (P=0.0171). .



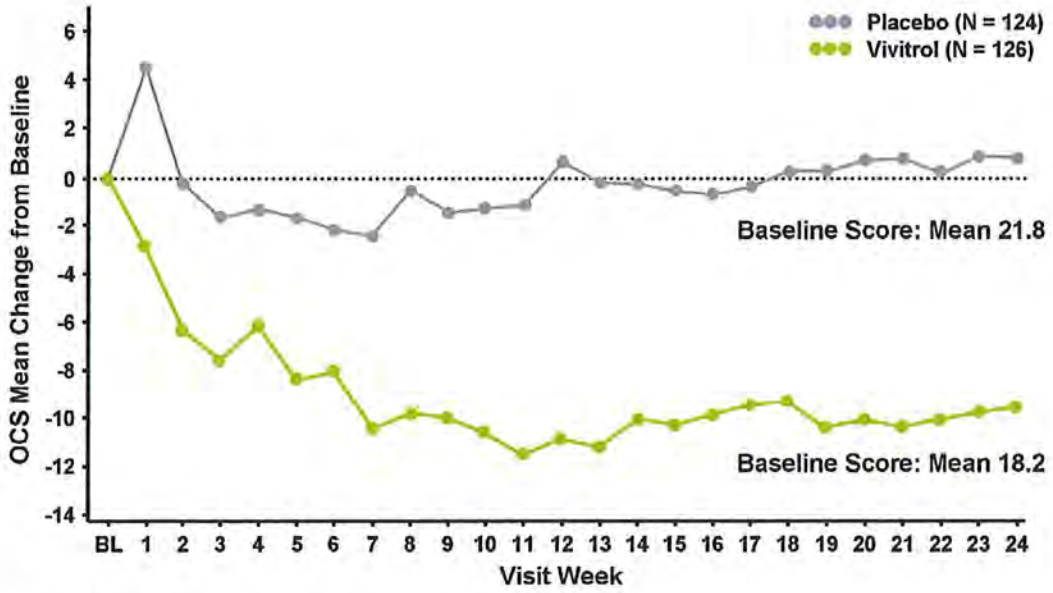
Source: ALK21-013 CSR Table 14.2.2.1

Figure 9: Time to Discontinuation: Part A (Full Analysis Set)

Key Secondary Endpoint Result: Opioid Craving

For the full study period, patients reported significantly less craving with the 380 mg dose of VIVITROL than with placebo at P<0.0002. The reduction in craving with VIVITROL treatment was about 50% from baseline, whereas patients treated with placebo showed no significant change compared to baseline (Figure 10). These data are summarized by study visit in Appendix Section 10.4, Table 20).

The observed reduction in opioid craving indicates that the treatment effects of VIVITROL extend beyond the blockade of drug induced euphoria/ re-enforcement. Although the mechanism of action of the observed effect is uncertain, the clinical benefit of reduction in drug craving is important and may contribute to overall treatment success.



Source: ALK21-013 CSR Table 14.2.3.1

Figure 10: Opioid Craving Score, Mean Change from Baseline using Last Observation Carried Forward (LOCF), Full Analysis Set

Secondary Endpoint Result: Self-Reported Opioid Use

During the study period, patients in the VIVITROL group reported significantly more opioid-free days than were reported by patients in the placebo group (P=0.0004). Patients in the VIVITROL group reported a median of 99.2% opioid-free days compared to 60.4% reported by patients in the placebo group Table 10. The primary prespecified analysis used baseline values.

Table 10: Percent Self-reported Opioid-Free Days (Part A)

Assessment	Statistic	Placebo n=124	VIVITROL n=126	P-Value[1]
Baseline[2]	Mean (SD)	9.17 (16.43)	12.04 (21.41)	0.5291
	Median	0.00	0.00	
Double Blind Period	Mean (SD)	60.59 (37.96)	77.79 (30.83)	**0.0004**
	Median	60.42	99.16	
Change from Baseline	Mean (SD)	51.42 (39.32)	65.75 (34.87)	**0.0031**
	Median	46.43	75.83	

Source: ALK21-013 CSR Table 14.2.5.1
[1] For VIVITROL vs. placebo from Van der Waerden test, Baseline Value Carried Forward.
[2] Rate during the 30-day period immediately prior to hospitalization for detoxification

Secondary Endpoint Result: Naloxone Challenge

Opioid withdrawal symptoms elicited by the naloxone challenge test performed during the study provided evidence that a patient has been using opioids to a sufficient degree that physical dependence has been re-established. The results indicate that the higher use of opioids among placebo treated patients translated into a higher incidence of relapse to physical dependence.

Per the prespecified analysis, a significantly greater proportion of patients in the placebo group (62.1%) relapsed to physiologic dependence as compared to 46.8% of patients in the VIVITROL group (P=0.0154) (Appendix Section 10.4, Table 21). The analysis categorized patients who had discontinued as having relapsed to opioid dependence data.

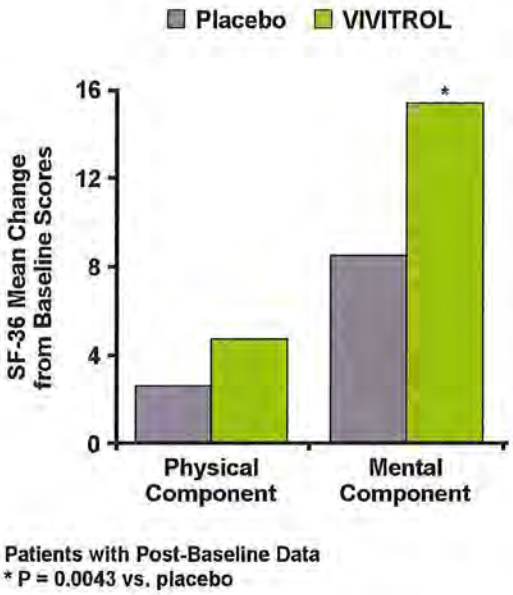
An additional analysis was performed to determine the incidence of positive naloxone challenge in Part A without categorizing discontinued patients as having relapsed. One VIVITROL and 17 placebo treated patients had a positive naloxone challenge in Part A of the study (Appendix Section 10.4, Table 22). The difference in incidence was statistically significant (0.8% vs. 13.7%, p<0.0001). The single patient in the VIVITROL group had a positive naloxone challenge at Week 16 after missing a dose of VIVITROL (Week 12), ie, 8 weeks since the last dose of VIVITROL. All 18 patients who had a positive test were administered the challenge in response to a positive urine drug test result.

6.1.3.4. Analysis of Exploratory Endpoints

The ALK21-013 study included a battery of exploratory outcome measures intended to provide further perspective of the impact, meaningfulness, and consequence of the reduction in opioid usage and retention in treatment captured by the primary and secondary endpoint analyses. Exploratory outcome measures included assessments of health-related QOL and risky behavior. Significant differences between VIVITROL and placebo were observed whereas other measures showed no difference from placebo. A full summary is provided in Appendix Section 10.5, Table 23 through Table 28.

The principal measure of QOL in the present study was the SF-36v2. Analysis of the SF-36v2 scores revealed that VIVITROL resulted in substantial improvements in mental-health-related QOL that were significantly greater than those observed with placebo treatment.

Baseline mental-health-related SF-36 scores for patients enrolled in the ALK21-013 study are consistent with substantially sub-normative mental health related QOL. With treatment, the mental health component summary score for all 4 mental health subscales showed improvements with VIVITROL compared to placebo (see Appendix Section 10.4, Table 23). These differences between VIVITROL and placebo were statistically significant. Improvement in the overall mental health summary score for VIVITROL at the end of Part A was greater than 1.5 SDs (placebo = 45.28; VIVITROL = 50.37; P=0.0043).



Baseline Summary Score

	Mean
Physical Component	50.5
Mental Component	35.2

	Placebo N	VIVITROL N
Baseline	122	125
Patients with Post-Baseline Data	76	91

Source: ALK21-013 CSR Table 14.3.3

Figure 11: Quality of Life Improvements with VIVITROL

In contrast to the mental component summary score, baseline SF-36v2 physical component summary scores were at or above norms for both groups at baseline and did not change significantly during treatment.

The Risk Assessment Battery (RAB) provides a measure of HIV risk in a substance-using population, which is based on drug and alcohol use in the past 30 days, and needle use and sexual behavior in the last 6 months [Metzger, 2001]. This type of risky behavior is a key factor in the transmission of viral hepatitis and AIDS among opioid dependent patients. Results of the RAB indicated that risky behavior was reduced during treatment with VIVITROL. The improvements with VIVITROL were significantly greater than those observed with placebo treatment. At the end of Part A, the VIVITROL group showed a 62% decrease from baseline, which was significantly greater than the 46% reduction for the placebo group (P=0.0212), indicating that the VIVITROL group lowered the overall risk of HIV infection significantly more than the placebo group (see see Appendix Section 10.4, Table 24).

Investigator's assessment of patients' severity of illness and changes in medical status were assessed using the CGI scale. Scores for the severity of opioid addiction at baseline were similar for the placebo and VIVITROL groups. At the end of Part A, patients in the VIVITROL group scored significantly higher (where higher indicates greater improvement) when assessed for severity of opioid addiction (P=0.0092) and global improvement (P=0.0011) than patients in the placebo group (see Appendix Section 10.4, Table 25).

6.1.4. Comparison of Results of Subpopulations

6.1.4.1. ALK21-013 Prespecified Stratification Analysis

To explore the influence of stratification factors and other clinically relevant baseline characteristics, the rate of opioid-free weeks was analyzed factoring in treatment group, sex, and sex-by-treatment interaction. Age, duration of opioid dependence, and duration of last prestudy inpatient detoxification treatment period were included as continuous covariates. There was no statistically significant effect of stratification factors on the rate of opioid-free weeks, indicating that the difference in rates of opioid-free weeks between placebo and VIVITROL groups was most likely due to the effect of study drug, and independent of patients' sex, age, duration of opioid dependence, or duration of last prestudy inpatient detoxification period. Least square mean estimates and 95% confidence limits of the rate of opioid-free weeks in each treatment group indicated the rate in VIVITROL group was statistically significantly higher than the rate in the placebo group (P=0.0009). This analysis further confirmed the robustness of the results of the primary analysis.

Treatment effect within study centers was also explored. Most sites (6 out of 7) that enrolled more than 10 patients reported higher average rates of opioid-free weeks for VIVITROL-treated patients than for those treated with placebo, indicating consistent treatment effect across study sites (see Appendix Section 10.4, Table 29).

6.1.4.2. ALK21-013 Prespecified Subgroup Analyses

Consistency of the treatment effect within various subgroups was analyzed. Response profiles by treatment group were summarized for subgroups defined by the following baseline characteristics:

- Sex
- Age
- Duration of opioid dependence
- Duration of last prestudy inpatient detoxification

Treatment by factor interaction was assessed with analysis of variance (ANOVA) models of the rate of opioid-free weeks. Separate ANOVA models including fixed effects for treatment, subgroup factor and treatment by factor interaction were used for each baseline characteristic. These results demonstrated that within each subgroup, the rate of opioid-free weeks in the VIVITROL group was consistently higher than the rate in the placebo group. No significant interaction effect was found between treatment and any of the subgroup factors.

6.1.5. Comparison of Efficacy Results of VIVITROL to Oral Naltrexone

In the absence of a direct head-to-head evaluation, a definitive comparison between the efficacy of VIVITROL and oral naltrexone cannot be made. Qualitatively, the robust efficacy signal observed with VIVITROL in the ALK21-013 study compares favorably to the aggregated published experience with oral naltrexone.

In the Cochrane meta-analysis [Minozzi, 2006], naltrexone efficacy as the percent of patients remaining on oral naltrexone relative to placebo was displayed as relative risk. A higher relative

risk indicated superiority of oral naltrexone in promoting retention, the chosen primary measure of efficacy. Study retention in groups receiving naltrexone or naltrexone plus psychosocial treatment versus groups receiving placebo or placebo plus psychosocial treatment had an overall relative risk of 1.08 (95% confidence interval: 0.74, 1.57). In comparison, results from the pivotal VIVITROL study ALK21-013 show the relative risk of 1.40 (favoring VIVITROL) with the 95% confidence interval of 1.06–1.85. By this measure, VIVITROL compares favorably with the oral naltrexone literature.

6.2. Supportive Evidence: ALK21-006 (Final Results), ALK21-021 (Interim Results) and ALK21-013 Part B (Interim Results)

The efficacy of VIVITROL in the treatment of opioid dependence (ALK21-013) is augmented by treatment retention experience in two open-label long-term studies of VIVITROL in the treatment of patients with opioid dependence (ALK21-006 and ALK21-021) in the United States. Both open-label studies show good retention rates and support the clinical utility of VIVITROL in the treatment of opioid dependence.

ALK21-006, ALK21-006-EXT

ALK21-006 was a multi-center, randomized, open-label, Phase 3 long-term safety study assessing the safety of repeat doses of VIVITROL 380. The objective of the study was to assess the safety of VIVITROL in patients with alcohol dependence, opioid dependence, and mixed alcohol-opioid dependence. The long-term retention data collected in study ALK21-006 are supportive of the efficacy seen in the pivotal study ALK21-013 and support the applicability of VIVITROL in the treatment of opioid dependence in the US.

The study enrolled 315 patients with a diagnosis of alcohol dependence alone, 69 with a diagnosis of opioid dependence alone, and 52 with a diagnosis of mixed dependence. To qualify for the study, a diagnosis of alcohol and/or opioid dependence based on the DSM-IV criteria was required.

Among patients with opioid or mixed opioid dependence the mean age was 34 years. The proportion of males to females was approximately 2:1 . Enrolled patients were white (84%) black (8%) and Hispanic (6%).

Opioid dependent patients in the ALK21-006 study demonstrated good adherence to VIVITROL therapy – similar to study ALK21-013 — with over 50% of patients remaining on VIVITROL treatment at 6 months, and over 30% of patients at 12 months.

ALK21-021

ALK21-021 is an open-label, 24-month study designed to evaluate the long-term efficacy and safety of VIVITROL in N=38 health-care professionals (physicians, osteopaths, nurses, pharmacists) who have a history of opioid dependence. Enrolled patients are participating in an extended outpatient treatment program including VIVITROL 380 mg injected IM once monthly for 24 months and concurrent psychosocial therapy.

Enrollment into this study has closed and the clinical portion is ongoing. The preliminary interim safety data from this ongoing study that are described here were provided in the 120-Day Safety Update recently received by the FDA. As of 03 May 2010, 32 (84%) patients were ongoing. Of these, 11 (29%) had received ≥6 months of VIVITROL treatment.

ALK21-013 (Part B)

Study ALK21-013 (N=250) is a phase 3, randomized, multi-center study being conducted in 2 parts, Part A and Part B. Part A, the blinded portion of the study was completed and unblinded as of 06 November 2009. Patients who completed Part A continued to Part B, which is an open-label phase to assess longer-term safety, durability of effect, health economics, and quality of life (QOL) in the continuing study population. In Part B, which remains ongoing, all patients are administered an IM injection of open-label VIVITROL 380 mg every 4 weeks (monthly) along with psychosocial support. At the conclusion of both parts, each completing subject will have received a total of 19 injections of study drug over approximately 1.5 years.

The preliminary interim safety data from this ongoing study that are described here were provided in the 120-Day Safety Update recently received by the FDA.

As of 03 May 2010, 114 patients (46%) had received >6 months of VIVITROL treatment, while 75 had received ≥12 months and 29 had received ≥18 months. Of these, 24 had completed the study, 57 were continuing on treatment and 33 had discontinued as of data cut-off.

7. VIVITROL SAFETY

This section will review VIVITROL safety. As noted previously, this Efficacy Supplement builds on the prior approval of VIVITROL for alcohol dependence. As such, the following discussion of safety will begin with the current package insert and postmarketing safety surveillance results. This will be followed by a detailed description of safety data from study ALK21-013. Relevant data from the open-label studies ALK21-006 and ALK21-006-EXT will be added to provide additional context to findings in opioid dependent patients.

VIVITROL is well tolerated and has a well-characterized safety profile in dependent adults. It was approved for use in alcohol dependence in 2006. This approval was based on experience in 1065 patients, most of them alcohol-dependent, who participated in 7 primary clinical trials and 3 extension studies. The data from those studies were incorporated into the VIVITROL package insert for alcohol dependence, which is provided in Appendix Section 10.1. As can be seen through review of the information in that label, adverse events with VIVITROL were generally mild or moderate in intensity. The most common included gastrointestinal symptoms (eg, nausea, vomiting, diarrhea, abdominal pain), injection site reactions, asthenic conditions, insomnia and sleep disorders, and infections such as nasopharyngitis or sinusitis.

The VIVITROL label describes the several precautions and warnings that will be reviewed in the context of postmarketing surveillance reports.

VIVITROL® (naltrexone for extended-release injectable suspension) has been available for use since June 2006. Though the approved indication is for the treatment of alcohol dependence, Alkermes is aware that VIVITROL is sometimes used in an off-label manner. However, it is impossible to accurately determine the extent of off-label use. As indicated below, Alkermes has received reports of adverse events in people who have received VIVITROL for opioid dependence. It is estimated that approximately 45,000 patients have been exposed to VIVITROL between the date of initial approval and 12 April 2010.

A review of the precautions and warnings from the VIVITROL label is presented below, along with the relevant postmarketing experience (see Table 11).

Table 11: VIVITROL Prescribing Information and Relevant Postmarketing Experience

VIVITROL Prescribing Information and Background	Relevant Postmarketing Experience
Hepatotoxicity There is a boxed warning regarding hepatotoxicity for oral naltrexone. The FDA requested a similar boxed warning in the VIVITROL package insert (see below). Of note, the warning states that "VIVITROL does not appear to be a hepatotoxin at the recommended doses." Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses. Naltrexone is contraindicated in acute hepatitis or liver failure, and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects. The margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury appears to be only five-fold or less. VIVITROL does not appear to be a hepatotoxin at the recommended doses. Patients should be warned of the risk of hepatic injury and advised to seek medical attention if they experience symptoms of acute hepatitis. Use of VIVITROL should be discontinued in the event of symptoms and/or signs of acute hepatitis.	Four postmarketing reports of hepatitis or liver disease have been reported. The VIVITROL population comprises individuals with a high rate of concomitant health problems, including liver disease.
Injection site reactions Based on signals observed in postmarketing surveillance, proposed label changes regarding injection-site reactions were submitted to the FDA. This topic was subsequently the subject of an FDA alert in August of 2008. Some key points in the revised labeling are: (1) VIVITROL injections may be followed by pain, tenderness, induration, swelling, erythema, bruising and pruritus; (2) some cases have required surgical intervention including debridement of necrotic tissue; (3) inadvertent subcutaneous administration of VIVITROL may increase the likelihood of severe injection site reactions, and (4) reported cases occurred primarily in female patients.	There have been 24 postmarketing reports of injection site reactions requiring surgical intervention. Postmarketing data with respect to injection site reactions have been incorporated into the current, revised package insert.
Eosinophilic pneumonia As described in the current package insert, there has been 1 confirmed and 1 suspected case of eosinophilic pneumonia during clinical trials. Both cases resolved with corticosteroid treatment.	Two postmarketing reports of eosinophilic pneumonia have been received. One of these cases was considered related to treatment, insufficient information for the second case precluded assessment.

VIVITROL Prescribing Information and Background	Relevant Postmarketing Experience
Opioid overdose In clinical trials, reports of opioid overdose occurred 3 times; 2 of those cases occurred more than 6 weeks after the most recent dose of VIVITROL.	Five postmarketing reports of opioid overdose have been received. Naltrexone is a competitive opioid antagonist, which will only be effective for the duration of therapy. Among the 3 patients with reported opioid overdoses, one was successfully treated in an emergency facility. In another case, the overdose occurred approximately 3 months after the last VIVITROL injection. In the third case, there is insufficient data to establish a meaningful causality assessment.
Opioid withdrawal As described in the current VIVITROL package insert for alcohol dependence, VIVITROL will precipitate withdrawal symptoms if administered to a patient dependent on opioids. As such, the physician must ensure that the subject is opioid free prior to initiation of VIVITROL treatment.	A total of 33 events of possible opioid withdrawal were reported. Of these 33 cases, 9 were considered serious adverse events. Many of these reports did not include history or physical findings adequate to reliably make a determination of opioid withdrawal. However, any signs or symptoms possibly illustrating opioid withdrawal syndrome were conservatively considered directly related to VIVITROL. In 2 cases, drug withdrawal was coded but was either unsubstantiated or clearly evocative of another clinical entity (dyskinesia) resulting in the inability to formally assess a causal relationship.
Depression and suicidality Alcohol and opioid dependence are known to be risk factors for depression and suicide. This risk is described in the current VIVITROL package inset.	Alkermes has received 11 reports of suicidal ideation, 5 reports of attempted suicide, and 3 reports of completed suicides during postmarketing surveillance.
Pain management A concern about giving opioid antagonists is the ability to manage unexpected, severe pain. No reported difficulties with pain management were observed in clinical trials despite patients having injuries and occasional surgical interventions. Guidance for pain management is detailed in the current VIVITROL package insert: "In an emergency situation in patients receiving VIVITROL, suggestions for pain management include regional analgesia or use of non-opioid analgesics. If opioid therapy is required as part of anesthesia or analgesia, such patients should be continuously monitored, in an anesthesia care setting, by persons not involved in the conduct of the surgical or diagnostic procedure. The opioid therapy must be provided by individuals specifically trained in the use of anesthetic drugs and the management of the respiratory effects of potent opioids, specifically the establishment and maintenance of a patent airway and assisted ventilation. Irrespective of the drug chosen to reverse VIVITROL blockade, the patient should be monitored closely by appropriately trained personnel in a setting equipped and staffed for cardiopulmonary resuscitation."	Alkermes has received 11 postmarketing reports containing information related to pain management. Of these, 10 were reports from patients. Primarily these patients conveyed information about pain medications which were perceived to be less effective since introduction of VIVITROL or describing pain medications prescribed following the initiation of treatment with VIVITROL which were not felt to be fully managing pain. However, Alkermes has received no reports of patients requiring hospitalization for pain management.

Summaries of postmarketing safety reports were submitted to the FDA as quarterly Periodic Adverse Drug Experience (ADE) Reports for the first 3 years following product launch in the US. Currently postmarketing safety summaries are submitted annually, as Periodic Safety Update Reports (PSURs). An internal review of all reports is conducted quarterly or more frequently if a possible safety signal is identified. This ongoing review of all postmarketing reports has not revealed any additional signals in the postmarketing period that would necessitate further changes in safety labeling.

Provider education can minimize many of the risks associated with VIVITROL administration. In addition to the Package Insert (Appendix Section 10.1) and Medication Guide (Appendix Section 10.2), Alkermes' field force has frequent interactions with the majority of VIVITROL prescribers. This has allowed for specific instructions to be given on proper injection technique, pain management, and performance of a naloxone challenge. Additional information on the Risk Evaluation and Mitigation Strategy (REMS) is described in Section 9.

7.1. Clinical Trial Experience

Building on the experience already described in the original NDA for alcohol dependence and summarized in the current VIVITROL package insert, is one new study (ALK21-013) which was conducted exclusively in opioid-dependent patients. The data from ALK21-013 together with the postmarketing safety data have not revealed any new safety issues with the use of VIVITROL in opioid dependence, and there were no findings that are inconsistent with the warnings or precautions sections of the current VIVITROL label. The clinical trial data are further supported by a review of the published literature which did not identify any issues that are not already adequately described in the VIVITROL package insert for alcohol dependence.

Study ALK21-006, is a 1-year, open-label, phase 3 study conducted in adults with alcohol and/or opioid dependence in support of the original NDA filing for alcohol dependence. Data from the 121 opioid-dependent patients (101 received VIVITROL, 20 received oral naltrexone) who enrolled in this trial have been extracted for this summary. Aggregate data from this study were previously submitted and contributed to the determination of safety in the original NDA for the alcohol dependence indication.

7.2. Adverse Events in the Pivotal Trial--ALK21-013

As described in the study design section of this document (Section 5), the pivotal efficacy trial in patients with opioid dependence (ALK21-013) was conducted in 2 parts: a 6-month placebo-controlled, double-blind evaluation of efficacy and safety (Part A), and an open-label safety extension (Part B) where patients received an additional 12 months of treatment. At the time of the submission of the sNDA under review, only Part A of Study ALK21-013 was complete. Part B is still ongoing. As such, the sections below focus on Part A data, the only placebo-controlled clinical data available in this population.

Of the 250 patients randomized into the study, 103 (41.2%) experienced at least 1 AE: 40 (32.3%) in the placebo group and 63 (50%) in the VIVITROL group. Table 12 presents a brief summary of treatment-emergent AEs sorted by treatment group and overall.

VIVITROL was generally well tolerated in Part A. There were no deaths reported in Part A, and no deaths have been reported in the ongoing Part B. All AEs were considered by investigators as

mild or moderate in intensity. No severe AEs were reported by any patient during Part A. Two (2) patients discontinued from Part A due to an AE; both patients were in the placebo group.

SAEs were reported by 7 (2.8%) patients. Of these, 4 (3.2%) patients were in the placebo group and 3 (2.4%) were in the VIVITROL group. Two of the placebo patients discontinued the study due to the events. No individual SAE was reported by more than 1 person and no treatment differences were noted. Serious adverse events are further described in Section 7.2.1.

The majority of patients had AEs considered by the PI to be unrelated to study drug including those reported by patients in the placebo group. In the VIVITROL group, a total of 4 (3%) patients experienced AEs of injection site pain that were judged to be definitely related to study drug.

Table 12: Overview of Adverse Events—ALK21-013 (Part A)

Patients, n (%)[1]	Number of patients (%)		
	Total	Placebo	VIVITROL
Dosed	250 (100.0)	124 (100.0)	126 (100.0)
With ≥1 AE	103 (41.2)	40 (32.3)	63 (50.0)
With ≥1 severe AE	0	0	0
With ≥1 drug-related[2] AE	45 (18.0)	12 (9.7)	33 (26.2)
With ≥1 serious AE	7 (2.8)	4 (3.2)	3 (2.4)
Who discontinued due to an AE	2 (0.8)	2 (1.6)	0
Due to drug-related[3] AE	0	0	0
Due to an SAE	2 (0.8)	2 (1.6)	0

Source: ALK21-013 CSR, Table 14.4.1.1

[1] Percent is out of number of patients dosed during Part A

[2] Events classified as possibly, probably, or definitely related to study drug by the investigator

Incidence rates of the most common clinical AEs reported in Part A are provided in Table 13. Incidence rates of the most common laboratory AEs reported in Part A are provided in Table 14.

Individual AEs that were reported by at least 2% of patients overall during Part A included four preferred terms related to liver function abnormalities. In the population treated in this study, 88.8% had a baseline diagnosis of hepatitis C infection (according to medical history) and 41.2% had a baseline diagnosis of HIV infection (by serology), making attribution of the relationship between study drug and the frequency of abnormal liver function test (LFT) results difficult. Of 306 elevated ALT, AST, or GGT test results, only 62 (20%) were classified as adverse events. Therefore, issues relating to changes in liver function are discussed in Section 7.3.6.2 in terms of actual laboratory values rather than by an individual physician's determination as to whether or not a given individual laboratory value constituted an AE. In addition, placebo-treated patients had a significantly greater dropout rate. Thus, with more laboratory investigations in the VIVITROL group, there was a greater opportunity to observe abnormal LFTs and a greater opportunity for these observed abnormalities to be considered AEs.

The most common clinical AEs reported during Part A among patients overall were: nasopharyngitis (12 patients [4.8%]); influenza (n=11 [4.4%]); hypertension (n=10 [4%]); insomnia (n=9 [3.6%]); and injection site pain, toothache, or headache (n=7 [2.8%], each).

Patients in the VIVITROL group more frequently reported nasopharyngitis (n=9, 7%), insomnia (n=8, 6%) and injection site pain (n=6, 5%) compared to patients in the placebo group ([n=3, 2%], [n=1, 1%], and [n=1, 1%], respectively). No severe AEs were reported by any patient during Part A. No patient discontinued from Part A due to a nonserious AE.

Table 13: Most Common[1] Clinical Adverse Events—ALK21-013 (Part A)

System Order Class / Preferred Term	All N=250	Placebo n=124	VIVITROL n=126
	Number (%) of Patients[2]		
Infections and Infestations	38 (15.2)	14 (11.3)	24 (19.0)
Nasopharyngitis	12 (4.8)	3 (2.4)	9 (7.1)
Influenza	11 (4.4)	5 (4.0)	6 (4.8)
Psychiatric Disorders	14 (5.6)	5 (4.0)	9 (7.1)
Insomnia	9 (3.6)	1 (0.8)	8 (6.3)
General Disorders and Administration Site Conditions	13 (5.2)	5 (4.0)	8 (6.3)
Injection site pain	7 (2.8)	1 (0.8)	6 (4.8)
Gastrointestinal Disorders	12 (4.8)	6 (4.8)	6 (4.8)
Toothache	7 (2.8)	2 (1.6)	5 (4.0)
Vascular Disorders	10 (4.0)	4 (3.2)	6 (4.8)
Hypertension	10 (4.0)	4 (3.2)	6 (4.8)
Nervous System Disorders	9 (3.6)	4 (3.2)	5 (4.0)
Headache	7 (2.8)	3 (2.4)	4 (3.2)

Source: ALK21-013 CSR, Table 14.4.1.2
[1] Most common adverse events are those reported by ≥2% of patients overall ("All" column) during Part A
[2] Percent is out of number of patients dosed

Table 14: Most Common[1] Laboratory Adverse Events—ALK21-013 (Part A)

System Order Class / Preferred Term	All N=250	Placebo n=124	VIVITROL n=126
	Number (%) of Patients[2]		
Investigations	38 (15.2)	12 (9.7)	26 (20.6)
Alanine aminotransferase increased	23 (9.2)	7 (5.6)	16 (12.7)
Aspartate aminotransferase increased	16 (6.4)	3 (2.4)	13 (10.3)
Gamma-glutamyl transferase increased	13 (5.2)	4 (3.2)	9 (7.1)

Source: ALK21-013 CSR, Table 14.4.1.2
[1] Most common adverse events are those reported by ≥2% of patients overall ("All" column) during Part A
Percent is out of number of patients dosed

Overall, the most common adverse events reported in the ALK21-013 trial are consistent with the types of events described in the current VIVITROL package insert for alcohol dependence. They are also consistent with the events reported in the ALK21-006 trial, where the most common events among opioid-dependent patients included nasopharyngitis, insomnia, headache, fatigue, and depression.

Review of AEs in this integrated safety database does not indicate safety findings among opioid-dependent patients unaddressed in the current VIVITROL label for alcohol dependence.

7.2.1. Serious Adverse Events

There were 7 (2.8%) patients who reported SAEs: 4 (3.2%) were in the placebo group and 3 (2.4%) were in the VIVITROL group (see Table 15).

No individual SAE was reported by more than one patient; none were considered related to study drug. Patients with SAEs of AIDS, HIV infection, and herpes virus infection were diagnosed with those conditions during screening; however, exacerbation of symptoms required hospitalization during the study. One patient with the SAE of drug dependence relapsed during the study, requiring hospitalization for the purpose of opioid detoxification. Two SAEs led to study withdrawal in Part A, each occurred in patients treated with placebo.

Table 15: Serious Adverse Events—ALK21-013 (Part A)

System Order Class Preferred Term (MedDRA)	Placebo n=124	VIVITROL n=126
	Number (%) of Patients[1]	
Infections and Infestations	2 (1.6)	3 (2.4)
Acquired immunodeficiency syndrome	0	1 (0.8)
Acute sinusitis	1 (0.8)	0
Adnexitis	0	1 (0.8)
HIV infection WHO clinical stage III	0	1 (0.8)
Herpes virus infection	0	1 (0.8)
Lobar pneumonia	1 (0.8)	0
Psychiatric Disorders	2 (1.6)	0
Drug dependence*	1 (0.8)	0
Psychotic disorder*	1 (0.8)	0
Gastrointestinal Disorders	1 (0.8)	0
Peptic ulcer	1 (0.8)	0

Source: ALK21-013 CSR, Table 14.4.1.4
[1] Percent is out of number of patients dosed during the corresponding period
* Event resulted in early withdrawal from the study.

In comparison, SAEs were infrequent among opioid dependent patients overall (including patients in the prior study ALK21-006). The only individual event terms reported by more than 1 patient were: drug dependence (5 patients); overdose (4 patients, includes 1 patient with

"intentional overdose"), affective disorder (2 patients), suicidal ideation (2 patients), suicide attempt (2 patients), and depression (2 patients).

In this population of opioid-dependent adults, SAEs of drug dependence, overdose, suicidal ideation, suicide attempt, and depression are not unexpected. None of these cases were fatal and none were considered by the investigator to be related to study drug. In these studies, SAEs of "drug dependence" represented an exacerbation of an underlying dependence diagnosis, where hospitalization for detoxification was initiated or recommended. SAEs of depression occurred in patients with a history of depression at baseline. Similarly, SAEs of affective disorder were reported as exacerbations of an underlying baseline condition. Only 2 of the SAEs of overdose involved overdoses of opioids. Other cases involved overdosing on other medications including benzodiazepines, anxiolytics, and antidepressants. Opioid overdose is discussed in Section 7.3.4. Adverse events of a suicidal nature are discussed in Section 7.3.1.

Overall, the SAEs reported during clinical trials in opioid-dependent patients are consistent with the types of SAEs described in the original NDA submission for alcohol dependence. No new issues have been identified.

7.2.2. Adverse Events Leading to Discontinuation

Two patients were discontinued from ALK21-013 due to SAEs, as shown in Table 15, above. No patient was discontinued from the study for a nonserious AE.

Overall, among opioid dependent patients, the only adverse event leading to discontinuation in more than 1 patient was pregnancy (4 cases). The 4 pregnancies occurred during Study ALK21-006, and the study protocol required immediate discontinuation of study drug for any subject becoming pregnant during the study.

Overall, the types of AEs leading to discontinuation of treatment among patients with opioid dependence are consistent with the data described in the original NDA, and described in the current VIVITROL package insert. No new issues have been identified.

7.2.3. Additional Safety Data from ALK21-013 (Part B)

The primary evaluation of safety in the ALK21-013 study comes from the 6-month, placebo-controlled portion of the study (Part A). Patients who completed Part A continued into the open-label extension portion of the study (Part B) which is still ongoing. Preliminary, interim safety data, as of 03 May 2010, are included in the 120-Day Safety Update report recently received by the FDA. A brief summary of the safety results from the 114 patients who participated in Part B are as follows:

- No deaths have been reported.
- 3 patients experienced a total of 4 SAEs (cardiomyopathy, acute pancreatitis, pulmonary tuberculosis and hepatitis A). Pulmonary tuberculosis and hepatitis A occurred in the same patient.
- The most common AEs were: GGT elevated (n=10 patients, 9%), AST elevated and ALT elevated (n=7 patients each, 6%), influenza (n=5 patients, 4%), toothache (n=4 patients, 4%), and injection site pain (n=3 patients, 4%).
- No patients developed an adverse event in Part B that led to discontinuation.

- Injection site reactions included: pain (n=3 events), and induration, extravasation, and swelling (n=1 event each)
- No new trends in laboratory data were observed

7.3. Safety Topics of Special Interest

7.3.1. Suicide and Depression

In an effort to thoroughly evaluate the incidence of adverse events suggestive of suicidal behavior, Alkermes performed a retrospective review of individual patient safety data. The review included a search of individual study databases (eg, physical examination, AEs) and questionnaire responses that could suggest depression. All findings were reviewed on a by-patient basis, to assure material contained in the patients' case report forms did not suggest suicidal behavior.

The results of the data mining exercise described above are as follows:

- In ALK21-013, the 24-week, placebo-controlled pivotal trial, AEs involving depressed mood or suicidal thinking were not reported by any patient in either treatment group (VIVITROL or placebo).
- In ALK21-006, an open-label, long-term safety study, AEs of a suicidal nature (depressed mood, suicidal ideation, suicide attempt) were reported by 5% of opioid-dependent patients treated with VIVITROL versus 10% of opioid-dependent patients treated with oral naltrexone.
- In ALK21-006-EXT, the long-term safety extension study, AEs of a suicidal nature were not reported by any of the opioid-dependent patients.

Opioid drug dependence is a risk factor for suicide. In addition, comorbidities common among people with this dependence (eg, depression) are also risk factors for suicidal behavior. It has been estimated that the lifetime risk for suicide is 25% or more in those with alcohol or opioid dependence, compared with 1% to 1.3% in the general population [Miller, 1991]. Suicidal behavior and depression are described in the current VIVITROL package insert, and a review of the data in opioid-dependent patients does not reveal any new findings that would warrant an adjustment to the current package insert language.

7.3.2. Injection Site Reactions

In ALK21-013, investigators trained in proper injection technique, and had the option of using either a 1.5" or a 2.0" administration needle. Any reported ISR was documented and reported as an AE.

Among all patients, injection site tenderness and injection site induration were the most commonly reported ISRs.

Overall, there was a low rate of ISRs among patients in the ALK21-013 study. A primary risk factor for ISRs appears to be the inadvertent administration of VIVITROL into the adipose layer instead of into the muscle. This may more frequently occurs in female patients, in patients with a higher body mass index (BMI), and/or from improper injection technique.

Patients were leaner in ALK21-013 versus ALK21-006 (eg, a BMI 23.2 vs. 26.3, respectively), and the overall population included a greater proportion of men (88% and 66%, respectively). In addition, investigators participating in the ALK21-013 study were well trained on the importance of proper injection technique and had the option of using a 2-inch administration needle—an option that was not available at the time that the 21-006 study was conducted. Alkermes believes these factors all contributed to the lower incidence of ISRs in the ALK21-013 study.

7.3.3. Opioid Withdrawal

In ALK21-013, the 24-week, placebo-controlled pivotal trial, AEs of opioid withdrawal (withdrawal syndrome) were not reported by any patient in either treatment group (VIVITROL or placebo).

In ALK21-006, an open-label, long term safety study, AEs of opioid withdrawal (withdrawal syndrome) were reported by 3 patients (2 in the VIVITROL group, 1 in the oral naltrexone group). None were SAEs, none were severe, and none resulted in study discontinuation (see ALK21-006 CSR).

In the open-label extension study (ALK21-006-EXT), AEs of opioid withdrawal were not reported by any patient.

Opioid withdrawal is described in the current VIVITROL package insert, and a review of the data pertaining to opioid-dependent patients did not reveal any new safety finding that would warrant an adjustment to the current package insert language.

7.3.4. Opioid Overdose

In ALK21-013, the 24-week, placebo-controlled pivotal trial, AEs of opioid overdose were not reported by any patient in either treatment group (VIVITROL or placebo).

In ALK21-006, AEs of opioid overdose were reported by 3 opioid-dependent patients; 2 in the VIVITROL group, and 1 in the oral naltrexone group. In the open-label extension study (ALK21-006-EXT), 1 overdose was reported by an opioid-dependent patient. Of these 4 overdoses, 2 were classified as SAEs due to hospitalization of the patient. The other 2 cases did involve hospitalization. Among patients in the VIVITROL treatment group, the events occurred between 25 and 81 days after the most recent dose of study drug. For the patient in the oral naltrexone group, the overdose occurred 28 days after the most recent drug dispensation visit; it is unclear whether this patient had been compliant with the daily dosing regimen. All patients recovered by the next day without sequelae.

Opioid overdose is described in the current VIVITROL package insert, and a review of the data in opioid-dependent patients does not reveal any new safety finding that would warrant an adjustment to the current package insert language.

7.3.5. Eosinophilic Pneumonia

There were no reports of eosinophilic pneumonia among the 371 opioid-dependent patients comprising the safety population.

Eosinophilic pneumonia is described in the current VIVITROL package insert, and a review of the data in opioid-dependent patients does not reveal any new safety finding that would warrant an adjustment to the current package insert language.

7.3.6. Hepatitis and Liver Disease

7.3.6.1. Clinical Adverse Events of Hepatitis and/or Liver Disease

Adverse events involving hepatitis and/or liver disease were infrequent among the opioid-dependent patients in these studies. A total of 5 patients reported such events, specifically: hepatitis C (2 patients, ALK21-013), liver disorder (1 patient, ALK21-013), hepatomegaly (1 patient, ALK21-006), and hepatic steatosis (1 patient, ALK21-006-EXT). The 2 patients with AEs of hepatitis C both had a medical history positive for hepatitis C infection, and both of these events were reported as exacerbations of the baseline condition. The patient reporting the AE of liver disorder had a baseline diagnosis of hepatitis B. Hepatomegaly and hepatic steatosis were reported by patients with no history of liver disease. Hepatomegaly occurred in a patient in the oral naltrexone group; hepatic steatosis occurred in a patient receiving VIVITROL. Both events were considered mild and the investigator deemed both definitely not related to study drug. Neither of these events was reported by more than 1 patient. Alkermes is unable to make a definitive assessment of the relationship between the episode of hepatic steatosis and the use of VIVITROL.

Hepatotoxicity is described in the current VIVITROL package insert, and a review of the data in opioid-dependent patients does not reveal any new safety finding that would warrant an adjustment to the current package insert language.

7.3.6.2. Liver Function Tests

ALK21-013

In the ALK21-013 study, 88% of patients reported a history of hepatitis C infection at baseline, consistent with the general population of IV drug users [Ghany, 2009], and liver function-related AEs were reported only among patients with a history of hepatitis C infection. Consistent with the clinical course in hepatitis C infection, many patients had abnormal (high) ALT, AST, and GGT results at baseline and at various times during the study.

Laboratory values for ALT and AST were lowest at baseline and subsequently increased on treatment in both the placebo and VIVITROL groups. By the Week 24 visit (end of Part A), there was little difference in the mean change from baseline when comparing the placebo and VIVITROL groups. GGT values did not show a similar increase from baseline. Mean bilirubin concentrations increased in both the placebo and VIVITROL groups; however, these changes were largely within the normal range.

Table 16: Summary of Select Liver Function Test Results--ALK21-013 (Part A)

		Placebo		VIVITROL	
		N	Mean (SD)	N	Mean (SD)
ALT (ULN=55 IU/mL)	Baseline	124	51.2 (29.9)	126	52.2 (28.9)
	Week 24	48	57.4 (41.2)	68	56.0 (55.1)
AST (ULN=45 IU/mL)	Baseline	124	37.9 (18.9)	126	39.8 (18.2)
	Week 24	48	44.4 (31.2)	68	44.0 (30.3)
GGT (ULN=50 IU/L)	Baseline	124	106.4 (111.7)	126	84.6 (72.5)
	Week 24	48	85.4 (121.7)	68	63.1 (62.7)

Source: ALK21-013 CSR Table 14.4.2.1

The shift analyses (Table 17) further demonstrate that VIVITROL did not adversely affect liver function relative to placebo. Patients who entered the study with normal ALT or AST were similarly likely to develop high or very high (>3×) ALT or AST, regardless of whether they were treated with placebo or VIVITROL. Importantly, the same findings were shown for patients who entered with high baseline ALT or AST. Additionally, in both the placebo and VIVITROL groups, many patients with high baseline ALT and AST levels had on-treatment levels within the normal range, and very few progressed to very high levels (>3×ULN). Few patients had high bilirubin values, and no differences were seen in the shift table analysis between the placebo and VIVITROL groups.

Table 17: Changes in Select Liver Function Test Abnormalities from Baseline to Week 24—ALK21-013 (Part A)

Week	Baseline Grade[1]	Placebo					VIVITROL				
		Low n (%)	Normal n (%)	High n (%)	3× High[2] n (%)	All n (%)	Low n (%)	Normal n (%)	High n (%)	3× High[2] n (%)	All n (%)
Alanine Aminotransferase (IU/L) Post-Baseline Grade											
24	Low	0	0	0	0	0	0	0	0	0	0
	Normal	0	17 (35.4)	9 (18.8)	1 (2.1)	27 (56.3)	0	33 (48.5)	11 (16.2)	3 (4.4)	47 (69.1)
	High	0	12 (25.0)	8 (16.7)	1 (2.1)	21 (43.8)	0	11 (16.2)	10 (14.7)	0	21 (30.9)
	3× High	0	0	0	0	0	0	0	0	0	0
	All	0	29 (60.4)	17 (35.4)	2 (4.2)	48 (100.0)	0	44 (64.7)	21 (30.9)	3 (4.4)	68 (100.0)
Aspartate Aminotransferase (IU/L) Post-Baseline Grade											
24	Low	0	0	0	0	0	0	0	0	0	0
	Normal	0	29(60.4)	7(14.6)	1 (2.1)	37 (77.1)	0	32 (47.1)	11 (16.2)	1 (1.5)	44 (64.7)
	High	0	5(10.4)	5(10.4)	1 (2.1)	11 (22.9)	0	12 (17.6)	11 (16.2)	1 (1.5)	24 (35.3)
	3× High	0	0	0	0	0	0	0	0	0	0
	All	0	34(70.8)	12(25.0)	2 (4.2)	48 (100.0)	0	44 (64.7)	22 (32.4)	2 (2.9)	68 (100.0)
Gamma-Glutamyl Transferase (IU/L) Post-Baseline Grade											
24	Low	0	0	0	0	0	0	0	0	0	0
	Normal	0	16 (33.3)	6 (12.5)	1 (2.1)	23 (47.9)	0	24 (35.3)	3 (4.4)	2 (2.9)	29 (42.6)
	High	0	8 (16.7)	8 (16.7)	0	16 (33.3)	0	13 (19.1)	11 (16.2)	2 (2.9)	26 (38.2)
	3× High	0	0	5 (10.4)	4 (8.3)	9 (18.8)	0	4 (5.9)	7 (10.3)	2 (2.9)	13 (19.1)
	All	0	24 (50.0)	19 (39.6)	5 (10.4)	48 (100.0)	0	41 (60.3)	21 (30.9)	6 (8.8)	68 (100.0)

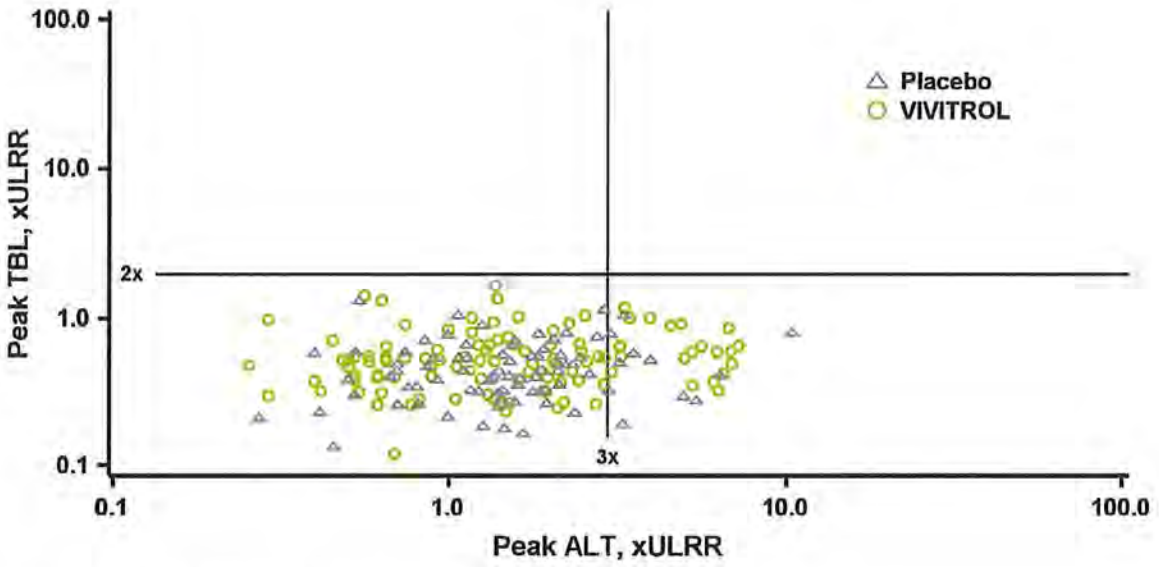
Note: Percentages are out of the number of patients with test results at baseline and the corresponding post-baseline visits for each treatment group

[1] Latest assessment made prior to the first dose;

[2] Higher than 3 times the normal limit

Source: ALK21-013 CSR Table 14.4.2.2

Another analysis of potential hepatotoxicity is presented in Figure 12. Each individual's peak post-baseline ALT is plotted against peak post-baseline total bilirubin. There are more data points for VIVITROL-treated patients (n=107) compared to placebo-treated patients (n=85), as more of the latter did not return after the initial study drug injection. In addition, the greater retention of patients in the VIVITROL arm resulted in an increased opportunity for patients with fluctuating ALT (due to underlying hepatitis C infection) to have higher ALT results. Nevertheless, though there are more VIVITROL treated patients with elevated ALT, no patients were found to have total bilirubin greater than twice the upper limit of normal. The fact that none of the data points extend into the upper right quadrant of this plot suggest that there is little concern of serious hepatotoxicity.



Source: ALK21-013 CSR Table 14.4.2.1

Figure 12: Edish Plot: Evaluation of Drug-Induced Serious Hepatotoxicity: ALK21-013

Thus, the reported increase in AEs of LFT abnormalities does not appear to be related to VIVITROL treatment, based upon the following findings:

- All of the patients for whom abnormal LFTs were reported as AEs had a history of hepatitis C infection at enrollment. It is most likely that the observed LFT abnormalities reflect the clinical course of hepatitis C infection rather than a drug-related effect.
- The majority of patients with reported AEs of abnormal LFTs had subsequent decreases in serum LFT levels despite remaining on treatment, which is more consistent with the clinical course of hepatitis C than drug toxicity.
- Over the 24-week period of observation, no differences were seen in mean ALT, AST, and GGT values between VIVITROL and placebo groups

- Analyses of shift tables revealed no meaningful difference in patients going from normal to high LFTs or from high to >3×ULN values when comparing the placebo and VIVITROL groups

ALK21-006 and ALK21-006-EXT

In the open-label safety study, there were no clinically significant changes in liver function parameters for either treatment group (VIVITROL or oral naltrexone).

7.4. Other Clinical Laboratory Evaluations

7.4.1. Eosinophils

Previous studies in alcohol-dependent patients demonstrated increases in mean eosinophil counts of VIVITROL versus placebo-treated patients.

In the ALK21-013 study, no group differences in mean eosinophil counts were seen.

In ALK21-006, VIVITROL patients had an increase in eosinophil count at Week 4, which returned to baseline over the course of the study. No changes in eosinophil count were noted for the oral naltrexone group.

In ALK21-006-EXT, no increases were seen.

7.4.2. Platelets

An association between VIVITROL and decreased platelet count is described in the current VIVITROL package insert. This association was also observed in study (ALK21-013). Both placebo and VIVITROL-treated patients had decreases in platelet counts from baseline. At 24 weeks, patients treated with VIVITROL experienced a mean decrease in platelet count of $32.3 \times 10^3/\mu L$, compared to $1.7 \times 10^3/\mu L$ in placebo patients. However, differences were not clinically significant, and analysis of shift tables shows more low values in the placebo group. There were no AEs related to bleeding.

Similar observations were made in study ALK21-006 for both the VIVITROL and oral naltrexone groups.

7.4.3. Serum Protein

In ALK21-013, more than half of the patients in both groups (VIVITROL and placebo) had elevated mean serum protein concentrations at baseline. Mean protein concentrations did not change over the course of the study. In view of the normal distribution of serum albumin concentrations at baseline, the high protein concentrations likely represent the effects of chronic inflammation (ie, hepatitis C and HIV infection) in this population.

In ALK21-006 and ALK21-006-EXT, where the rates of HIV and hepatitis C were much lower, there were no clinically significant group changes in total protein noted.

7.5. Overall Safety Summary

The data summarized in the sections above indicate that VIVITROL is safe and well-tolerated in the population of alcohol and/or opioid-dependent adults. No new safety issues were identified,

and there were no findings that are inconsistent with the warnings or precautions sections of the current VIVITROL label. These clinical trial data are further supported by a review of the published literature which did not identify any issues that are not already described in the VIVITROL package insert.

The REVIA® (oral naltrexone) label states, "Among opioid free individuals, REVIA administration at the recommended dose has not been associated with a predictable profile of serious or untoward events." Consistent with the package insert for oral naltrexone, patients with opioid dependence reported lower rates of adverse events in comparison to patients with alcohol dependence. Injection site reactions were more commonly observed in alcohol-dependent patients compared to opioid-dependent patients. This may be explained by the reduced likelihood of inadvertent subcutaneous injection of VIVITROL in the opioid-dependence trials based upon a greater proportion of lean male patients, improved injection training for investigators, and access to 2" needles. For other adverse events, the lower incidence observed in patients with opioid dependence could be explained by underlying disease state and demographic factors.

Key safety findings from Alkermes clinical trials in patients with opioid dependence are as follows:

- No deaths occurred.
- SAEs were infrequent and were consistent with the warnings and precautions sections of the current VIVITROL package insert.
- The most common AEs (those occurring in at least 5% of patients in any treatment group) included nasopharyngitis, influenza, upper respiratory tract infection, sinusitis, insomnia, depression, headache, dizziness, nausea, upper abdominal pain, diarrhea, fatigue, and back pain. All of these events are described in the current VIVITROL package insert.
- Injection site reactions are consistent with those described in the current VIVITROL package insert.
- Laboratory test results, particularly liver function tests, eosinophil counts, and platelet counts were reviewed and found to be consistent with the language included in the current VIVITROL package insert.

Important safety findings are addressed in the warnings and precautions sections of the current VIVITROL label for alcohol dependence. Addition of specific information regarding common adverse events in opioid dependent patients would adequately inform physicians of the safety of VIVITROL in these populations.

8. GENERALIZABILITY TO THE TREATMENT OF OPIOID DEPENDENCE IN THE UNITED STATES

8.1. Introduction

This section reviews the applicability and generalizability of the VIVITROL program to the treatment of opioid dependence in United States. The discussion highlights several key factors including (1) the fundamental and well-characterized neuropharmacologic mechanism of opioid dependence and opioid antagonist treatment, (2) the correspondence between the population of patients enrolled in the VIVITROL clinical program and the expected clinical population in the US, and (3) the similarity of the ALK21-013 study centers and the ALK21-013 treatment methodology to the anticipated treatment context of VIVITROL within the US health care system. This evidence, together with the robust efficacy finding in the ALK21-013 study and patient experience in multiple US clinical studies, indicates that VIVITROL will yield important health benefits in the treatment of opioid dependent patients in this country.

The VIVITROL opioid development program consists of reference to the prior FDA approval of oral naltrexone for blockade of exogenous opioids, reference to published studies of oral naltrexone in the treatment of opioid dependence performed worldwide, and clinical studies performed by Alkermes with VIVITROL. Clinical studies of VIVITROL in patients with opioid dependence include one study of safety and efficacy (ALK21-013) conducted in Russia and 3 clinical studies conducted in the US, ALK21-004 "opioid challenge," ALK21-006 long-term safety, and ALK21-021 "health care professionals".

There exists a significant amount of safety experience with VIVITROL in the treatment of opioid dependent patients in the US though previously conducted (ALK21-006, ALK21-006-EXT) and ongoing (ALK21-021) studies. The opioid submission also includes post market safety surveillance data of VIVITROL in the US. Given the extent of experience in the US, the VIVITROL program should adequately address safety in the US treatment population. As such, the primary focus of this discussion is ALK21-013, the pivotal efficacy study.

8.2. Opioid Dependence – Neuropharmacology and Pharmacokinetics

Two essential elements, (1) the neuropharmacologic mechanism of action of naltrexone and (2) the pharmacokinetic exposure of naltrexone in VIVITROL treated patients are both well characterized. These factors are operative across mammalian species, cultures, and continents and function irrespective of the type of opioid abused. Thus, from a mechanistic perspective, the effects of extended-release μ-opioid blockade that were evaluated in the ALK21-013 study, apply directly to clinical use in the United States.

The fundamental brain processes at the level of pharmacodynamic and brain reward circuitry responses to opioids are similar across mammals and even more so among humans. Opioid dependence disorder, as a disease, originates with exogenous μ-opioid agonists. Upon administration and entry into the brain, μ-opioid agonists cause dependence through a combination of supra-physiologic positive reinforcement, ie, euphoria and reward, and with repeated use, negative reinforcement, ie, withdrawal distress [Nestler and Malenka 2004]. Naltrexone is a potent and selective antagonist of the μ-opioid receptor. As with the

development of dependence, the principal mechanism of action, μ-opioid competitive blockade of exogenously administered opioids, is well established and has been demonstrated in preclinical and human laboratory studies.

The underlying pharmacologic mechanism, μ-opioid agonism and blockade by a competitive μ-antagonist, functions across mammalian species including humans and is common to people of all cultures, races, and ethnicities. Indeed, opioid dependence is reported on all continents with a remarkably similar incidence (1 to 2% of the general population) [Mathers, 2008]. This fundamental mechanism of agonism and competitive antagonism functions regardless of the type of opioid agonist used and irrespective of treatment context or culture. The same pharmacologic mechanism evaluated in the ALK21-013 clinical study is operative in the treatment of opioid dependence in the US.

Essential to its efficacy is sustained exposure. VIVITROL releases naltrexone for greater than 30 days following IM administration and its metabolism is unaffected by CYP enzymes. The pharmacokinetics of VIVITROL are well characterized and have been observed to be consistent using a broad population pharmacokinetic approach [Dunbar, 2007;Dunbar, 2006].

8.3. Patient Population

The patient population studied in the VIVITROL program is relevant to the treatment of opioid dependence in the US. In particular, there are strong parallels in the underlying motivation and external support between the 013 study population and the anticipated VIVITROL treated patient in the US.

Patients enrolled in the ALK21-013 study all met DSM-IV criteria for opioid abuse. The DSM criteria were developed in the US and are used to define the clinical diagnosis of opioid dependence in the US.

The ALK21-013 study patients were primarily male (88%) and white (99%). Similarly, heroin and non-medical users of other opioids in the US are predominantly male (69%) and white (91% white overall and 66% white among IV heroin users) [National Survey on Drug Use and Health (NSDUH) 2005]. No black patients were enrolled in the ALK21-013 study, however, from the perspective of safety and treatment retention, there does exist a significant body of VIVITROL experience with African-Americans and other ethnicities. This experience derives from the ALK21-006 study as well as from a substantial number of patients previously enrolled in the VIVITROL alcohol dependence program.

VIVITROL is currently approved for the treatment of alcohol dependence. Based on anecdotal reports, postmarketing surveillance, and published literature [Fishman, 2010] it is known that patients with opioid dependence are also currently being treated with VIVITROL by physicians in the US. A defining feature of patients treated or anticipated to be treated with VIVITROL is high patient motivation and willingness to accept regular IM injections. High motivation for treatment, especially treatment with antagonist therapy, is not universal among US opioid dependent patients. Archetypical VIVITROL patients have a high level of motivation and commitment to therapy and include patients with strong direct parental or spousal support, and patients who are philosophically opposed to agonist replacement therapy, as well as professionals who are not permitted to use agonist replacement therapy (eg, health care

professionals, active-duty soldiers, interstate truck drivers, airplane pilots, and police, fire and other public safety personnel).

There are strong parallels between the patients enrolled in the ALK21-013 study and patients and the anticipated VIVITROL treatment population in the US in terms of motivation. Patients enrolled in the ALK21-013 study had a high motivation for treatment with antagonist therapy as evidenced by their willingness to participate in the study, and undergo IM injections. Importantly in Russia, there is no legal use of opioid agonist replacement therapy; no other medication based therapies are available. The absence of agonist therapy in Russia is analogous to patients who are specifically motivated to use antagonist therapy in the US as described above.

Another parallel is the availability of family supervision – nearly all patients in the ALK21-013 study were residing with parents or other family members at the time of treatment initiation. Based on experience in the US, strong family support is a common feature of VIVITROL-treated patients.

8.4. Treatment Context

An important question in assessing translatability concerns the treatment context. The environment established in the VIVITROL program and specifically the ALK21-013 study are reflective of the anticipated treatment setting of VIVITROL in the US health care system. The relatedness of treatment setting lends further support to the generalizability of the ALK21-013 study results to the use of VIVITROL in the US.

The ALK21-013 study sites were staffed by healthcare professionals experience with expertise in the medical treatment of addiction. The sites were fully equipped with personnel and logistics to provide gluteal injections on a longitudinal basis. The sites provided concurrent psychosocial therapy. The psychosocial therapy provided, IDC [Crits-Christoph, 1997], was developed in the US under the aegis of NIDA. IDC and utilizes counseling themes commonly invoked in US clinical practice.

The treatment of opioid dependence in the US is heterogeneous; there is no single uniform standard of care. There exists a variety of treatment models, philosophies and treatment settings entailing public, private, inpatient, out-patient, and residential facilities as well as dedicated methadone maintenance clinics [Substance Abuse and Mental Health Services Administration (SAMHSA) 2007]. Some facilities perform opioid detoxification whereas others do not perform this service. Some treatment centers utilize medication based treatments whereas others advocate abstinence oriented approaches.

Within this heterogeneity, the clinical facilities in the US that actually use VIVITROL are quite similar the 013 study sites. Currently VIVITROL is being prescribed in the US in 400 facilities. Approximately 1100 physicians prescribe VIVITROL and about 50% of VIVITROL prescriptions are written by 130 physicians [Alkermes data on file]. Prescribers of VIVITROL are largely physicians with a specific experience and expertise in the treatment of chemical dependence and ability provide or coordinate concurrent psychosocial therapy. The treatment facilities have personnel to manage access logistics, reimbursement, refrigeration, and gluteal IM injection, on a longitudinal basis. In the context of an approved indication for opioid dependence, it is anticipated that treatment in US would be provided by experienced physicians and treatment facilities that offer this range of services.

9. BENEFIT-TO-RISK PROFILE SUMMARY

The rationale underlying VIVITROL (naltrexone for extended-release injectable suspension) development was formally first stated in 1975 as the National Institute on Drug Abuse began multiple initiatives in search of such a preparation. An effective extended release formulation of an antagonist was seen as advantageous compared to a daily oral antagonist. Opioid dependence disrupts the brain's sense of self-preservation and thereby impairs motivation for daily self-administration of needed medication. VIVITROL was designed to deliver measurable plasma levels of naltrexone for one month. The VIVITROL phase 3 clinical trial (ALK21-013) demonstrates a consistent pattern of clinical efficacy for initiating opioid abstinence, maintaining abstinence, achieving medication adherence, maintaining retention, protecting against re-establishment of opioid physical dependence and reducing craving for opioids, while at the same time showing good safety and tolerability.

These findings of efficacy and safety are particularly important because VIVITROL would represent the first extended-release, non-agonist, alternative pharmacotherapy for the treatment of opioid dependence disorder. Given the difficulties described in the literature with daily oral naltrexone treatment [National Institute on Drug Abuse (NIDA) 1976;National Institute on Drug Abuse (NIDA) Treatment Workgroup 1997], the only widely-used approach to date has been agonist therapy with either methadone or buprenorphine. Yet there are substantial obstacles to agonist treatment for opioid dependence, including problems with access, risk of abuse and or division, the philosophies of many treatment providers and criminal justice systems that vehemently oppose agonist approaches, employment and licensure restrictions, and Federal regulations (U.S. 42 CFR 8.12(e) *Patient admission criteria*). Community opposition to methadone clinics and fears among primary care medical practices about agonist-maintained addicts seriously limits access to care in the US [Center for Substance Abuse Treatment (CSAT) 2005].

As a result of these and other obstacles, more individuals with opioid dependence cannot or do not avail themselves of treatment than those who do engage in treatment. These may include patients who have not had a sufficient duration or severity of opioid dependence to justify maintenance agonist therapy, and patients who feel stigmatized, have medical contraindications, or who are philosophically opposed to agonist therapy. The mechanism of action makes it suitable for patients whose employment or professional license prohibits agonist treatment eg, health care professionals, transportation workers, public safety officials, military personnel.

Given that the majority of individuals in the U.S. with opioid dependence do not receive treatment [Center for Substance Abuse Treatment (CSAT) 2005], access to a safe and effective antagonist may represent an important alternative treatment option with meaningful public health impact.

9.1. Summary of Expected Benefits

VIVITROL is effective in the treatment of opioid dependence, as demonstrated by a statistically significant and clinically meaningful greater proportion of opioid-free weeks with patients in the VIVITROL group compared to those in the placebo group in a 24-week trial in 250 adults (ALK21-013) diagnosed with DSM-IV opioid dependence disorder. The results with

VIVITROL compare favorably with historical results observed with consistent daily oral naltrexone [National Institute on Drug Abuse (NIDA) Treatment Workgroup 1997].

Efficacy was shown in a population with a broad age range. The sample had considerable duration of dependence on opioids. Efficacy was not found to vary by age, gender or duration of opioid dependence. At baseline, the use of opioids other than heroin was reported by approximately 25% of patients. Hepatitis C was present in the vast majority of patients and there was also a substantial proportion that was positive for HIV, known comorbidities in this patient population. The characteristics of this sample on these important baseline clinical variables support the relevance of the findings for the opioid dependent population [Brown, Jr., 2007].

Efficacy of VIVITROL for promoting abstinent days was evident within weeks of treatment (ALK21-013 CSR). This early response for initiating abstinence suggests that VIVITROL may serve as a pharmacological foundation upon which the benefits of other treatment components may be built. An anti-craving effect was developed over the initial 8 weeks, and a benefit on retention was evident during the first month. Drug abstinence, reduction in craving and retention are crucial elements for establishing a platform for counseling and recovery activities. The rapid onset of effect with VIVITROL may facilitate other components of the treatment plan by allowing time for these additional components to begin to exert their effects.

Beyond the formulation's characteristic of effectively overcoming daily administration compliance or adherence fluctuations, an effect on month-to-month persistence was also found. In addition to its role in initiating outpatient abstinent days, VIVITROL shows a durable benefit for maintaining abstinence over time when used in combination with psychosocial management.

The combination of its effect of increasing abstinent days as well as its reduction in re-dependence on opioids indicates that VIVITROL provided a protective effect against both slips, ie, brief sampling of opioids, and relapse, ie, repeat self-administration of opioids that leads to physical dependence. This anti-relapse effect has implications for maintaining recovery, because it is easier for patients who only slip to retain their continuity in treatment, whereas relapse and reinstatement of physiological dependence may necessitate an interruption in the continuity of care in order to undergo repeat detoxification, or, conversion to agonist maintenance treatment [Center for Substance Abuse Treatment (CSAT) 2005]. By providing a combination of extended anti-craving effects, blockade of reinforcement in the effect of slips, protection against relapse and preventing reinstatement of physical dependence, VIVITROL is intended to facilitate abstinence.

9.1.1. Impact of Increased Rate of Abstinence

VIVITROL would be an important new option for treating opioid dependence disorder. It helps initiate and maintain abstinence, or opioid-free days, via antagonism at the μ-opioid receptor. The pharmacologic blockade occurs in the absence of agonism and thus is a categorical, rather than relative mechanism, ie, it offers none of the effects of the fundamental neurotransmitter disease process, as opposed to approved agonist agents, which provide relatively less of the agonist neurotransmitter effects than the illicit opioids. The treatment benefits of methadone occur via a combination of a pharmacodynamic mechanism of action that is similar to short-acting opioids but pharmacologically slower in onset and longer in duration of action [Center for Substance Abuse Treatment (CSAT) 2005]. The treatment effect of VIVITROL, in contrast, is

pharmacodynamically opposite from opioids, with a rapid onset and greatly extended duration of action.

VIVITROL's extended duration of action and pharmacologic blockade confer a categorical abstinence, which has an impact on both proximal and distal disease phenomena. Proximal disease phenomena include drug use, reinforcement and reinstatement of physiologic dependence. Distal disease phenomena include sequelae such as psychological function, family and social interactions and quality of life. In combination, these opioid dependence disorder consequences lead to high risk for a variety of morbidities, including social dysfunction, vocational dysfunction, health and safety neglect, trauma, infection, contagiousness, criminality, overdose and death. These processes and their consequent risks threaten the individual, families, communities, public health and public safety on a national scale [Center for Substance Abuse Treatment (CSAT) 2005].

The impact of VIVITROL's effect on abstinence extends benefits for many of these other consequences. Blockade of the euphoric effects of opioids in the event the patient slips helps to protect the patient from both the reinforcement of the high and the negative reinforcement of the acute withdrawal as opioid drug levels decline. The extended-release formulation confers a persistence with the medication itself, plus, it improves retention in overall treatment. This dual persistence/retention benefit is demonstrated in HIV and Hepatitis C patients. This is a category of patients whose health and survival depend on retention in treatment and adherence to challenging medication regimens [National Institutes of Health (NIH) 2002;Sandelowski, 2009]. With these regimens, drug addiction relapse can be profoundly disruptive and life-threatening. These patients are at known severe risk for viral disease transmission, and VIVITROL demonstrated reductions in such high risk behaviors.

Opioid addicts have high rates of mental health dysfunction [Mason, 1998;Substance Abuse and Mental Health Services Administration (SAMHSA) 2002]. VIVITROL in combination with psychosocial management confers subjectively and functionally important benefits on all four components of the Mental Health composite of the SF-36: functional mental health, emotional role performance, social functioning and vitality. This functional impact was similarly evident in the self-assessment of overall health state. The sum of these proximal and distal clinical and psychosocial benefits may also impact patient care through enhanced acceptability of the treatment and improved compliance. Finally, these functional and quality of life patient self-report benefits were also validated by investigators' objective observations of global clinical improvement, which was observed in the vast majority of patients.

9.1.2. Specific Clinical Benefits

The VIVITROL formulation offers several specific features that distinguish it from the currently available opioid dependence disorder pharmacotherapies.

- The IM delivery route ensures that the patient has received the medication. This provides direct assurance of treatment adherence for the patient, the patient's family members, and the health care providers.
- The extended-release formulation assures month-long continuity of effect, overcoming the high risk of non-adherence that has been common with the daily oral

regimen. The formulation also dispenses with any need for daily supervised administration.

- The absence of physical dependence on VIVITROL means that the agent has no potential for producing withdrawal symptoms upon discontinuation.
- The antagonist mechanism of action means that patients who have not had sufficient duration or severity of opioid dependence to meet criteria for agonist maintenance therapy will be able to choose a effective maintenance pharmacotherapy.
- The mechanism of action makes it suitable for patients who feel stigmatized, have medical contraindications, or who are philosophically opposed to agonist therapy Also, VIVITROL is uniquely suitable for patients whose employment or professional license prohibits agonist treatment eg, health care professionals, transportation workers, public safety officials, and military personnel.
- The agent does not pose a diversion risk.

9.2. Potential Risks

On the market since 2006 as a treatment for alcohol dependence, VIVITROL has a well-defined risk profile resulting from its use by over 45,000 patients. To prevent AEs from occurring, and minimizing the negative consequences when they do occur, Alkermes provides several educational resources and materials to VIVITROL providers and patients intended to prevent or minimize the consequences.

The available data from clinical studies document that VIVITROL is generally well tolerated by patients with opioid dependence. The most common AEs included nasopharyngitis, influenza, upper respiratory tract infection, sinusitis, insomnia, depression, headache, dizziness, nausea, upper abdominal pain, diarrhea, fatigue, and back pain. The current VIVITROL prescribing information lists all these AEs.

Some patients on VIVITROL have had reactions at the injection site. Based on signals observed in postmarketing surveillance, proposed label changes regarding injection-site reactions were submitted to the FDA. This topic was subsequently the subject of an FDA alert in August of 2008. These injection site reactions have been determined to possibly be related to injection into adipose tissue instead of muscle (see Section 7.3.2).

In March 2010, FDA approved a Risk Evaluation and Mitigation Strategy (REMS) developed to inform patients about the risks of VIVITROL, including the risk of injection site reactions. As part of the REMS, a Medication Guide is distributed with all packages of VIVITROL. The Medication Guide describes signs and symptoms of injection site reaction, and directs patients to call their doctor immediately if any of these occur. Alkermes offers injection technique education at medical conferences. To further reinforce use of proper injection techniques, a VIVITROL administration DVD is also in development and will be distributed from field sales directly to the health-care provider and staff.

There is no evidence to expect the frequency of this AE would differ between alcohol-dependent and opioid-dependent patients. Therefore, these efforts to prevent injection site reaction, including implementation of the REMS, will be consistent between indications.

Since a primary risk factor for ISRs appears to be the inadvertent administration of VIVITROL into the adipose layer a goal of the risk mitigation program has been to increase the likelihood of injection into muscle tissue. Alkermes is working with the FDA to supply a longer, 2" IM needle, to supplement the existing 1.5" IM needle in the VIVITROL kit. The longer needle is intended to facilitate injection into the gluteal muscle in patients with greater BMI, ie, a thicker layer of subcutaneous fat.

Hepatic safety issues did not emerge in the opioid population with high rates of Hepatitis C and HIV. All patients with AEs related to abnormal LFTs had histories of Hepatitis C at enrollment. Throughout the study actual ALT and AST concentrations were similar in the VIVITROL and placebo groups, even in this high risk population. None of the ALT or AST elevations were associated with elevations of bilirubin.

Opioid overdose may occur with efforts to over-ride the blockade while on VIVITROL as well as an increased sensitivity to opioids after VIVITROL treatment due to loss of tolerance. Because VIVITROL will be used in patients with a history of opioid abuse, there is a risk that patients will attempt to over-ride the blockade actions of VIVITROL by using greater amounts of opioids. Further, after discontinuation of VIVITROL these patients may have an increased sensitivity to opioids due to loss of tolerance.

To prevent the occurrence overdose, Alkermes educates prescribers about the risk of opioid overdose and how to avoid it. Educational materials describe how opioid overdose can occur and the potential consequences, and direct prescribers to address this risk with their patients. Additionally, patients are provided with materials that describe the risk and effects of opioid overdose, including the likelihood of increased sensitivity, and how to avoid it. Patient materials include the Medication Guide, a brochure and a wallet card indicating the patient is taking VIVITROL.

Risks of known and potential drug interactions are limited to the interaction between opioids and naltrexone. Specifically, the risks are: a) precipitation of opioid withdrawal upon initiation of VIVITROL treatment in an opioid-dependent patient, and b) blockade of opioid analgesics in patients maintained on VIVITROL. These risks are detailed in the current product label.

If VIVITROL is dosed while the patient has opioids in their system, withdrawal will occur. To mitigate this risk, current prescribing information details the potential for and consequences of precipitation of opioid withdrawal and also provides specific information on the conduct and interpretation of a naloxone challenge test. This information is also included in educational programs. This activity will continue with the opioid dependence indication.

Inadequate pain treatment may occur in cases of planned medical procedures (if the patient fails to inform the health care provider about their use of VIVITROL) and unplanned procedures (for example, if a patient is in an accident). As with the alcohol dependence indication, Alkermes will continue educate physicians to warn patients about the risk of inadequate pain treatment, how to avoid this scenario, and how to facilitate access to resources about alternatives to opioid treatments for pain management. Printed materials reiterate this information. The Alkermes patient welcome kit also includes information about this risk, and the previously mentioned patient wallet card indicates the patient is taking VIVITROL and that care must be taken to manage pain.

Treatment with VIVITROL is largely administered by physicians with a specific focus and expertise in the treatment of chemical dependence and ability provide or coordinate concurrent psychosocial therapy. Currently VIVITROL is being prescribed by approximately 1100 physicians in the US in 400 facilities. Approximately 50% of VIVITROL prescriptions are written by 130 physicians [Alkermes data on file]. Treatment facilities typically require personnel to manage access logistics, reimbursement, refrigeration, and gluteal IM injection on a longitudinal basis. If approved for the treatment of opioid dependence, it is anticipated that treatment in US would continue to be provided by physicians and treatment facilities that offer this range of services. It is expected that the number of physicians who will prescribe VIVITROL for the treatment of opioid dependence be limited to those types as described above and therefore permit Alkermes to continue to provide education in an effective and ongoing manner.

9.3. Summary of Benefits and Risks

Overall, the benefit versus risk relationship for the treatment of opioid dependence disorder with VIVITROL is favorable, with broad and substantial impact on a devastating disorder. It has proven efficacy, as demonstrated by a statistically significant and clinically meaningful increase in the frequency of abstinent weeks in opioid-dependent patients. VIVITROL was generally well tolerated. Its formulation is unique, yielding benefits that are sustained and suitable for important components of the opioid dependent population, features that are not available with currently approved agents for opioid dependence.

The benefits of VIVITROL administration in an opioid dependent population outweigh the risks of administration of VIVITROL. The current package insert for VIVITROL will be modified to add the specific details required to adequately addresses the management of risks to promote the safe use of the product in the treatment of opioid dependence disorder.

10. APPENDICES

10.1. Approved Package Insert (for alcohol dependence)

Vivitrol®

(naltrexone for extended-release injectable suspension)

380 mg/vial

DESCRIPTION:

VIVITROL® (naltrexone for extended-release injectable suspension) is supplied in a microsphere formulation of naltrexone for reconstitution, to be administered by intramuscular injection. Naltrexone is an opioid antagonist with little, if any, opioid agonist activity.

Naltrexone is designated chemically as morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-(5α) (C$_{20}$H$_{23}$NO$_4$ • HCl • $\frac{1}{2}$H$_2$O, and its molecular weight is 376.41 in the anhydrous form (i.e., < 1% moisture/water content). The structural formula is:

Naltrexone base anhydrous is an off-white to light tan powder with a melting point of 168-170°C (334-338°F). It is insoluble in water and is soluble in ethanol.

VIVITROL is provided as a carton containing a vial each of VIVITROL microspheres and diluent, one 5-mL syringe, one 1-inch 20-gauge preparation needle, two 1½-inch 20-gauge administration needles with safety device.

VIVITROL microspheres consist of a sterile, off-white to light tan powder that is available in a dosage strength of 380 mg naltrexone per vial. Naltrexone is encapsulated in 75:25 polylactide-co-glycolide (PLG) at a concentration of 337 mg of naltrexone per gram of microspheres.

The diluent is a clear, colorless solution. The composition of the diluent includes carboxymethylcellulose sodium, polysorbate 20, sodium chloride, and water for Injections. The microspheres must be suspended in the diluent prior to injection.

CLINICAL PHARMACOLOGY:

Pharmacodynamics

Mechanism of Action

Naltrexone is an opioid antagonist with highest affinity for the mu opioid receptor. Naltrexone has few, if any, intrinsic actions besides its opioid blocking properties. However, it does produce some pupillary constriction, by an unknown mechanism.

The administration of VIVITROL is not associated with the development of tolerance or dependence. In subjects physically dependent on opioids, VIVITROL will precipitate withdrawal symptomatology.

Occupation of opioid receptors by naltrexone may block the effects of endogenous opioid peptides. The neurobiological mechanisms responsible for the reduction in alcohol consumption observed in alcohol-dependent patients treated with naltrexone are not entirely understood. However, involvement of the endogenous opioid system is suggested by preclinical data.

Naltrexone blocks the effects of opioids by competitive binding at opioid receptors. This makes the blockade produced potentially surmountable, but overcoming full naltrexone blockade by administration of opioids may result in non-opioid receptor-mediated symptoms such as histamine release.

VIVITROL is not an aversive therapy and does not cause a disulfiram-like reaction either as a result of opiate use or ethanol ingestion.

Pharmacokinetics

Absorption:

VIVITROL is an extended-release, microsphere formulation of naltrexone designed to be administered by intramuscular (IM) gluteal injection every 4 weeks or once a month. After IM injection, the naltrexone plasma concentration-time profile is characterized by a transient initial peak, which occurs approximately 2 hours after injection, followed by a second peak observed approximately 2 - 3 days later. Beginning approximately 14 days after dosing, concentrations slowly decline, with measurable levels for greater than 1 month.

Maximum plasma concentration (C_{max}) and area under the curve (AUC) for naltrexone and 6β-naltrexol (the major metabolite) following VIVITROL administration are dose proportional. Compared to daily oral dosing with naltrexone 50 mg over 28 days, total naltrexone exposure is 3 to 4-fold higher following administration of a single dose of VIVITROL 380 mg. Steady state is reached at the end of the dosing interval following the first injection. There is minimal accumulation (< 15%) of naltrexone or 6β-naltrexol upon repeat administration of VIVITROL.

Distribution:

In vitro data demonstrate that naltrexone plasma protein binding is low (21%).

Metabolism

Naltrexone is extensively metabolized in humans. Production of the primary metabolite, 6β-naltrexol, is mediated by dihydrodiol dehydrogenase, a cytosolic family of enzymes. The cytochrome P450 system is not involved in naltrexone metabolism. Two other minor metabolites are 2-hydroxy-3-methoxy-6β-naltrexol and 2-hydroxy-3-methoxy-naltrexone. Naltrexone and its metabolites are also conjugated to form glucuronide products.

Significantly less 6β-naltrexol is generated following IM administration of VIVITROL compared to administration of oral naltrexone due to a reduction in first pass hepatic metabolism.

Elimination

Elimination of naltrexone and its metabolites occurs primarily via urine, with minimal excretion of unchanged naltrexone.

The elimination half-life of naltrexone following VIVITROL administration is 5 to 10 days and is dependent on the erosion of the polymer. The elimination half-life of 6β-naltrexol following VIVITROL administration is 5 to 10 days.

Special Populations

Hepatic Impairment: The pharmacokinetics of VIVITROL are not altered in subjects with mild to moderate hepatic impairment (Groups A and B of the Child-Pugh classification). Dose adjustment is not required in subjects with mild or moderate hepatic impairment. VIVITROL pharmacokinetics were not evaluated in subjects with severe hepatic impairment (**see PRECAUTIONS**).

Renal Impairment: A population pharmacokinetic analysis indicated mild renal clearance (creatinine clearance of 50-80 mL/min) had little or no influence on VIVITROL pharmacokinetics and that no dosage adjustment is necessary (**see PRECAUTIONS**). VIVITROL pharmacokinetics have not been evaluated in subjects with moderate and severe renal insufficiency (**See PRECAUTIONS**).

Gender: In a study in healthy subjects (n= 18 females and 18 males), gender did not influence the pharmacokinetics of VIVITROL.

Age: The pharmacokinetics of VIVITROL have not been evaluated in the geriatric population.

Race: The effect of race on the pharmacokinetics of VIVITROL has not been studied.

Pediatrics: The pharmacokinetics of VIVITROL have not been evaluated in a pediatric population.

Drug-Drug Interactions

Clinical drug interaction studies with VIVITROL have not been performed.

Naltrexone antagonizes the effects of opioid-containing medicines, such as cough and cold remedies, antidiarrheal preparations and opioid analgesics (**see PRECAUTIONS**).

CLINICAL STUDIES:

The efficacy of VIVITROL in the treatment of alcohol dependence was examined in a 24-week, placebo-controlled, multi-center, double-blind, randomized trial of alcohol dependent (DSM-IV criteria) outpatients. Subjects were treated with an injection every 4 weeks of VIVITROL 190 mg, VIVITROL 380 mg or placebo. Oral naltrexone was not administered prior to the initial or subsequent injections of study medication. Psychosocial support was provided to all subjects in addition to medication.

Subjects treated with VIVITROL 380 mg demonstrated a greater reduction in days of heavy drinking than those treated with placebo. Heavy drinking was defined as self report of 5 or more standard drinks consumed on a given day for male patients and 4 or more drinks for female patients. Among the subset of patients (n=53, 8% of the total study population) who abstained completely from drinking during the week prior to the first dose of medication, compared with placebo-treated patients, those treated with VIVITROL 380 mg had greater reduction in the number of drinking days and the number of heavy drinking days. In this subset, patients treated with VIVITROL were also more likely than placebo-treated patients to maintain complete abstinence throughout treatment. The same treatment effects were not evident among the subset of patients (n=171, 22% of the total study population) who were actively drinking at the time of treatment initiation.

INDICATIONS AND USAGE:

VIVITROL is indicated for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with VIVITROL.

Patients should not be actively drinking at the time of initial VIVITROL administration.

Treatment with VIVITROL should be part of a comprehensive management program that includes psychosocial support.

CONTRAINDICATIONS:

VIVITROL is contraindicated in:

- Patients receiving opioid analgesics (**see PRECAUTIONS**).
- Patients with current physiologic opioid dependence (**see WARNINGS**)
- Patients in acute opiate withdrawal (**see WARNINGS**).
- Any individual who has failed the naltrexone challenge test or has a positive urine screen for opioids.
- Patients who have previously exhibited hypersensitivity to naltrexone, PLG, carboxymethylcellulose, or any other components of the diluent.

WARNINGS:

Hepatotoxicity

Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses.

Naltrexone is contraindicated in acute hepatitis or liver failure, and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects.

The margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury appears to be only five-fold or less. VIVITROL does not appear to be a hepatotoxic at the recommended dose.

Patients should be warned of the risk of hepatic injury and advised to seek medical attention if they experience symptoms of acute hepatitis. Use of VIVITROL should be discontinued in the event of symptoms and/or signs of acute hepatitis.

Injection Site Reactions

VIVITROL injections may be followed by pain, tenderness, induration, swelling, erythema, bruising, or pruritus; however, in some cases injection site reactions may be very severe. In the clinical trials, one patient developed an area of induration that continued to enlarge after 8 weeks, with subsequent development of necrotic tissue that required surgical excision. In the postmarketing period, additional cases of injection site reactions with features including induration, cellulitis, hematoma, abscess, sterile abscess, and necrosis, have been reported. Some cases required surgical intervention, including debridement of necrotic tissue. Some cases resulted in significant scarring. The reported cases occurred primarily in female patients.

VIVITROL is administered as a gluteal intramuscular injection, and inadvertent subcutaneous injection of VIVITROL may increase the likelihood of severe injection site reactions. The needle provided in the carton is a contoured needle. VIVITROL must not be injected using any other needle. The needle length may not be adequate in every patient because of body habitus. Body habitus should be assessed prior to each injection for each patient to ensure that needle length is adequate for intramuscular administration. Healthcare providers should ensure that the VIVITROL injection is given correctly, and should consider alternate treatment for those patients whose body habitus precludes a gluteal intramuscular injection with the provided needle.

Patients should be informed that any concerning injection site reactions should be brought to the attention of the healthcare provider (**see INFORMATION FOR PATIENTS**). Patients exhibiting signs of abscess, cellulitis, necrosis, or extensive swelling should be evaluated by a physician to determine if referral to a surgeon is warranted.

Eosinophilic pneumonia

In clinical trials with VIVITROL, there was one diagnosed case and one suspected case of eosinophilic pneumonia. Both cases required hospitalization, and resolved after treatment with antibiotics and corticosteroids. Should a person receiving VIVITROL develop progressive dyspnea and hypoxemia, the diagnosis of eosinophilic pneumonia should be considered (**see ADVERSE REACTIONS**). Patients should be warned of the risk of eosinophilic pneumonia, and advised to seek medical attention should they develop symptoms of pneumonia. Clinicians should consider the possibility of eosinophilic pneumonia in patients who do not respond to antibiotics.

Unintended Precipitation of Opioid Withdrawal

In present occurrence of an acute abstinence syndrome (withdrawal) in patients dependent on opioids, or exacerbation of a pre-existing subclinical abstinence syndrome, patients must be opioid-free for a minimum of 7-10 days before starting VIVITROL treatment. Since the absence of an opioid drug in the urine is often not sufficient proof that a patient is opioid-free, a naloxone challenge test should be employed if the prescribing physician feels there is a risk of precipitating a withdrawal reaction following administration of VIVITROL.

Opioid Overdose Following an Attempt to Overcome Opiate Blockade

VIVITROL is not indicated for the purpose of opioid blockade or the treatment of opiate dependence. Although VIVITROL is a potent antagonist with a prolonged pharmacological effect, the blockade produced by VIVITROL is surmountable. This poses a potential risk to individuals who attempt, on their own, to overcome the blockade by administering large amounts of exogenously administered opioids. Indeed, any attempt by a patient to overcome the antagonism by taking opioids is very dangerous and may lead to fatal overdose. Injury may arise because the plasma concentration of exogenous opioids attained immediately following their acute administration may be sufficient to overcome the competitive receptor blockade. As a consequence, the patient may be in immediate danger of suffering life-endangering opioid intoxication (e.g., respiratory arrest, circulatory collapse). Patients should be told of the serious consequences of trying to overcome the opioid blockade (**see INFORMATION FOR PATIENTS**).

There is also the possibility that a patient who had been treated with VIVITROL will respond to lower doses of opioids than previously used. This could result in potentially life-threatening opioid intoxication (respiratory compromise or arrest, circulatory collapse, etc.). Patients should be aware that they may be more sensitive to lower doses of opioids after VIVITROL treatment is discontinued (**see INFORMATION FOR PATIENTS**).

PRECAUTIONS:

General

When Reversal of VIVITROL Blockade is Required for Pain Management

In an emergency situation in patients receiving VIVITROL, suggestions for pain management include regional analgesia or use of non-opioid analgesics. If opioid therapy is required as part of anesthesia or analgesia, such patients should be continuously monitored, in an anesthesia care setting, by persons not involved in the conduct of the surgical or diagnostic procedure. The opioid therapy must be provided by individuals specifically trained in the use of anesthetic drugs and the management of the respiratory effects of potent opioids, specifically the establishment and maintenance of a patent airway and assisted ventilation.

Irrespective of the drug chosen to reverse VIVITROL blockade, the patient should be monitored closely by appropriately trained personnel in a setting equipped and staffed for cardiopulmonary resuscitation.

Depression and Suicidality

In controlled clinical trials of VIVITROL, adverse events of a suicidal nature (suicidal ideation, suicide attempts, completed suicides) were infrequent overall, but were more common in patients treated with VIVITROL than in patients treated with placebo (1% vs. 0). In some cases, the suicidal thoughts or behavior occurred after study discontinuation, but were in the context of an episode of depression which began while the patient was on study drug. Two completed suicides occurred, both involving patients treated with VIVITROL.

Depressive-related events associated with premature discontinuation of study drug were also more common in patients treated with VIVITROL (~1%) than in placebo-treated patients (0).

In the 24-week, placebo-controlled clinical trial, adverse events involving depressed mood were reported by 10% of patients treated with VIVITROL 380 mg, as compared to 5% of patients treated with placebo injections.

Alcohol-dependent patients, including those taking VIVITROL, should be monitored for the development of depression or suicidal thinking. Families and caregivers of patients being treated with VIVITROL should be alerted to the need to monitor patients for the emergence of symptoms of depression or suicidality, and to report such symptoms to the patient's healthcare provider.

Renal Impairment

VIVITROL pharmacokinetics have not been evaluated in subjects with moderate or severe renal insufficiency. Because naltrexone and its primary metabolite are excreted primarily in the urine, caution is recommended in administering VIVITROL to patients with moderate to severe renal impairment.

Alcohol Withdrawal

Use of VIVITROL does not eliminate nor diminish alcohol withdrawal symptoms.

Intramuscular Injections

As with any intramuscular injection, VIVITROL should be administered with caution to patients with thrombocytopenia or any coagulation disorder (e.g., hemophilia and severe hepatic failure).

Information for Patients

Physicians should discuss the following issues with patients for whom they prescribe VIVITROL:

- Patients should be advised to carry documentation to alert medical personnel to the fact that they are taking VIVITROL (naltrexone for extended-release injectable suspension). This will help to ensure that the patient obtains adequate medical treatment in an emergency.
- Patients should be advised that a reaction at the site of VIVITROL injection may occur. Reactions include pain, tenderness, induration, swelling, erythema, bruising, or pruritus. Serious injection site reactions including necrosis may occur. Patients should receive their injection from a healthcare provider qualified to administer the injection. Patients should be advised to seek medical attention for worsening skin reactions.
- Patients should be advised that administration of large doses of heroin or any other opioid while on VIVITROL may lead to serious injury, coma, or death.
- Patients should be advised that because VIVITROL can block the effects of opiates and opiate-like drugs, patients will not perceive any effect if they attempt to self-administer heroin or any other opioid drug in small doses while on VIVITROL. Also, patients on VIVITROL may not experience the same effects from opioid containing analgesic, antitussive, or antidiarrheal medications.
- Patients should be advised that if they previously used opioids, they may be more sensitive to lower dosages of opioids after VIVITROL treatment is discontinued.
- Patients should be advised that VIVITROL may cause liver injury in people who develop liver disease from other causes. Patients should immediately notify their physician if they develop symptoms and/or signs of liver disease.
- Patients should be advised that VIVITROL may cause an allergic pneumonia. Patients should immediately notify their physician if they develop signs and symptoms of pneumonia, including dyspnea, coughing, or wheezing.
- Patients should be advised that they may experience nausea following the initial injection of VIVITROL. These episodes of nausea tend to be mild and subside within a few days post-injection. Patients are less likely to experience nausea in subsequent injections.
- Patients should be advised that because VIVITROL is an intramuscular injection, as well as an implanted device, once VIVITROL is injected, it is not possible to remove it from the body.
- Patients should be advised that VIVITROL has been shown to treat alcohol dependence only when used as part of a treatment program that includes counseling and support.
- Patients should be advised that dizziness may occur with VIVITROL treatment, and they should avoid driving or operating heavy machinery until they have determined how VIVITROL affects them.
- Patients should be advised to notify their physician if they:
  - become pregnant or intend to become pregnant during treatment with VIVITROL.
  - are breast-feeding.
  - experience respiratory symptoms such as dyspnea, coughing, or wheezing after taking VIVITROL.
  - have nausea or prolonged pain, swelling, changes of skin color or signs of overall ill health (e.g., hard nodule [s], blistering, an open wound or dark scab) at site injection site.
  - experience other unusual or significant side effects while on VIVITROL therapy.

Drug Interactions

Patients taking VIVITROL may not benefit from opioid-containing medicines (**see PRECAUTIONS, Pain Management**).

Because naltrexone is not a substrate for CYP drug metabolizing enzymes, inducers or inhibitors of these enzymes are unlikely to change the clearance of VIVITROL. No clinical drug interaction studies have been performed with VIVITROL to evaluate drug interactions, therefore prescribers should weigh the risks and benefits of concomitant drug use.

The safety profile of patients treated with VIVITROL concomitantly with naltrexone was similar in that of patients taking VIVITROL without antidepressants.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with VIVITROL.

Carcinogenicity studies of oral naltrexone hydrochloride (administered via the diet) have been conducted in rats and mice. In rats, there were small increases in the numbers of testicular mesotheliomas in males and uterine/cervical polyps in females and females. The clinical significance of these findings is not known.

Naltrexone was negative in the following in vitro genotoxicity studies: bacterial reverse mutation assay (Ames test), the forward mutation assay, CHO cell clastogenicity assay, and the mouse lymphoma gene mutation assay. Naltrexone was also negative in an in vivo mouse micronucleus assay. In general, naltrexone is not positive in the following assays: Drosophila recessive lethal frequency assay, and specific DNA damage in repair tests with E. coli and WI-38 cells, and animals for methylated histidine reversion.

Naltrexone given orally caused a significant increase in pseudopregnancy and a decrease in pregnancy rates in rats at 100 mg/kg/day (600 mg/m^2/day). There was no effect on male fertility at this dose level. The relevance of these observations to human fertility is not known.

Pregnancy Category C

Reproduction and developmental studies have not been conducted for VIVITROL. Studies with naltrexone administered via the oral route have been conducted in pregnant rats and rabbits.

Teratogenic Effects: Oral naltrexone has been shown to increase the incidence of early fetal loss in rats administered ≥ 30 mg/kg/day (180 mg/m^2/day) and rabbits administered ≥ 60 mg/kg/day (720 mg/m^2/day).

There are no adequate and well-controlled studies of either naltrexone or VIVITROL in pregnant women. VIVITROL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The potential effect of VIVITROL on duration of labor and delivery in humans is unknown.

Nursing Mothers

Transfer of naltrexone and 6β-naltrexol into human milk has been reported with oral naltrexone. Because of the potential for tumorigenicity shown for naltrexone in animal studies, and because of the potential for serious adverse reactions in nursing infants from VIVITROL, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and efficacy of VIVITROL have not been established in the pediatric population.

Geriatric Use

In trials of alcohol dependent subjects, 2.6% (6/231) of subjects were ≥65 years of age, and one patient was ≥75 years of age. Clinical studies of VIVITROL did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

In all controlled and uncontrolled trials during the premarketing development of VIVITROL, more than 900 patients with alcohol and/or opioid dependence have been treated with VIVITROL. Approximately 400 patients have been treated for 6 months or more, and 230 for 1 year or longer.

Adverse Events Leading to Discontinuation of Treatment

In controlled trials of 6 months or less, 9% of patients treated with VIVITROL discontinued treatment due to an adverse event, as compared to 7% of the patients treated with placebo. Adverse events in the VIVITROL 380 mg group that led to more frequent were injection site reactions (3%), nausea (2%), pregnancy (1%), headache (1%), and vascular-related events (0.3%). In the placebo group, 1% of patients withdrew due to injection site reactions, and 0% of patients withdrew due to the other adverse events.

Common Adverse Events

The table lists all adverse events, regardless of causality occurring in ≥5% of patients with alcohol dependence for which the incidence was greater in the combined VIVITROL group than in the placebo group. A majority of patients treated with VIVITROL in clinical studies had adverse events with a maximum intensity of "mild" or "moderate."

Postmarketing Reports

Reports From Other Intramuscular Drug Products Containing Polylactide-co-glycolide (PLG) Microspheres – Not With VIVITROL

Retinal Artery Occlusion

Retinal artery occlusion after injection with another drug product containing polylactide-co-glycolide (PLG) microspheres has been reported very rarely during postmarketing surveillance. This event has been reported to the presence of abnormal arteriovenous anastomosis. No cases of retinal artery occlusion have been reported during VIVITROL clinical trials or postmarketing surveillance. VIVITROL should be administered by intramuscular (IM) injection into the gluteal muscle, and care must be taken to avoid inadvertent injection into a blood vessel (**see DOSAGE AND ADMINISTRATION**).

For additional information, visit
www.vivitrol.com
or call
1-800-848-4876

Vivitrol®

380 mg/vial

Alkermes®

Manufactured and marketed by:
Alkermes, Inc.
852 Winter Street
Waltham, MA 02451

Directions for Use and Package Insert

Printed in U.S.A.
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Common Adverse Events (by body system and preferred term/high level group term) in ≥5% of Patients Treated with VIVITROL

Body System	Adverse Event/Preferred Term	Placebo	Naltrexone for extended-release injectable suspension							
		N = 214	400 mg N = 25		380 mg N = 205		190 mg N = 210		All N = 440	
		N	%	N	%	N	%	N	%	N	%
Gastrointestinal disorders	Nausea	24	11	8	32	66	33	53	25	129	29
	Vomiting NOS	12	6	3	12	28	14	22	10	53	12
	Diarrhea[1]	21	10	3	12	27	13	27	13	57	13
	Abdominal pain[2]	17	8	4	16	23	11	23	11	50	11
	Dry mouth	9	4	6	24	10	5	8	4	24	5
Infections and infestations	Upper respiratory tract infection, Other[3]	29	13	0	0	27	13	25	12	52	12
	Pharyngitis[4]	23	11	0	0	22	11	35	17	57	13
Psychiatric disorders	Insomnia, sleep disorder	25	12	2	8	29	14	27	13	58	13
	Anxiety[5]	17	8	2	8	24	12	16	8	42	10
	Depression	9	4	0	0	17	8	7	3	24	5
General disorders and administration site conditions	Any ISR	106	50	23	88	142	69	123	58	288	65
	Injection site reactions	85	39	18	72	92	44	99	47	199	45
	Injection site induration	18	8	7	28	71	35	52	25	130	30
	Injection site pain	16	7	0	0	34	17	22	10	56	13
	Other ISR (granuloma, nodules, swelling)	8	4	4	16	32	16	15	7	51	12
	Injection site pruritus	0	0	0	0	21	10	13	6	34	8
	Injection site erythema	13	6	0	0	14	7	9	4	23	5
	Asthenic conditions[6]	26	12	3	12	47	23	49	19	99	23
Musculoskeletal and connective tissue disorders	Arthralgia, arthritis, joint stiffness	14	5	1	4	24	12	12	6	37	9
	Back pain, back stiffness	10	5	1	4	12	6	14	7	27	6
	Muscle cramps[7]	3	1	0	0	16	8	5	2	21	5
Skin and subcutaneous tissue disorders	Rash[8]	8	4	3	12	12	6	10	5	25	6
Nervous system disorders	Headache[9]	39	18	9	36	51	25	34	16	94	21
	Dizziness, vertigo	9	4	4	16	27	13	21	10	58	13
	Somnolence, sedation	2	1	3	12	8	4	9	4	20	5
Metabolism and nutrition disorders	Anorexia, appetite decreased, felt injected/inserted NOS	6	3	3	20	30	14	13	6	49	11

1 Includes the preferred terms: diarrhea NOS, frequent bowel movements, gastrointestinal upset, loose stools
2 Includes the preferred terms: abdominal pain NOS, abdominal pain upper, stomach discomfort, abdominal pain lower
3 Includes the preferred terms: upper respiratory tract infection NOS, laryngitis NOS, sinusitis NOS
4 Includes the preferred terms: nasopharyngitis, pharyngitis streptococcal, pharyngitis NOS
5 Includes the preferred terms: anxiety NOS, anxiety aggravated, agitation, tension, panic disorder, panic attack, nervousness, psychomotor hyperactivity
6 Includes the preferred terms: malaise, fatigue, those terms in the majority of cases)
lethargy, sluggishness
7 Includes the preferred terms: muscle cramps, spasms, tightness, twitching, stiffness, rigidity
8 Includes the preferred terms: rash NOS, rash pustular, hot rash
9 Includes the preferred terms: headache NOS, sinus headache, migraine, frontal headache

Laboratory Tests

In clinical trials, subjects on VIVITROL had increases in eosinophil count cumulative to subjects on placebo. With continued use of VIVITROL, eosinophil counts returned to normal over a period of several months.

VIVITROL 380 mg was associated with a decrease in platelet count. Patients treated with high dose VIVITROL experienced a mean maximal decrease in platelet count of 17.8 x 10^3/μL, compared to 2.6 x 10^3/μL in placebo patients. In controlled controlled trials, VIVITROL was not associated with an increase in bleeding-related adverse events.

In short-term, controlled trials, the incidence of AST elevations associated with VIVITROL treatment was similar to that observed with oral naltrexone treatment (1.5% each) and slightly higher than observed with placebo treatment (0.9%).

In short-term controlled trials, more patients treated with VIVITROL 380 mg (11%) and oral naltrexone (17%) shifted from abnormal creatinine phosphokinase (CPK) levels before treatment to abnormal CPK levels at the end of the trials, compared to placebo patients (8%). In open-label trials, 16% of patients dosed for more than 6 months had increases in CPK. For both the oral naltrexone and VIVITROL 380 mg groups, CPK abnormalities were most frequently in the range of 1-2 x ULN. However, there were reports of CPK abnormalities as high as 6x ULN for the oral naltrexone group, and 35 x ULN for the VIVITROL 380 mg group. Overall, there were no differences between the placebo and naltrexone (oral or injectable) groups with respect to the proportions of patients with a CPK value at least three times the upper limit of normal. No factors other than naltrexone exposure were associated with the CPK elevations.

VIVITROL may be cross-reactive with certain immunoassay methods for the detection of drugs of abuse, specifically opioids in urine. For further information, reference to the specific immunoassay instructions is recommended.

Other Events Observed During the Premarketing Evaluation of VIVITROL
The following is a list of preferred terms that reflect events reported by medical and/or opiate dependent subjects treated with VIVITROL in controlled trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

Gastrointestinal Disorders – constipation, toothache, flatulence, gastroesophageal reflux disease, hemorrhoids, colitis, gastrointestinal hemorrhage, paralytic ileus, perirectal abscess

Infections and Infestations – influenza, bronchitis, urinary tract infection, gastroenteritis, tooth abscess, pneumonia, cellulitis

General Disorders and Administration Site Conditions – pyrexia, lethargy, edema, chest pain, chest tightness, weight decreased

Psychiatric Disorders – irritability, libido decreased, abnormal dreams, alcohol withdrawal syndrome, agitation, euphoric mood, delirium

Nervous System Disorders – dysgeusia, disturbance in attention, migraine, mental impairment, convulsion, ischemic stroke, cerebral arterial aneurysm

Musculoskeletal and Connective Tissue Disorders – pain in limb, muscle spasms, joint stiffness

Skin and Subcutaneous Tissue Disorders – sweating increased, night sweats, pruritus

Respiratory, Thoracic, and Mediastinal Disorders – pharyngolaryngeal pain, dyspnea, sinus congestion, chronic obstructive airways disease

Metabolism and Nutrition Disorders – appetite increased, heat intolerance, dehydration, hypercholesterolemia

Vascular Disorders – hypertension, hot flashes, deep venous thrombosis, pulmonary embolism

Eye Disorders – conjunctivitis

Blood and Lymphatic System Disorders – lymphadenopathy (including cervical adenitis), white blood cell count increased

Cardiac Disorders – palpitations, atrial fibrillation, myocardial infarction, angina pectoris, angina unstable, cardiac failure congestive, coronary artery atherosclerosis

Immune System Disorders – seasonal allergy, hypersensitivity reaction (including anaphylactic edema and urticaria)

Pregnancy, Puerperium, and Perinatal Conditions – abortion missed

Hepatobiliary Disorders – cholelithiasis, aspartate aminotransferase increased, alanine aminotransferase increased, cholecystitis acute

DRUG ABUSE AND DEPENDENCE:
Controlled Substance Class
VIVITROL is not a controlled substance.

Physical and Psychological Dependence
Naltrexone, the active ingredient in VIVITROL, is a pure opioid antagonist that does not lead to physical or psychological dependence. Tolerance to the opioid antagonist effect is not known to occur.

OVERDOSAGE:
There is limited experience with overdose of VIVITROL. Single doses up to 784 mg were administered to 6 healthy subjects. There were no serious or severe adverse events. The most common effects were injection site reactions, nausea, abdominal pain, somnolence, and dizziness. There were no significant increases in hepatic enzymes. In the event of an overdose, appropriate supportive treatment should be initiated.

DOSAGE AND ADMINISTRATION:
VIVITROL must be administered by a healthcare professional.

The recommended dose of VIVITROL is 380 mg delivered intramuscularly every 4 weeks or once a month. The injection should be administered by a healthcare professional as an intramuscular (IM) gluteal injection, alternating buttocks for each subsequent injection, using the carton components provided (see HOW SUPPLIED). The needle provided in the carton is a coaxial-shield needle. VIVITROL must not be injected using any other needle. The needle length may not be adequate in every patient because of body habitus. Body habitus should be assessed prior to each injection for each patient to assure that needle length is adequate for intramuscular administration. Healthcare providers should ensure that the VIVITROL injection is given correctly, and should consider alternate treatment for those patients whose body habitus precludes a gluteal intramuscular injection with the provided needle.

VIVITROL must not be administered intravenously or subcutaneously.

If a patient misses a dose, he/she should be instructed to receive the next dose as soon as possible.

Pretreatment with oral naltrexone is not required before using VIVITROL.

In an emergency situation in patients receiving VIVITROL, suggestions for pain management include regional analgesia or use of non-opioid analgesics. If opioid therapy is required as part of anesthesia or analgesia, such patients should be continuously monitored, by an anesthesia care setting, by persons not involved in the conduct of the surgical or diagnostic procedure. The opioid therapy must be provided by individuals specifically trained in the use of anesthetic drugs and the management of the respiratory effects of potent opioids, specifically the establishment and maintenance of a patent airway and assisted ventilation.

Rehabilitation of Treatment in Patients Previously Discontinued
There are no data to specifically address reinitiation of treatment.

Switching From Oral Naltrexone for Alcohol Dependence
There are no pharmacokinetic collected data that specifically address the switch from oral naltrexone to VIVITROL.

Preparation of Dose
VIVITROL must be suspended only in the diluent supplied in the carton and must be administered with the needle supplied in the carton. All components (i.e., the microspheres, diluent, preparation needle, and an administration needle with safety device) are required for administration. A spare administration needle is provided in case of clogging. Do not substitute any other components for the components of the carton.

HOW SUPPLIED:
VIVITROL (naltrexone for extended-release injectable suspension) is supplied in single use cartons. Each carton contains one 380 mg vial of VIVITROL microspheres, one vial containing 4 mL (to deliver 3.4 mL) Diluent for the suspension of VIVITROL, one 5-mL prepackaged syringe, one 20-gauge 1-inch needle, and two 25-gauge 1½-inch needles with safety device: NDC 65757-330-01.

Storage and Handling
The entire dose pack should be stored in the refrigerator (2 - 8 °C, 36 - 46 °F). Unrefrigerated, VIVITROL can be stored at temperatures not exceeding 25 °C (77 °F) for no more than 7 days prior to administration. Do not expose the product to temperatures above 25 °C (77 °F). VIVITROL should not be frozen.

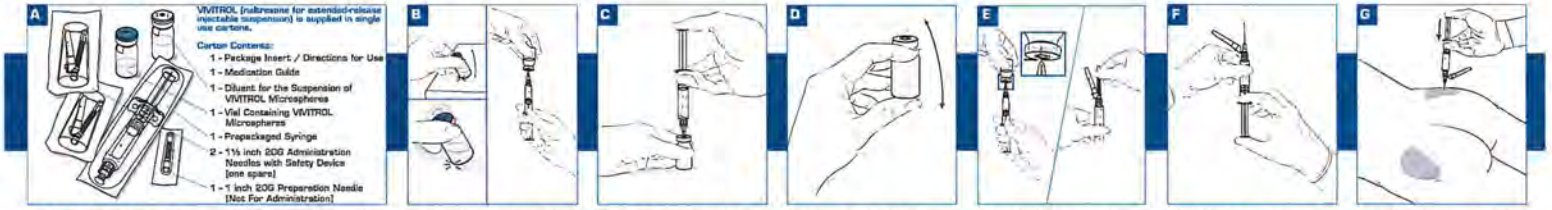
Parenteral products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit. A properly mixed suspension will be milky white, will not contain clumps, and will move freely down the wall of the vial.

Keep out of Reach of Children.

US Patent Nos. 5,650,173; 5,654,008; 5,792,477; 5,916,598; 6,110,503; 6,194,006; 6,264,987; 6,331,317; 6,379,703; 6,379,704; 6,395,304; 6,403,116; 6,495,164; 6,495,166; 6,534,092; 6,537,586; 6,540,393; 6,596,316; 6,667,061; 6,705,757; 6,713,090; 6,861,016; 6,939,833

Directions for Use:
To ensure proper dosing, it is important that you follow the preparation and administration instructions outlined in this document.

Product to be prepared and administered by a healthcare professional.
Do not substitute carton components.
Keep out of reach of children.
Prepare and administer the VIVITROL suspension using aseptic technique.



A

VIVITROL (naltrexone for extended-release injectable suspension) is supplied in single use cartons.

Carton Contents:
- 1 - Package Insert / Directions for Use
- 1 - Medication Guide
- 1 - Diluent for the Suspension of VIVITROL Microspheres
- 1 - Vial Containing VIVITROL Microspheres
- 1 - Prepackaged Syringe
- 2 - 1½ inch 20G Administration Needles with Safety Device (one spare)
- 1 - 1 inch 20G Preparation Needle (Not For Administration)

THE CARTON SHOULD NOT BE EXPOSED TO TEMPERATURES EXCEEDING 25 °C (77 °F).

VIVITROL must be suspended only in the diluent supplied in the carton, and must be administered with the needle supplied in the carton. Do not make any substitutions for components of the carton.

The entire carton should be stored in the refrigerator (2-8 °C, 36-46 °F). Unrefrigerated, VIVITROL Microspheres can be stored at temperatures not exceeding 25 °C (77 °F) for no more than 7 days prior to administration. Do not expose unrefrigerated product to temperatures above 25 °C (77 °F). VIVITROL should not be frozen.

Parenteral products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

B

1. Remove the carton from refrigeration. Prior to preparation, allow drug to reach room temperature (approximately 45 minutes).

2. To ease mixing, firmly tap the vial on a hard surface, ensuring the powder moves freely. (see Figure B)

3. Remove flip-off caps from both vials. DO NOT USE IF FLIP-OFF CAPS ARE BROKEN OR MISSING.

4. Wipe the vial tops with an alcohol swab.

5. Place the 1 inch preparation needle on the syringe and withdraw 3.4 mL of the diluent from the diluent vial. Some diluent will remain in the diluent vial. (see Figure B)

C

Inject the 3.4 mL of diluent into the VIVITROL Microspheres vial. (see Figure C)

D

Mix the powder and diluent by **vigorously** shaking the vial for approximately 1 minute. (see Figure D) Ensure that the dose is thoroughly suspended prior to proceeding to Step E.

A PROPERLY MIXED SUSPENSION WILL BE MILKY WHITE, WILL NOT CONTAIN CLUMPS, AND WILL MOVE FREELY DOWN THE WALLS OF THE VIAL.

E

1. Immediately after suspension, withdraw 4.2 mL of the suspension into the syringe using the same preparation needle.

2. Remove the preparation needle and replace with a 1½ inch administration needle for immediate use. (see Figure E)

F

Prior to injecting, tap the syringe to release any air bubbles, then push gently on the plunger until 4 mL of the suspension remains in the syringe. (see Figure F)

THE SUSPENSION IS NOW READY FOR IMMEDIATE ADMINISTRATION.

G

1. Administer the suspension by deep intramuscular (IM) injection into a gluteal muscle, alternating buttocks per injection. Remember to aspirate for blood before injection. (see Figure G)

2. Inject the suspension in a smooth and continuous motion.

3. If blood aspirates or the needle clogs, do not inject. Change to the spare needle provided in the carton and administer into an adjacent site in the same gluteal region, again aspirating for blood before injection.

VIVITROL must NOT be given intravenously or subcutaneously.

After the injection is administered, cover the needle by pressing the safety sheath against a hard surface using a one-handed motion away from self and others. (see Figure H)

Activation of the safety sheath may cause minimum splatter of fluid that may remain on the needle after injection.

DISPOSE OF USED AND UNUSED ITEMS IN PROPER WASTE CONTAINERS

FREQUENTLY ASKED QUESTIONS:

1. Can I prepare the suspension prior to my patient's arrival?

No. You may remove the carton from the refrigerator prior to the patient's arrival, but once the diluent is added to the VIVITROL Microspheres, the dose should be mixed and the suspension administered immediately. It is very important to use proper aseptic technique when preparing the suspension.

2. How much time do I have between preparing and administering the dose?

It is recommended that the suspension be administered **immediately** once the product has been suspended and transferred into the syringe. If a few minutes' delay occurs after suspension but before transfer into the syringe (Figure D), the vial can be inverted a few times to resuspend and then transferred into the syringe for immediate use.

3. Can I use needles other than those provided in the carton?

The needles in the carton are specially designed for administration of VIVITROL. Do not make any substitutions for components of the carton.

4. The suspension is milky white upon mixing with the diluent. Is this normal?

Yes. VIVITROL Microspheres will form a milky white suspension when mixed with the provided diluent.

5. What if a needle clog occurs during administration of the product?

If a clog occurs during administration, the needle should be withdrawn from the patient, capped with the attached safety device, and replaced with the spare administration needle provided. Gently push on the plunger until a bead of the suspension appears at the tip of the needle. The remainder of the suspension should then be administered into an adjacent site in the same gluteal region.

Vivitrol®

10.2. Medication Guide

VIVITROL®

(naltrexone for extended-release injectable suspension)

MEDICATION GUIDE

9002142-02

REV MAR2010

MEDICATION GUIDE

VIVITROL® [vĭv´ĭ-trōl]
(naltrexone for extended-release injectable suspension)

Read this Medication Guide before you start getting VIVITROL injections and each time you get an injection. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is the most important information I should know about VIVITROL?

1. Some people on VIVITROL treatment have had severe reactions at the site of the injection (injection site reactions), including tissue death (necrosis). Some of these injection site reactions have required surgery. Call your doctor right away if you have any of the following things happen at any of your injection sites:

- intense pain
- the area feels hard
- large area of swelling
- lumps
- blisters
- an open wound
- a dark scab

Tell your doctor about any reaction at an injection site that concerns you, gets worse over time or does not get better by two weeks after the injection.

2. The active ingredient in VIVITROL (naltrexone) has been associated with liver damage (including liver failure) or hepatitis when given in amounts greater than the recommended dose. VIVITROL does not appear to cause liver damage or hepatitis at the recommended dose.

Tell your doctor if you have any of the following symptoms of liver problems:

- stomach area pain lasting more than a few days
- dark urine
- yellowing of the whites of your eyes
- tiredness

3. VIVITROL blocks the effects of opioid-containing medicines and opioid street drugs.

- You may not feel the usual effects of opioid-containing medicines including medicines for pain, cough and diarrhea while on VIVITROL.
- You may not feel the usual effects if you use or abuse heroin and other illegal (street) opioids while on VIVITROL.
- Do not take large amounts of opioids, including opioid-containing medicines, such as prescription pain pills, or heroin, to overcome effects of VIVITROL. This can lead to overdose including serious injury, coma, or death.
- If you have used opioid-containing medicines or opioid street drugs in the past, you may be more sensitive to lower doses of opioids after VIVITROL treatment stops. This can lead to overdose.

4. Some people on VIVITROL treatment have had severe allergic pneumonia.

- Call your doctor immediately if you have shortness of breath, coughing, or wheezing. You may need to go to the hospital for treatment with antibiotic and steroid medicines.

5. Carry written information with you at all times to alert medical personnel that you are taking VIVITROL, so that they can treat you properly in an emergency.

What is VIVITROL?

- VIVITROL is a prescription injectable medicine used to treat alcohol dependence in adults 18 years and older.
- You should stop drinking before starting VIVITROL.
- To be effective, treatment with VIVITROL must be used along with other alcoholism recovery programs such as counseling.

VIVITROL may not work for everyone.
VIVITROL has not been studied in children under the age of 18 years.

Who should not take VIVITROL?

Do not take VIVITROL if you:

- are using and/or have a physical dependence on opioid-containing medicines or opioid street drugs.
  - You must not take opioid-containing medicines or opioid street drugs for 7-10 days before you start taking VIVITROL. (See "What is the most important information I should know about VIVITROL?")
  - To see whether you have a physical dependence on opioid-containing medicines or opioid street drugs, your doctor may give you a small injection of a medicine called naloxone. This is called a naloxone challenge test. If you develop symptoms of opioid withdrawal after the naloxone challenge test, you should not start treatment with VIVITROL at that time. Your doctor may repeat the test after you have stopped using opioids to see whether it is safe to start VIVITROL.
- have opioid withdrawal symptoms.
  - Opioid withdrawal symptoms may occur when you have been taking opioid-containing medicines or opioid street drugs regularly and then stop. These symptoms may include anxiety, sleeplessness, yawning, fever, sweating, teary eyes, runny nose, goose bumps, shakiness, hot or cold flushes, muscle aches, muscle twitches, restlessness, nausea and vomiting, diarrhea, or stomach cramps. (See "What is the most important information I should know about VIVITROL?")
- are allergic to VIVITROL or any of the ingredients in the liquid used to mix VIVITROL (diluent). See the end of this leaflet for a complete list of ingredients in VIVITROL and the diluent.

What should I tell my doctor before starting VIVITROL?

Tell your doctor about all of your medical conditions, including if you:

- have liver problems
- use opioid-containing medicines
- use or abuse street (illegal) drugs
- have hemophilia or other bleeding problems
- have kidney problems
- are pregnant or plan to become pregnant. It is not known if VIVITROL will harm your unborn baby.
- are breastfeeding. It is not known if VIVITROL passes into your milk, and if it can harm your baby. Naltrexone, the active ingredient in VIVITROL, is the same active ingredient in tablets taken by mouth that contain naltrexone. Naltrexone from tablets passes into breast milk. Talk to your doctor about whether you will breast feed or take VIVITROL; you should not do both.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Especially tell your doctor if you take any opioid-containing medicines for pain, cough, or diarrhea. (See "What is the most important information I should know about VIVITROL?")

How should I take VIVITROL?

- VIVITROL is given as an injection into a muscle in your buttocks using a special needle that comes with VIVITROL.
- VIVITROL is injected by a healthcare provider, about once a month.
- Once VIVITROL is injected, it lasts for a month and it cannot be removed from the body.
- If you miss your appointment for VIVITROL injection, schedule another appointment as soon as possible. Whenever you need medical treatment, be sure to tell the treating doctor or nurse that you are receiving VIVITROL injections.

What should I avoid while taking VIVITROL?

VIVITROL may make you feel dizzy. Do not drive a car, operate machinery, or do other dangerous activities until you know how VIVITROL affects you (See "What are the possible side effects of VIVITROL?")

What are the possible side effects of VIVITROL?

VIVITROL can cause serious side effects. (See "What is the most important information I should know about VIVITROL?")

Other serious side effects include: depressed mood, sometimes leading to suicide, suicidal thoughts, and suicidal behavior. Tell your family members that you are taking VIVITROL.

You or a family member should call your doctor right away if you become depressed or have any of the following symptoms of depression, especially if they are new, worse, or worry you:

- You feel sad or have crying spells.
- You are no longer interested in seeing your friends or doing things you used to enjoy.
- You are sleeping a lot *more* or a lot *less* than usual.
- You feel hopeless or helpless.
- You are more irritable, angry or aggressive than usual.
- You are more or less hungry than usual or notice a big change in your body weight.
- You have trouble paying attention.
- You feel tired or sleepy all the time.
- You have thoughts about hurting yourself or ending your life.

Common side effects of VIVITROL include:

- nausea. Nausea usually improves within a few days after the first VIVITROL injection. Nausea is less likely with future injections of VIVITROL.
- tiredness
- headache
- dizziness
- vomiting
- decreased appetite
- painful joints
- muscle cramps

Tell your doctor about any side effect that bothers you or that does not go away.
These are not all the side effects of VIVITROL. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about VIVITROL

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. VIVITROL was prescribed for your medical condition.

This leaflet summarizes the most important information about VIVITROL. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about VIVITROL that is written for health professionals. For additional information about VIVITROL call 1-800-848-4876 or visit www.vivitrol.com.

What are the ingredients in VIVITROL?

Active ingredient: naltrexone
Inactive ingredients: polylactide-co-glycolide (PLG)
Diluent ingredients: carboxymethylcellulose sodium salt, polysorbate 20, sodium chloride, and water for injection

This Medication Guide has been approved by the U.S. Food and Drug Administration

Manufactured and marketed by:
Alkermes, Inc.
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Waltham, MA 02451
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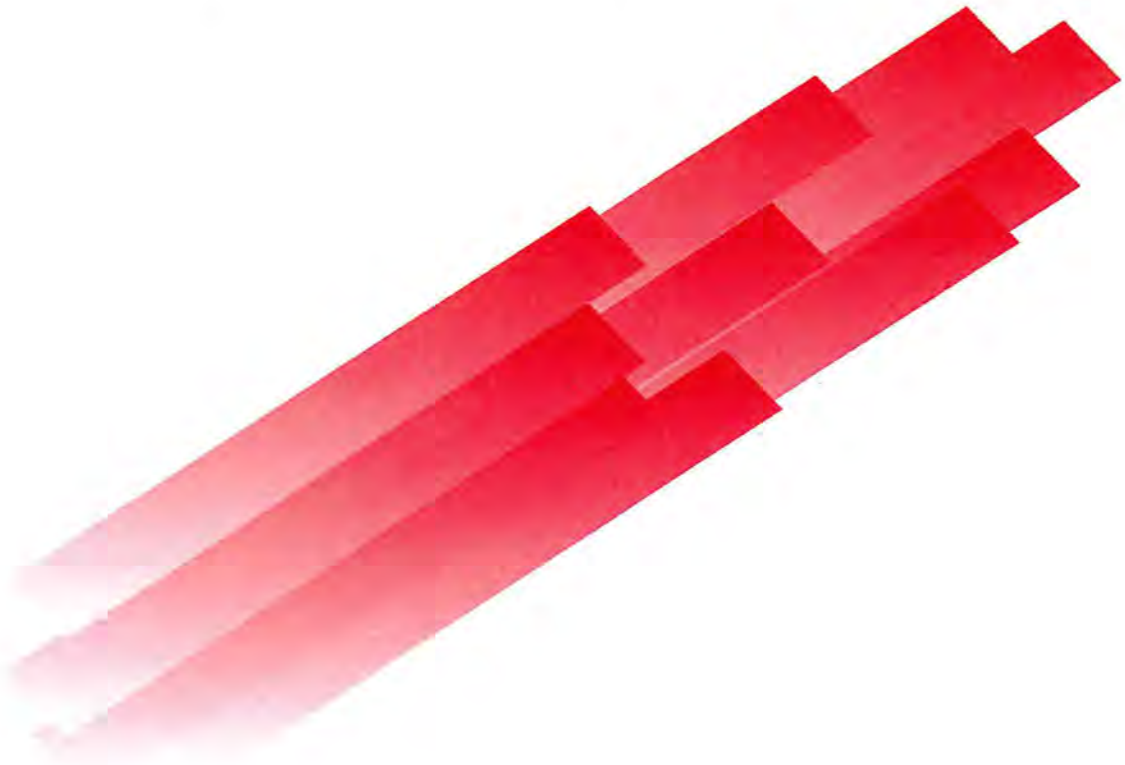
10.3. Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products

Guidance for Industry

Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 1998
Clinical 6

Guidance for Industry

Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products

Additional copies are available from:
the Drug Information Branch (HFD-210),
Center for Drug Evaluation and Research (CDER),
5600 Fishers Lane, Rockville, MD 20857 (Tel) 301-827-4573
Internet at http://www.fda.gov/cder/guidance/index.htm
or
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Training, and Manufacturers Assistance (HFM-40)
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1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm
(Fax) 888-CBERFAX or 301-827-3844
(Voice Information) 800-835-4709 or 301-827-1800

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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GUIDANCE FOR INDUSTRY[1]

Providing Clinical Evidence of Effectiveness[2] for Human Drug and Biological Products

I. INTRODUCTION

This document is intended to provide guidance to applicants planning to file new drug applications (NDAs), biologics license applications (BLAs), or applications for supplemental indications on the evidence to be provided to demonstrate effectiveness.

This document is also intended to meet the requirements of subsections 403(b)(1) and (2) of the Food and Drug Administration Modernization Act (the Modernization Act) of 1997 for human drug and biological products (P.L. 105-115).[3] Subsection 403(b)(1) directs FDA to provide guidance on the circumstances in which published matter may be the basis for approval of a supplemental application for a new indication. Section III of this guidance satisfies this requirement by describing circumstances in which published matter may partially or entirely support approval of a supplemental application. Subsection 403(b)(2) directs FDA to provide guidance on data requirements that will avoid duplication of previously submitted data by recognizing the availability of data previously submitted in support of an original application to support approval of a supplemental application. Section II of this guidance satisfies this requirement by describing a range of circumstances in which related existing data, whether from an original application or other sources, may be used to support approval of a supplemental application.

In 1962, Congress amended the Federal Food, Drug, and Cosmetic Act to add a requirement that, to obtain marketing approval, manufacturers demonstrate the effectiveness of their products through the conduct of adequate and well-controlled studies. Since then, the issue of what constitutes sufficient evidence of effectiveness has been debated by the Agency, the scientific community, industry, and others. Sound evidence of effectiveness is a crucial component of the Agency's benefit-risk assessment of a new product or use. At the same time, the demonstration of effectiveness represents a major component of drug development time and cost; the amount

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[1] This guidance document represents the agency's current thinking on providing clinical evidence of effectiveness for human drug and biological products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

[2] As used in this guidance, the term efficacy refers to the findings in an adequate and well-controlled clinical trial or the intent of conducting such a trial and the term effectiveness refers to the regulatory determination that is made on the basis of clinical efficacy and other data.

[3] The Modernization Act requirements in Section 403 also apply to animal drugs and medical devices. These products will be addressed in separate guidances.

and nature of the evidence needed can therefore be an important determinant of when and whether new therapies become available to the public. The public health is best served by the development of sound evidence of effectiveness in an efficient manner.

The science and practice of drug development and clinical evaluation have evolved significantly since the effectiveness requirement for drugs was established, and this evolution has implications for the amount and type of data needed to support effectiveness in certain cases. As a result of medical advances in the understanding of pathogenesis and disease staging, it is increasingly likely that clinical studies of drugs will be more narrowly defined to focus, for example, on a more specific disease stage or clinically distinct subpopulation. As a consequence, product indications are often narrower, the universe of possible indications is larger, and data may be available from a number of studies of a drug in closely related indications that bear on a determination of its effectiveness for a new use. Similarly, there may be studies of a drug in different populations, studies of a drug alone or in combination, and studies of different doses and dosage forms, all of which may support a particular new use of a drug. At the same time, progress in clinical evaluation and clinical pharmacology have resulted in more rigorously designed and conducted clinical efficacy trials, which are ordinarily conducted at more than one clinical site. This added rigor and scope has implications for a study's reliability, generalizability, and capacity to substantiate effectiveness.

Given this evolution, the Agency has determined that it would be appropriate to articulate its current thinking concerning the quantitative and qualitative standards for demonstrating effectiveness of drugs and biologics. FDA hopes that this guidance will enable sponsors to plan drug development programs that are sufficient to establish effectiveness without being excessive in scope. The guidance should also bring greater consistency and predictability to FDA's assessment of the clinical trial data needed to support drug effectiveness.

Another major goal of this guidance is to encourage the submission of supplemental applications to add new uses to the labeling of approved drugs. By articulating how it currently views the quantity and quality of evidence necessary to support approval of a new use of a drug, FDA hopes to illustrate that the submission of supplements for new uses need not be unduly burdensome.

II. QUANTITY OF EVIDENCE NECESSARY TO SUPPORT EFFECTIVENESS

A. Legal Standards for Drug and Biological Products

Drugs: The effectiveness requirement for drug approval was added to the Federal Food, Drug, and Cosmetic Act (the Act or the FDC Act) in 1962. Between passage of the Act in 1938 and the 1962 amendments, drug manufacturers were required to show only that their drugs were safe. The original impetus for the effectiveness requirement was Congress's growing concern about the misleading and unsupported claims being made by pharmaceutical companies about their drug products coupled with high drug prices. After two years of hearings on these issues, Congress adopted the 1962 Drug Amendments,

which included a provision requiring manufacturers of drug products to establish a drug's effectiveness by "substantial evidence." *Substantial evidence* was defined in section 505(d) of the Act as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

Since the 1962 Amendments added this provision to the statute, discussions have ensued regarding the quantity and quality of the evidence needed to establish effectiveness. With regard to quantity, it has been FDA's position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness. (See e.g., Final Decision on Benylin, 44 FR 51512, 518 (August 31, 1979); *Warner-Lambert Co. V. Heckler,* 787 F. 2d 147 (3d Cir. 1986)). FDA's position is based on the language in the statute[4] and the legislative history of the 1962 amendments. Language in a Senate report suggested that the phrase "adequate and well-controlled investigations" was designed not only to describe the quality of the required data but the "quantum" of required evidence. (S. Rep. No. 1744, Part 2, 87th Cong. 2d Sess. 6 (1962))

Nevertheless, FDA has been flexible within the limits imposed by the congressional scheme, broadly interpreting the statutory requirements to the extent possible where the data on a particular drug were convincing. In some cases, FDA has relied on pertinent information from other adequate and well-controlled studies of a drug, such as studies of other doses and regimens, of other dosage forms, in other stages of disease, in other populations, and of different endpoints, to support a single adequate and well-controlled study demonstrating effectiveness of a new use. In these cases, although there is only one study of the exact new use, there are, in fact, multiple studies supporting the new use, and expert judgment could conclude that the studies together represent substantial evidence of effectiveness. In other cases, FDA has relied on only a single adequate and well-controlled efficacy study to support approval — generally only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds.

In section 115(a) of the Modernization Act, Congress amended section 505(d) of the Act to make it clear that the Agency may consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute substantial

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[4] Section 505(d) of the Act uses the plural form in defining "substantial evidence" as "adequate and well-controlled investigations, including clinical investigations." See also use of "investigations" in section 505(b) of the Act, which lists the contents of a new drug application.

evidence if FDA determines that such data and evidence are sufficient to establish effectiveness. In making this clarification, Congress confirmed FDA's interpretation of the statutory requirements for approval and acknowledged the Agency's position that there has been substantial progress in the science of drug development resulting in higher quality clinical trial data.

Biologics. Biological products are approved under authority of section 351 of the Public Health Service Act (PHS Act) (42 U.S.C.§ 262). Under section 351, as in effect since 1944, licenses for biologics have been issued only upon a showing that the products meet standards designed to ensure the "continued safety, purity, and potency" of the products. *Potency* has long been interpreted to include effectiveness (21 CFR 600.3(s)). In 1972, FDA initiated a review of the safety and effectiveness of all previously licensed biologics. The Agency stated then that proof of effectiveness would consist of controlled clinical investigations as defined in the provision for "adequate and well-controlled studies" for new drugs (21 CFR 314.126), unless waived as not applicable to the biological product or essential to the validity of the study when an alternative method is adequate to substantiate effectiveness (21 CFR 601.25 (d) (2)). One such adequate alternative was identified to be serological response data where a previously accepted correlation with clinical effectiveness exists. As with nonbiological drug products, FDA has approved biological products based on single, multicenter studies with strong results.

Although section 123(a) of the Modernization Act amended section 351 of the PHS Act to make it clear that separate licenses are not required for biological products and the establishments at which the products are made, the evidentiary standard for a biological product was not changed: the product must be shown to be "safe, pure, and potent" (section 351 (a)(2) of the PHS Act as amended). In the Modernization Act (section 123(f)) Congress also directed the agency to take measures to "minimize differences in the review and approval" of products required to have approved BLAs under section 351 of the PHS Act and products required to have approved NDAs under section 505(b)(1) of the FDC Act.

B. Scientific Basis for the Legal Standard

The usual requirement for more than one adequate and well-controlled investigation reflects the need for *independent substantiation* of experimental results. A single clinical experimental finding of efficacy, unsupported by other independent evidence, has not usually been considered adequate scientific support for a conclusion of effectiveness. The reasons for this include the following.

- Any clinical trial may be subject to unanticipated, undetected, systematic biases. These biases may operate despite the best intentions of sponsors and investigators, and may lead to flawed conclusions. In addition, some investigators may bring conscious biases to evaluations.

- The inherent variability in biological systems may produce a positive trial result by chance alone. This possibility is acknowledged, and quantified to some extent, in the statistical evaluation of the result of a single efficacy trial. It should be noted, however, that hundreds of randomized clinical efficacy trials are conducted each year with the intent of submitting favorable results to FDA. Even if all drugs tested in such trials were ineffective, one would expect one in forty of those trials to "demonstrate" efficacy by chance alone at conventional levels of statistical significance.[5] It is probable, therefore, that false positive findings (i.e., the chance appearance of efficacy with an ineffective drug) will occur and be submitted to FDA as evidence of effectiveness. Independent substantiation of a favorable result protects against the possibility that a chance occurrence in a single study will lead to an erroneous conclusion that a treatment is effective.

- Results obtained in a single center may be dependent on site or investigator specific factors (e.g., disease definition, concomitant treatment, diet). In such cases, the results, although correct, may not be generalizable to the intended population. This possibility is the primary basis for emphasizing the need for independence in substantiating studies.

- Rarely, favorable efficacy results are the product of scientific fraud.

Although there are statistical, methodologic, and other safeguards to address the identified problems, they are often inadequate to address these problems in a single trial. Independent substantiation of experimental results addresses such problems by providing consistency across more than one study, thus greatly reducing the possibility that a biased, chance, site-specific, or fraudulent result will lead to an erroneous conclusion that a drug is effective.

The need for independent substantiation has often been referred to as the need for replication of the finding. Replication may not be the best term, however, as it may imply that precise repetition of the same experiment in other patients by other investigators is the only means to substantiate a conclusion. Precise replication of a trial is only one of a number of possible means of obtaining independent substantiation of a clinical finding and, at times, can be less than optimal as it could leave the conclusions vulnerable to any systematic biases inherent to the particular study design. Results that are obtained from studies that are of different design and independent in execution, perhaps evaluating different populations, endpoints, or dosage forms, may provide support for a conclusion of effectiveness that is as convincing as, or more convincing than, a repetition of the same study.

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[5] p-value = 0.05, two-tailed, which implies an error rate in the efficacy (false positive) tail of 0.025 or one in forty.

C. The Quantity of Evidence to Support Effectiveness

The following three sections provide guidance on the quantity of evidence needed in particular circumstances to establish substantial evidence of effectiveness. Section 1 addresses situations in which effectiveness of a new use may be extrapolated entirely from existing efficacy studies. Section 2 addresses situations in which a single adequate and well-controlled study of a specific new use can be supported by information from other related adequate and well-controlled studies, such as studies in other phases of a disease, in closely related diseases, of other conditions of use (different dose, duration of use, regimen), of different dosage forms, or of different endpoints. Section 3 addresses situations in which a single multicenter study, without supporting information from other adequate and well-controlled studies, may provide evidence that a use is effective.

In each of these situations, it is assumed that any studies relied on to support effectiveness meet the requirements for adequate and well-controlled studies in 21 CFR 314.126. It should also be appreciated that reliance on a single study of a given use, whether alone or with substantiation from related trial data, leaves little room for study imperfections or contradictory (nonsupportive) information. In all cases, it is presumed that the single study has been appropriately designed, that the possibility of bias due to baseline imbalance, unblinding, post-hoc changes in analysis, or other factors is judged to be minimal, and that the results reflect a clear prior hypothesis documented in the protocol. Moreover, a single favorable study among several similar attempts that failed to support a finding of effectiveness would not constitute persuasive support for a product use unless there were a strong argument for discounting the outcomes in the studies that failed to show effectiveness (e.g., study obviously inadequately powered or lack of assay sensitivity as demonstrated in a three-arm study by failure of the study to show efficacy of a known active agent).

Whether to rely on a single study to support an effectiveness determination is not often an issue in contemporary drug development. In most drug development situations, the need to find an appropriate dose, to study patients of greater and lesser complexity or severity of disease, to compare the drug to other therapy, to study an adequate number of patients for safety purposes, and to otherwise know what needs to be known about a drug before it is marketed will result in more than one adequate and well-controlled study upon which to base an effectiveness determination.

This guidance is not intended to provide a complete listing of the circumstances in which existing efficacy data may provide independent substantiation of related claims; rather, it provides examples of the reasoning that may be employed. The examples are applicable whether the claim arises in the original filing of an NDA or BLA, or in a supplemental application.

1. Extrapolation from Existing Studies

In certain cases, effectiveness of an approved drug product for a new indication, or effectiveness of a new product, may be adequately demonstrated without additional adequate and well-controlled clinical efficacy trials. Ordinarily, this will be because other types of data provide a way to apply the known effectiveness to a new population or a different dose, regimen or dosage form. The following are examples of situations in which effectiveness might be extrapolated from efficacy data for another claim or product.

a. Pediatric uses

The rule revising the Pediatric Use section of product labeling (21 CFR 201.57(f)(9)(iv)) makes allowance for inclusion of pediatric use information in labeling without controlled clinical trials of the use in children. In such cases, a sponsor must provide other information to support pediatric use, and the Agency must conclude that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to permit extrapolation from adult efficacy data to pediatric patients. Evidence that could support a conclusion of similar disease course and similar drug effect in adult and pediatric populations includes evidence of common pathophysiology and natural history of the disease in the adult and pediatric populations, evidence of common drug metabolism and similar concentration-response relationships in each population, and experience with the drug, or other drugs in its therapeutic class, in the disease or condition or related diseases or conditions. Examples in which pediatric use labeling information has been extrapolated from adult efficacy data include ibuprofen for pain and loratidine for seasonal allergic rhinitis.

b. Bioequivalence

The effectiveness of alternative formulations and new dosage strengths may be assessed on the basis of evidence of bioequivalence.

c. Modified-release dosage forms

In some cases, modified release dosage forms may be approved on the basis of pharmacokinetic data linking the new dosage form to a previously studied immediate-release dosage form. Because the pharmacokinetic patterns of modified-release and immediate-release dosage forms are not identical, it is generally important to have some understanding of the relationship of blood concentration to response, including an understanding of the time course of that relationship, to extrapolate the immediate-release

data to the modified-release dosage form.

d. Different doses, regimens, or dosage forms

Dose-response relationships are generally continuous such that information about the effectiveness of one dose, dosage regimen, or dosage form is relevant to the effectiveness of other doses, regimens, or dosage forms. Where blood levels and exposure are not very different, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data alone. Even if blood levels are quite different, if there is a well-understood relationship between blood concentration and response, including an understanding of the time course of that relationship, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data without an additional clinical efficacy trial. In this situation, pharmacokinetic data, together with the well-defined pharmacokinetic/pharmacodynamic (PK/PD) relationship, are used to translate the controlled trial results from one dose, regimen, or dosage form to a new dose, regimen, or dosage form (See also section II.C.2.a).

2. Demonstration of Effectiveness by a Single Study of a New Use, with Independent Substantiation From Related Study Data

The discussion that follows describes specific examples in which a single study of a new use, with independent substantiation from study data in related uses, could provide evidence of effectiveness. In these cases, the study in the new use and the related studies support the conclusion that the drug has the effect it is purported to have. Whether related studies are capable of substantiating a single study of a new use is a matter of judgment and depends on the quality and outcomes of the studies and the degree of relatedness to the new use.

a. Different doses, regimens, or dosage forms

As discussed in Sections II.C.1.d, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data without an additional clinical efficacy trial where blood levels and exposure are not very different or, even if quite different, there is a well-understood relationship between blood concentration and response. Where the relationship between blood concentration and response is not so well understood and the pharmacokinetics of the new dose, regimen, or dosage form differ from the previous one, clinical efficacy data will likely be necessary to support effectiveness of a new regimen. In this case, a single additional efficacy study should ordinarily be sufficient. For example, a single controlled trial was needed to support the recent approval of a once

daily dose of risperidone because the once daily and twice daily regimens had different pharmacokinetics and risperidone's PK/PD relationship was not well understood.

b. Studies in other phases of the disease

In many cases, therapies that are effective in one phase of a disease are effective in other disease phases, although the magnitude of the benefit and benefit-to-risk relationship may differ in these other phases. For example, if a drug is known to be effective in patients with a refractory stage of a particular cancer, a single adequate and well-controlled study of the drug in an earlier stage of the same tumor will generally be sufficient evidence of effectiveness to support the new use.

c. Studies in other populations

Often, responses in subsets of a particular patient population are qualitatively similar to those in the whole population. In most cases, separate studies of effectiveness in demographic subsets are not needed (see also discussion of the pediatric population in section II.C.1.a) However, where further studies are needed, a single study would ordinarily suffice to support effectiveness in age, race, gender, concomitant disease, or other subsets for a drug already shown to be generally effective in a condition or to be effective in one population. For example, a single study was sufficient to support tamoxifen use in breast cancer in males.

d. Studies in combination or as monotherapy

For a drug known to be effective as monotherapy, a single adequate and well-controlled study is usually sufficient to support effectiveness of the drug when combined with other therapy (as part of a multidrug regimen or in a fixed-dose combination). Similarly, known effectiveness of a drug as part of a combination (i.e., its contribution to the effect of the combination is known) would usually permit reliance on a single study of appropriate design to support its use as monotherapy, or as part of a different combination, for the same use. For example, a single study of a new combination vaccine designed to demonstrate adequate immune response will ordinarily provide sufficient evidence of effectiveness if the new combination contains products or antigens already proven to be effective alone or in other combinations. These situations are common for oncologic and antihypertensive drugs, but occur elsewhere as well.

e. Studies in a closely related disease

Studies in etiologically or pathophysiologically related conditions, or studies of a symptom common to several diseases (e.g., pain) can support each other, allowing initial approval of several uses or allowing additional claims based on a single adequate and well-controlled study. For example, certain anti-coagulant or anti-platelet therapies could be approved for use in two different settings based on individual studies in unstable angina/acute coronary syndrome and in the postangioplasty state. Because the endpoints studied and the theoretical basis for use of an anti-coagulant or anti-platelet drug are similar, each study supports the other for each claim. Similarly, single analgesic studies in several painful conditions would ordinarily be sufficient to support either a general analgesic indication or multiple specific indications. The recent approval of lamotrigine for treatment of Lennox-Gastaut Syndrome (a rare, largely pediatric, generalized seizure disorder) was based on a single adequate and well-controlled trial, due in part to related data showing efficacy of the drug in partial-onset seizures in adults.

f. Studies in less closely related diseases, but where the general purpose of therapy is similar

Certain classes of drug therapy, such as antimicrobials and antineoplastics, are appropriate interventions across a range of different diseases. For therapies of this type, evidence of effectiveness in one disease could provide independent substantiation of effectiveness in a quite different disease. For example, it is possible to argue that evidence of effectiveness of an antimicrobial in one infectious disease setting may support reliance on a single study showing effectiveness in other settings where the causative pathogens, characteristics of the site of infection that affect the disease process (e.g., structure and immunology) and patient population are similar.[6] Similarly, for an oncologic drug, evidence of effectiveness in one or more tumor types may support reliance on a single study showing effectiveness against a different kind of tumor, especially if the tumor types have a common biological origin.

g. Studies of different clinical endpoints

Demonstration of a beneficial effect in different studies on two different clinically meaningful endpoints could cross-substantiate a claim for

[6] See Division of Anti-Infective Drug Products: Points to Consider in the Clinical Development and Labeling of Anti-Infective Drug Products, October 1992.

effectiveness for each outcome. For example, the initial claim for effectiveness of enalapril for heart failure was supported by one study showing symptom improvement over several months and a second study showing improved survival in a more severely ill population. The two different findings, each from an adequate and well-controlled study, led to the conclusion that enalapril was effective in both treating symptoms and improving survival.

h. Pharmacologic/pathophysiologic endpoints

When the pathophysiology of a disease and the mechanism of action of a therapy are very well understood, it may be possible to link specific pharmacologic effects to a strong likelihood of clinical effectiveness. A pharmacologic effect that is accepted as a validated surrogate endpoint can support ordinary approval (e.g., blood pressure effects, cholesterol-lowering effects) and a pharmacologic effect that is considered reasonably likely to predict clinical benefit can support accelerated approval under the conditions described in 21 CFR 314 Subpart H and 21 CFR 601 Subpart E (e.g., CD4 count and viral load effects to support effectiveness of anti-viral drugs for HIV infection). When the pharmacologic effect is not considered an acceptable effectiveness endpoint, but the linkage between it and the clinical outcome is strong, not merely on theoretical grounds but based on prior therapeutic experience or well-understood pathophysiology, a single adequate and well-controlled study showing clinical efficacy can sometimes be substantiated by persuasive data from a well-controlled study or studies showing the related pharmacologic effect.

For example, a single clearly positive trial can be sufficient to support approval of a replacement therapy such as a coagulation factor, when it is combined with clear evidence that the condition being treated is caused by a deficiency of that factor. Demonstration of physical replacement of the deficient factor or restoration of the missing physiologic activity provides strong substantiation of the clinical effect. The corrective treatment of an inborn error of metabolism could be viewed similarly. In the case of preventive vaccines, one adequate and well-controlled clinical trial may be supported by compelling animal challenge/protection models, human serological data, passive antibody data, or pathogenesis information. The more evidence there is linking effects on the pharmacologic endpoint to improvement or prevention of the disease, the more persuasive the argument for reliance on a single clinical efficacy study.

Note, however, that plausible beneficial pharmacologic effects have often not correlated with clinical benefit, and, therefore, caution must be observed in relying on a pharmacologic effect as contributing to evidence

of effectiveness. For example, pharmacologic effects such as arrhythmia suppression by Type 1 antiarrhythmics and increased cardiac output by phosphodiesterase inhibitors or beta adrenergic inotropes resulted in increased mortality, rather than, as was expected, decreased sudden death and improved outcome in heart failure. The reasons for the absence of an expected correlation between pharmacologic and clinical effects are diverse and can include an incompletely understood relationship between the pharmacologic effect and the clinical benefit and the presence of other pharmacologic effects attributable to a drug in addition to the effect being measured and thought to be beneficial. Generally, the utility of pharmacologic outcomes in providing independent substantiation will be greatest where there is prior experience with the pharmacologic class. Even in this case, however, it is difficult to be certain that a pharmacologic effect that correlates with a clinical benefit accounts for all the clinical benefit or that other effects are not present and relevant.

3. Evidence of Effectiveness from a Single Study

When the effectiveness requirement was originally implemented in 1962, the prevailing efficacy study model was a single institution, single investigator, relatively small trial with relatively loose blinding procedures, and little attention to prospective study design and identification of outcomes and analyses. At present, major clinical efficacy studies are typically multicentered, with clear, prospectively determined clinical and statistical analytic criteria. These studies are less vulnerable to certain biases, are often more generalizable, may achieve very convincing statistical results, and can often be evaluated for internal consistency across subgroups, centers, and multiple endpoints.

The added rigor and size of contemporary clinical trials have made it possible to rely, in certain circumstances, on a single adequate and well-controlled study, without independent substantiation from another controlled trial, as a sufficient scientific and legal basis for approval. For example, the approval of timolol for reduction of post-infarction mortality was based on a single, particularly persuasive (low p-value), internally consistent, multicenter study that demonstrated a major effect on mortality and reinfarction rate. For ethical reasons, the study was considered unrepeatable. The Center for Biologics Evaluation and Research has also approved a number of products based upon a single persuasive study. The Agency provided a general statement in 1995 describing when a single, multicenter study may suffice (60 FR 39181; August 1, 1995), but the Agency has not comprehensively described the situations in which a single adequate and well-controlled study might be considered adequate support for an effectiveness claim, or the characteristics of a single study that could make it adequate support for an effectiveness claim.

Whether to rely on a single adequate and well-controlled study is inevitably a matter of judgment. A conclusion based on two persuasive studies will always be more secure than a conclusion based on a single, comparably persuasive study. For this reason, reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. For example, sequential repetition of strongly positive trials that demonstrated a decrease in post-infarction mortality, prevention of osteoporotic fractures, or prevention of pertussis would present significant ethical concerns. Repetition of positive trials showing only symptomatic benefit would generally not present the same ethical concerns.

The discussion that follows identifies the characteristics of a single adequate and well-controlled study that could make the study adequate support for an effectiveness claim. Although no one of these characteristics is necessarily determinative, the presence of one or more in a study can contribute to a conclusion that the study would be adequate to support an effectiveness claim.

a. Large multicenter study

In a large multicenter study in which (1) no single study site provided an unusually large fraction of the patients and (2) no single investigator or site was disproportionately responsible for the favorable effect seen, the study's internal consistency lessens concerns about lack of generalizability of the finding or an inexplicable result attributable only to the practice of a single investigator. If analysis shows that a single site is largely responsible for the effect, the credibility of a multicenter study is diminished.

b. Consistency across study subsets

Frequently, large trials have relatively broad entry criteria and the study populations may be diverse with regard to important covariates such as concomitant or prior therapy, disease stage, age, gender or race. Analysis of the results of such trials for consistency across key patient subsets addresses concerns about generalizability of findings to various populations in a manner that may not be possible with smaller trials or trials with more narrow entry criteria. For example, the timolol postinfarction study randomized patients separately within three severity strata. The study showed positive effects on survival in each stratum supporting a conclusion that the drug's utility was not limited to a particular disease stage (e.g., relatively low or high severity).

c. Multiple *studies* in a single study

Properly designed factorial studies may be analyzed as a series of pairwise comparisons, representing, within a single study, separate demonstrations of activity of a drug as monotherapy and in combination with another drug. This model was successfully used in ISIS II, which showed that for patients with a myocardial infarction both aspirin and streptokinase had favorable effects on survival when used alone and when combined (aspirin alone and streptokinase alone were each superior to placebo; aspirin and streptokinase in combination were superior to aspirin alone and to streptokinase alone). This represented two separate (but not completely independent) demonstrations of the effectiveness of aspirin and streptokinase.

d. Multiple endpoints involving different events

In some cases, a single study will include several important, prospectively identified primary or secondary endpoints, each of which represents a beneficial, but different, effect. Where a study shows statistically persuasive evidence of an effect on more than one of such endpoints, the internal weight of evidence of the study is enhanced. For example, the approval of beta-interferon (Betaseron) for prevention of exacerbations in multiple sclerosis was based on a single multicenter study, at least partly because there were both a decreased rate of exacerbations and a decrease in MRI-demonstrated disease activity — two entirely different, but logically related, endpoints.

Similarly, favorable effects on both death and nonfatal myocardial infarctions in a lipid-lowering, postangioplasty, or postinfarction study would, in effect, represent different, but consistent, demonstrations of effectiveness, greatly reducing the possibility that a finding of reduced mortality was a chance occurrence. For example, approval of abciximab as adjunctive treatment for patients undergoing complicated angioplasty or atherectomy was supported by a single study with a strong overall result on the combined endpoint (decreased the combined total of deaths, new infarctions, and need for urgent interventions) and statistically significant effects in separate evaluations of two components of the combined endpoint (decreased new infarctions and decreased need for urgent interventions). In contrast, a beneficial effect on multiple endpoints that evaluate essentially the same phenomenon and correlate strongly, such as mood change on two different depression scales or SGOT and CPK levels postinfarction, does not significantly enhance the internal weight of the evidence from a single trial.

Although two consistent findings within a single study usually provide reassurance that a positive treatment effect is not due to chance, they do not protect against bias in study conduct or biased analyses. For example, a treatment assignment not well balanced for important prognostic variables could lead to an apparent effect on both endpoints. Thus, close scrutiny of study design and conduct are critical to evaluating this type of study.

e. Statistically very persuasive finding

In a multicenter study, a very low p-value indicates that the result is highly inconsistent with the null hypothesis of no treatment effect. In some studies it is possible to detect nominally statistically significant results in data from several centers, but, even where that is not possible, an overall extreme result and significance level means that most study centers had similar findings. For example, the thrombolysis trials of streptokinase (ISIS II, GISSI) had very sizable treatment effects and very low p-values, greatly adding to their persuasiveness. Preventive vaccines for infectious disease indications with a high efficacy rate (e.g., point estimate of efficacy of 80% or higher and a reasonably narrow 95% confidence interval) have been approved based on a single adequate and well-controlled trial.

4. Reliance on a Single, Multicenter Study — Caveats

While acknowledging the persuasiveness of a single, internally consistent, strong multicenter study, it must be appreciated that even a strong result can represent an isolated or biased result, especially if that study is the only study suggesting efficacy among similar studies. Recently, the apparent highly favorable effect of vesnarinone, an inotropic agent, in heart failure (60% reduction of mortality in what appeared to be a well-designed, placebo-controlled, multicenter trial with an extreme p-value) has proven to be unrepeatable. In an attempt to substantiate the finding, the same dose of the drug that seemed lifesaving in the earlier study significantly increased mortality (by 26%), and a lower dose also appeared to have a detrimental effect on survival. Although the population in the second study was, on the whole, a sicker population than in the first, the outcomes in similarly sick patients in each study were inconsistent so this factor does not explain the contradictory results.

When considering whether to rely on a single multicenter trial, it is critical that the possibility of an incorrect outcome be considered and that all the available data be examined for their potential to either support or undercut reliance on a single multicenter trial. In the case of vesnarinone, there were other data that were not consistent with the dramatically favorable outcome in the multicenter study. These data seemed to show an inverse dose-response relationship, showed no suggestion

of symptomatic benefit, and showed no effect on hemodynamic endpoints. These inconsistencies led the Agency, with the advice of its Cardio-Renal Advisory Committee, to refuse approval — a decision borne out by the results of the subsequent study.

This example illustrates how inadequacies and inconsistencies in the data, such as lack of pharmacologic rationale and lack of expected other effects accompanying a critical outcome, can weaken the persuasiveness of a single trial. Although an unexplained failure to substantiate the results of a favorable study in a second controlled trial is not proof that the favorable study was in error — studies of effective agents can fail to show efficacy for a variety of reasons — it is often reason not to rely on the single favorable study.

III. DOCUMENTATION OF THE QUALITY OF EVIDENCE SUPPORTING AN EFFECTIVENESS CLAIM

When submitting the requisite quantity of data to support approval of a new product or new use of an approved product, sponsors must also document that the studies were adequately designed and conducted. Essential characteristics of adequate and well-controlled trials are described in 21 CFR 314.126. To demonstrate that a trial supporting an effectiveness claim is adequate and well-controlled, extensive documentation of trial planning, protocols, conduct, and data handling is usually submitted to the Agency, and detailed patient records are made available at the clinical sites.

From a scientific standpoint, however, it is recognized that the extent of documentation necessary depends on the particular study, the types of data involved, and the other evidence available to support the claim. Therefore, the Agency is able to accept different levels of documentation of data quality, as long as the adequacy of the scientific evidence can be assured. This section discusses the factors that influence the extent of documentation needed, with particular emphasis on studies evaluating new uses of approved drugs.

For the purposes of this section, the phrase *documentation of the quality of evidence* refers to (1) the completeness of the documentation and (2) the ability to access the primary study data and the original study-related records (e.g., subjects' medical records, drug accountability records) for the purposes of verifying the data submitted as evidence. These interrelated elements bear on a determination of whether a study is adequate and well-controlled.

In practice, to achieve a high level of documentation, studies supporting claims are ordinarily conducted in accordance with good clinical practices (GCPs). Sponsors routinely monitor all clinical sites, and FDA routinely has access to the original clinical protocols, primary data, clinical site source documents for on-site audits, and complete study reports.

However, situations often arise in which studies that evaluate the efficacy of a drug product lack the full documentation described above (for example, full patient records may not be available) or in which the study was conducted with less monitoring than is ordinarily seen in commercially sponsored trials. Such situations are more common for supplemental indications because postapproval studies are more likely to be conducted by parties other than the drug sponsor and those parties may employ less extensive monitoring and data-gathering procedures than a sponsor. Under certain circumstances, it is possible for sponsors to rely on such studies to support effectiveness claims, despite less than usual documentation or monitoring. Some of those circumstances are described below.

A. Reliance on Less Than Usual Access to Clinical Data or Detailed Study Reports

FDA's access to primary data has proven to be important in many regulatory decisions. There are also reasons to be skeptical of the conclusions of published reports of studies. Experience has shown that such study reports do not always contain a complete, or entirely accurate, representation of study plans, conduct and outcomes. Outright fraud (i.e., deliberate deception) is unusual. However, incompleteness, lack of clarity, unmentioned deviation from prospectively planned analyses, or an inadequate description of how critical endpoint judgments or assessments were made are common flaws. Typically, journal article peer reviewers only have access to a limited data set and analyses, do not see the original protocol and amendments, may not know what happened to study subjects that investigators determined to be non-evaluable, and thus may lack sufficient information to detect critical omissions and problems. The utility of peer review can also be affected by variability in the relevant experience and expertise of peer reviewers. FDA's experiences with the Anturane Reinfarction Trial, as well as literature reports of the efficacy of tacrine and the anti-sepsis HA-1A antibody, illustrate its concerns with reliance on the published medical literature.

Notwithstanding these concerns, the presence of some of the factors discussed below can make it possible for FDA to rely on studies for which it has less than usual access to data or detailed study reports to partially or entirely (the so-called *paper* filing) support an effectiveness claim. FDA's reliance on a literature report to support an effectiveness claim is more likely if FDA can obtain additional critical study details. Section 1 below describes additional information that, if available, would increase the likelihood that a study could be relied on to support an effectiveness claim. Section 2 describes factors that may make efficacy findings sufficiently persuasive to permit reliance on the published literature alone. Note that the factors outlined in Section 2 are relevant to an assessment of the reliability of literature reports generally, whether alone, or accompanied by other important information as discussed in Section 1.

1. Submission of Published Literature or Other Reports in Conjunction with Other Important Information that Enhances the Reliability of the Data

If a sponsor wishes to rely on a study conducted by another party and cannot obtain the primary data from the study, for most well-conducted studies it is possible to obtain other important information, such as a protocol documenting the prospective plans for the trial, records of trial conduct and procedures, patient data listings for important variables, and documentation of the statistical analysis. FDA has considerable experience evaluating large multicenter outcome studies sponsored by U.S. and European government agencies (NIH, British Medical Research Council) and private organizations (the ISIS studies, the SAVE study) for which there was limited access to primary study data, but for which other critical information was available. Providing as many as possible of the following important pieces of information about a study, in conjunction with the published report, can increase the likelihood that the study can be relied on to support an effectiveness claim:

a. The protocol used for the study, as well as any important protocol amendments that were implemented during the study and their relation to study accrual or randomization.

b. The prospective statistical analysis plan and any changes from the original plan that occurred during or after the study, with particular note of which analyses were performed pre- and post-unblinding.

c. Randomization codes and documented study entry dates for the subjects.

d. Full accounting of all study subjects, including identification of any subjects with on-treatment data who have been omitted from analysis and the reasons for omissions, and an analysis of results using all subjects with on-study data.

e. Electronic or paper record of each subject's data for critical variables and pertinent baseline characteristics. Where individual subject responses are a critical variable (e.g., objective responses in cancer patients, clinical cures and microbial eradications in infectious disease patients, death from a particular cause), detailed bases for the assessment, such as the case report, hospital records, and narratives, should be provided when possible.

f. Where safety is a major issue, complete information for all deaths and drop-outs due to toxicity. For postapproval supplemental uses, however, there is generally less need for the results of lab tests or for details of adverse event reports and, consequently, much more limited documentation may be sufficient (e.g., only for unexpected deaths and previously undescribed serious adverse effects). Exceptions to this

approach would include situations in which the population for the supplemental use is so different that existing safety information has limited application (e.g., thrombolysis in stroke patients versus myocardial infarction patients) or where the new population presents serious safety concerns (e.g., extension of a preventive vaccine indication from young children to infants).

2. Submission of Published Literature Reports Alone

The following factors increase the possibility of reliance on published reports alone to support approval of a new product or new use:

a. Multiple studies conducted by different investigators where each of the studies clearly has an adequate design and where the findings across studies are consistent.

b. A high level of detail in the published reports, including clear and adequate descriptions of statistical plans, analytic methods (prospectively determined), and study endpoints, and a full accounting of all enrolled patients.

c. Clearly appropriate endpoints that can be objectively assessed and are not dependent on investigator judgment (e.g., overall mortality, blood pressure, or microbial eradication). Such endpoints are more readily interpreted than more subjective endpoints such as cause-specific mortality or relief of symptoms.

d. Robust results achieved by protocol-specified analyses that yield a consistent conclusion of efficacy and do not require selected post hoc analyses such as covariate adjustment, subsetting, or reduced data sets (e.g., analysis of only responders or compliant patients, or of an "eligible" or "evaluable" subset).

e. Conduct of studies by groups with properly documented operating procedures and a history of implementing such procedures effectively.

There have been approvals based primarily or exclusively on published reports. Examples include the initial approval of secretin for evaluation of pancreatic function and recent approvals of bleomycin and talc for malignant pleural effusion and doxycycline for malaria.

B. Reliance on Studies with Alternative, Less Intensive Quality Control/On-Site Monitoring

Industry-sponsored studies typically use extensive on-site and central monitoring and auditing procedures to assure data quality. Studies supported by other sponsors may employ less stringent procedures and may use no on-site monitoring at all. An International Conference on Harmonisation guideline on good clinical practices,[7] recently accepted internationally, emphasizes that the extent of monitoring in a trial should be based on trial-specific factors (e.g., design, complexity, size, and type of study outcome measures) and that different degrees of on-site monitoring can be appropriate. In recent years, many credible and valuable studies conducted by government or independent study groups, often with important mortality outcomes, had very little on-site monitoring. These studies have addressed quality control in other ways, such as by close control and review of documentation and extensive guidance and planning efforts with investigators. There is a long history of reliance on such studies for initial approval of drugs as well as for additional indications. Factors that influence whether studies with limited or no monitoring may be relied on include the following:

1. The existence of a prospective plan to assure data quality.

2. Studies that have features that make them inherently less susceptible to bias, such as those with relatively simple procedures, noncritical entry criteria, and readily assessed outcomes.

3. The ability to sample critical data and make comparisons to supporting records (e.g., hospital records).

4. Conduct of the study by a group with established operating procedures and a history of implementing such procedures effectively.

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[7] International Conference on Harmonisation Guidance for Industry E6, *Good Clinical Practice: Consolidated Guideline*, April 1996.

10.4. Statistical Analysis Plan—ALK21-013

ALK21-013

EFFICACY AND SAFETY OF VIVITROL® (NALTREXONE FOR EXTENDED RELEASE INJECTABLE SUSPENSION) IN ADULTS WITH OPIOID DEPENDENCE

STATISTICAL ANALYSIS PLAN

FINAL
30 JANUARY 2009

AMENDMENT 1
26 JUNE 2009

2. TABLE OF CONTENTS

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations

Abbreviation	Definition
AE	adverse event
ANCOVA	analysis of covariance
ASI	Addiction Severity Index
BDI	Beck Depression Inventory
CGI	Clinical Global Impression scale
CRF	case report form
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
ECG	electrocardiogram
EQ-5D	Euro-Qol Health Questionnaire
FAS	full analysis set
IDC	Individual Drug Counseling
IM	intramuscular
ITT	intent-to-treat
LOCF	last observation carried forward
MADRS	Montgomery-Åsberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
PPS	per protocol set
QOL	Quality of Life
RAB	Risk Assessment Battery
SAP	statistical analysis plan
SAE	serious adverse event
SD	standard deviation
SFHUQ	Social Functioning and Healthcare Utilization Questionnaire
TEAE	treatment-emergent adverse event
TLFB	Timeline FollowBack

4. INTRODUCTION

ALK21-013 is a Phase 3, randomized, placebo-controlled, double-blind, multi-center confirmatory study to evaluate the efficacy and safety of Vivitrol® in opioid dependent adults. This study is being conducted in 2 parts: Part A and Part B. Part A will be a double-blind, placebo-controlled assessment of efficacy and safety. After completing Part A, subjects will continue to Part B. Part B will be an open-label extension to assess long-term (up to 1.5 years) durability of effect, health economics, and quality of life (QOL). During Part A, eligible subjects will be randomized to receive 6 injections of either VIVITROL 380 mg or placebo, approximately 28 days apart for 24 weeks. After completing Part A subjects will continue to Part B. During Part B, each subject will receive 13 additional injections of VIVITROL 380 mg in an open-label fashion, for approximately 52 weeks. Thus, subjects who received placebo during Part A will cross over to VIVITROL during Part B.

The purpose of this statistical analysis plan (SAP) is to ensure the credibility of study outcomes by pre-specifying the statistical methods and data handling conventions for key analyses. In conformity with study design, data analyses will be conducted in two stages. Primary analysis to evaluate the clinical efficacy of 24 weeks of treatment with VIVITROL versus placebo will be conducted once all subjects complete Part A of the study. Following completion of the entire study (Part A and B), all remaining data will be analyzed to explore the durability of effect, long term safety, and health economic and QOL outcomes.

The primary objective of this SAP is to pre-specify the unblinded analysis of double-blind Part A data.

The SAP was amended to incorporate recommendations made by FDA after reviewing the initial version (dated 30JAN2009). Two revisions were made:

1. Opioid use during the treatment period will be determined using weekly urine drug tests incorporating self-reported drug use from TLFB data (see Section 8.1.1).
2. To seek claims based on secondary efficacy outcomes, a hierarchical testing procedure will be used to control the Type I error (see Section 6.5).

In addition, appropriate revisions were made to reflect the extension of the duration of open-label phase, Part B, from 7 additional doses to 13 doses, by the fifth protocol amendment finalized on 04JUN2009.

5. STUDY OVERVIEW

5.1. Study Objectives

5.1.1. Primary Objective

The primary objective of this study is to evaluate the clinical efficacy of 24 weeks of treatment with VIVITROL versus placebo administered to adults with opioid dependence every 4 weeks after completion of opioid detoxification.

5.1.2. Secondary Objectives

A secondary objective of this study is to evaluate the clinical safety of VIVITROL administered every 4 weeks for up to 1.5 years for the treatment of opioid dependence.

An additional secondary objective of this study is to assess long-term (up to 1.5 years) durability of effect of monthly VIVITROL administration as a treatment for opioid dependence.

5.1.3. Exploratory Objective

An exploratory objective of this study is to assess long-term (up to 1.5 years) health economics and QOL outcomes with monthly VIVITROL administration as a treatment for opioid dependence.

5.2. Study Design

The study is currently being conducted at 13 sites in Russia. The total planned enrollment is 250 adult (18 years of age or older) subjects who have been diagnosed with opioid dependence, based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). Subjects must be completing or have recently completed up to 30 days of inpatient treatment for opioid detoxification, and have been off all opioid (including buprenorphine and methadone) for at least 7 days. Female subjects who are pregnant or breastfeeding and subjects with clinically significant medical conditions are excluded from participation. See Section 5 of the protocol for detailed list of inclusion and exclusion criteria.

The study will be conducted in two parts: Part A – a double-blind, placebo-controlled assessment of efficacy and safety; and Part B – an open-label extension to assess long-term (up to 1.5 years) durability of effect, health economics, and QOL.

5.2.1. Part A, Double-Blind Placebo-Controlled Phase

Part A is a double-blind, placebo-controlled assessment of efficacy and safety over a 24-week treatment period. Approximately 250 subjects will be randomized to receive 6 intramuscular (IM) injections of either VIVITROL 380 mg or placebo in a 1:1 ratio. Injections are administered approximately 4 weeks apart. Randomization is performed using an interactive voice response system (IVRS), and is stratified by site and gender. The first dose of study medication is administered on the day of, or within 1 week after discharge from inpatient treatment for opioid detoxification.

At the end of Part A, unblinded data analyses will be performed to assess the efficacy and safety of 24 weeks of treatment with VIVITROL versus placebo.

5.2.2. Part B, Open-Label Phase

Subjects who complete Part A will continue to Part B and receive 13 additional IM injection of VIVITROL 380 mg in an open-label fashion. Those subjects who receive placebo during Part A will cross over to receive VIVITROL during Part B.

5.3. Endpoints

5.3.1. Efficacy Endpoints

The primary endpoint to determine the clinical efficacy of VIVITROL for opioid dependence is the response profile based on the rate of urine drug tests that are negative for opioids during the last 20 weeks of the 24-week double-blind treatment period. The rate of negative urine drug tests will be calculated per subject as a percent of scheduled weekly tests. The response profile per treatment arm will be generated as a cumulative density function of the percent negative drug tests.

Secondary efficacy endpoints are:

- Study retention during the double-blind period
- Craving score
- Incidence of physiologic opioid dependence (physiologic dependence is defined as a positive naloxone challenge)
- Percent of self-reported opioid-free days from Timeline FollowBack (TLFB) data

5.3.2. Safety Endpoints

The safety of VIVITROL will be assessed with following endpoints:

- Incidence of treatment-emergent adverse events (TEAEs) and laboratory abnormalities
- Laboratory test results
- Vital signs
- Electrocardiogram (ECG) findings
- Injection site assessments

5.3.3. Exploratory Endpoints

Long-term (up to 1.5 years) health economics and QOL outcomes with monthly VIVITROL administration as a treatment for opioid dependence will be explored with responses to following questionnaires:

- Social Functioning and Healthcare Utilization Questionnaire (SFHUQ)
- Addiction Severity Index (ASI)

- SF-36v2™
- Euro-Qol (EQ-5D)
- Revised Clinical Global Impression (CGI) scale
- Risk Assessment Battery (RAB)

5.4. Sample Size Considerations

A re-analysis of data from a placebo-controlled Phase II study of oral naltrexone for opioid dependence, which was conducted in Russia, resulted in mean (SD) of percent opioid-negative urine tests of 48.7 (37.8) for 97 subjects who received oral naltrexone for 6 months compared to 24.6 (31.2) for 95 subjects who were treated with placebo. The projected sample size of the current study will provide sufficient power to detect a smaller treatment effect assuming a higher placebo effect with the extended-release formulation. A sample size of 125 subjects per treatment group in the proposed study will provide 85% and 96% power to detect an effect size of Cohen's d=0.4 and 0.5, respectively, by a Wilcoxon rank-sum test at a 0.05 two-sided significance level.

5.5. Schedule of Assessments and Data Collection

The study flow chart with the schedule of assessments for Part A is presented in Table 2. Table 3 presents the study flow chart for Part B.

Table 2: Study Flow Chart for Part A

Visit	1 [a]	2 [a]	3-5, 7-9, 11-13, 15-17, 19-21, 23-25	6, 10, 14, 18, 22	26 (Part A)
Day	-14 to -2	0	7, 14, 21, 35, 42, 49, 63, 70, 77, 91, 98, 105, 119, 126, 133, 147, 154, 161	28, 56, 84, 112, 140	168
Procedure					
Informed Consent	X				
Demographics, height	X				
Medical history	X [a]				
Concomitant medication	X	X	X	X	X
Naloxone challenge		X	X [b]	X [b]	X
Physical examination, ECG	X [c]				X
Vital sign measurement	X	X	X	X	X
Weight	X	X		X	X
Human immunodeficiency virus (HIV) antibody test	X				
Urine drug testing	X	X	X	X	X
Urine pregnancy test [d]	X	X		X	X
Biochemistry, hematology, urinalysis samples	X			X	X
Confirmation of eligibility		X			
Randomization		X			
IDC		X	X [e]	X	X
BDI, MADRS		X			
Revised CGI scale, ASI, RAB		X			X
SF-36v2		X		X (Visit 14 only)	X
SF-36v2 Questions #5 and #9 only			X	X (Every visit *except* Visit 14)	
EQ-5D		X			X
SFHUQ		X		X	X
TLFB [f]	X	X	X	X	X
Opiate craving scale	X	X	X	X	X
AE assessment	X	X	X	X	X
Injection site assessment		X		X	X
Administration of study drug		X		X	
Distribution of Part A emergency treatment card		X			
Confirmation of emergency treatment card possession			X	X	
Collection of emergency treatment card					X

a. Including documentation of DSM-IV-TR opioid dependence and number of detoxifications in the past 12 months.
b. A naloxone challenge will be performed if the urine drug test is positive for opioids.
c. Includes waist circumference and hip circumference measurements. Note: waist and hip circumference measurements were added to the screening examination procedures with the approval of Protocol Amendment #2. For subjects who completed the screening examination (Visit 1) prior to the approval of Amendment #2, waist and hip circumference measurements should be collected at the next scheduled visit.
d. For women of childbearing potential only.
e. At Visits 4, 8, 12, 16, 20, and 24 only.
f. At screening (Visit 1) TLFB data will be collected for the previous 60 days. At all other visits, TLFB data will be collected since the last visit.

Table 3: Study Flow Chart for Part B

Visit	26 (Part B) [a]	27 through 38	39
Day	168	196 through 504	532
Procedure			
Physical examination, ECG		X (Visit 32, only)	X
Concomitant medication		X	X
Vital signs, weight		X	X
Urine pregnancy test [b]		X	X
Urine drug testing		X	X
Naloxone challenge		X [c]	X
Biochemistry, hematology, urinalysis samples		X(Visits 27, 30, 33, and 36 only)	X
IDC		X	X
Revised CGI scale, ASI, RAB		X (Visit 32 only)	X
SF-36v2		X (Visit 29, 32, and 36 only)	X
SF-36v2 Questions #5 and #9		X (Every visit *except* Visit 29, 32, and 36)	
EQ-5D		X (Visit 29, 32, and 36 only)	X
SFHUQ		X	X
TLFB		X	X
Opiate craving scale		X	X
AE assessment		X	X
Injection site assessment		X	X
Administration of VIVITROL 380 mg	X	X	
Distribution of Part B emergency treatment card	X		
Confirmation of emergency treatment card possession		X	
Collection of emergency treatment card			X

a. Only procedures specific to Part B are listed here. Refer to the study flowchart for Part A for additional procedures to be conducted at this visit.
b. For women of childbearing potential only.
c. A naloxone challenge will be performed if the urine drug test is positive for opioids

All the data, except laboratory test results will be collected on case report forms (CRF). Electronic laboratory test results will be downloaded from the central laboratory. The contract research organization, PSI Co. Ltd, will build the database and transfer to Alkermes as SAS® datasets for analysis.

6. GENERAL ANALYSIS DEFINITIONS

6.1. Study Periods and Analysis Time Points

By design, this study consists of two periods: Part A (placebo-controlled, double-blind period) and Part B (single arm, open-label period), as described in Section 5.2. In conformity with this design, the data analyses will take place in two stages:

1. An analysis of efficacy and safety of the 24-week treatment with either VIVITROL 380 mg or placebo, administered once every 4 weeks, will be conducted using data collected during Part A – the randomized, double-blind, placebo-controlled phase of the study. All efficacy and safety assessment data collected prior to the administration of study drug during Visit 26 (ie, Dose 7 or the first dose in Part B) will be included in this analysis. Adverse events with dates of onset after the first injection and prior to seventh injection will be included. For subjects who discontinue prior to study drug administration at Visit 26, all data will be used. Once Part A data for all subjects is collected and verified, and outcomes for all key efficacy and safety endpoints are determined, the study will be unblinded for this analysis.
2. Analyses of the long-term (up to 1.5 years) durability of effect, safety, health economics and QOL outcomes will be conducted at the end of the entire study using both Part A and Part B data.

All results will be presented in the Clinical Study Report (CSR).

6.2. Study Baseline

The day of first study drug administration will be considered as the baseline for this study. The last measurements assessed prior to the first injection will be considered as the baseline measurements for each clinical parameter. For the majority of clinical parameters, assessments preformed at randomization (Visit 2) will provide baseline measurements. For assessments that are not scheduled at randomization, the last available assessments will serve as baseline measurements. Baseline percent opioid-free days, as reported by TLFB data, will be calculated using data for the 30-day period immediately prior to the hospitalization for inpatient opioid detoxification treatment before study enrollment.

6.3. Analysis Sets

To analyze the efficacy of VIVITROL in comparison with placebo, the following two sets of subjects will be defined (as described in the regulatory guideline, International Conference on Harmonisation (ICH) E9: Statistical Principles for Clinical Trials):

1. **Full Analysis Set (FAS)** will consist of all randomized subjects who receive at least one dose of study drug. This set of subjects will be used for the intent-to-treat (ITT) analysis of all efficacy endpoints. Randomized subjects who did not receive study drug will be excluded from the full analysis set, and will be documented prior to unblinding the study.
2. **Per Protocol Set (PPS)** will be defined as the subset of FAS who complete first 3 consecutive months of dosing without a major protocol violation that could affect the

interpretation of the primary endpoint. Such violations will include greater than 2-week delays in study drug administration and taking prohibited medications during the double-blind period. Any other unforeseen violations may be considered as reasons for exclusion after a blinded review of all protocol violations. This subset of subjects will be used to explore efficacy of VIVITROL with adherence to treatment plan. FAS subjects excluded from the PPS along with reasons for exclusion will be documented before unblinding the study.

For the analysis of durability of treatment effect, subjects who continued to open-label phase will be used.

Safety and tolerability analysis will be based on all subjects who receive at least one dose of study drug (FAS, as defined for efficacy analysis).

6.4. Tabulating Descriptive Statistics

Tables will be presented with descriptive statistics summarizing endpoints by treatment group and schedule time point. In general, continuous variables will be summarized with N, mean, SD, median, quartiles, minimum and maximum. For categorical variables, number and percent of subjects in each category will be presented.

6.5. Statistical Significance and Multiplicity

All statistical comparisons and confidence limits will be two-sided, and will use the conventional α=0.05 as the level of statistical significance.

To confirm the clinical efficacy of VIVITROL for the treatment of opioid dependence, the primary comparison will be testing the single null hypothesis based on the primary endpoint.

Additional efficacy claims will be made with following two key secondary endpoints:

1. Study retention
2. Opioid craving score

A hierarchical testing procedure will be used to preserve the family wise error rate with efficacy conclusions. The primary endpoint will serve as the gatekeeper and will be tested at the 0.05 level of significance. Should the primary endpoint achieve statistical significance, these two key secondary endpoints will be tested using Bonferroni-Holm method[1] to preserve the family wise error rate at 0.05. If $p_{(1)}$ and $p_{(2)}$ are ordered p-values derived from testing these two secondary endpoints, then the adjusted p-values, $\tilde{p}_{(1)}$ and $\tilde{p}_{(2)}$ will be calculated as:

$$\tilde{p}_{(1)} = 2 \times p_{(1)}$$
$$\tilde{p}_{(2)} = \max\left[\tilde{p}_{(1)}, p_{(2)}\right]$$

The other two secondary endpoints (as specified in Section 5.3) will be considered supportive and be compared at a 0.05 level of significance without adjusting for multiplicity.

For safety analyses, no multiplicity adjustment will be made since an analysis without multiplicity adjustments will be conservative, and will enhance power to detect untoward effects, if present.

6.6. Handling of Missing Data

For the primary endpoint, the rate of opioid negative urine drug tests will be calculated using the number of scheduled weekly tests (20) as the denominator. All missing urine drug test results will be imputed as positive for opioid. These will include missing test results due to early termination and failure to provide urine samples according to the study schedule. Calculation methods are detailed in Section 8.1.1.

For VIVITROL versus placebo comparisons of secondary endpoints during the double-blind period, the following imputation methods will be used:

- Time to dropout will be calculated from baseline to the day of last visit for those who discontinue before the first visit of the open-label period (Visit 26). Subjects who continue to the open-label period will be censored at the day of the first open-label dose (Visit 26).
- Missing opioid craving scores at weekly visits will be imputed using the last observation carried forward (LOCF) method.
- To determine the incidence of physiological opioid dependence, subjects who drop out during the double-blind period will be imputed as positive for naloxone challenge.
- To calculate the percent of self-reported opioid-free days from TLFB data, missing data for the period after discontinuation will be imputed using the baseline rate (the rate during the 30 pre-detoxification days). See Section 8.2.4 for details.

VIVITROL versus placebo comparisons of safety endpoints will be performed using available data. Adverse events (AEs) with dates of onset on or after the first injection of study drug will be counted as TEAEs. An AE with incomplete timing information (start and stop dates) will be excluded if it can be determined explicitly that the AE was present prior to the first injection, using available data. Summary tables will present descriptive statistics of laboratory data and vitals signs by scheduled visit. An additional row consisting of descriptive statistics of the last postdose observation will be included to describe the outcome at the end of treatment..

To assess efficacy during the open-label period (Part B), endpoints will not be imputed for those who discontinue during the double-blind period (Part A). Efficacy endpoints for Part B will be assessed using the imputation methods used for Part A for subjects who enter Part B, ie, who receive at least one open-label injection. Safety will be assessed with available data. Incidence of AEs for Part B will be calculated using the number of subjects who received at least one open-label injection as the denominator.

6.7. Early Termination Follow-up Visit

The follow-up visit at the end of study (Visit 39; Day 532) will occur approximately 28 days after the last scheduled open-label dose. For those who discontinue early, the follow-up visit will be performed on the day of discontinuation, and data collected at this visit will be counted as assessments made during a scheduled visit, as follows:

- If the visit after the subject's last scheduled visit is to be performed a week later, and the follow-up visit occurs within 5 to 10 days, then follow-up visit data will be used as data for the next scheduled visit. For instance, if a subject discontinues after Day 21, and the follow-up visit occurs 6 days after Day 21, then data from the follow-up visit will be used as Day 28 assessments. If a subject discontinues after Day 28, and the follow-up visit occurs 6 days after Day 28, then the craving score from the follow-up visit will be used as Day 35 craving score, but labs, vital signs, etc. will not be counted for Day 56 data, since those assessments are too early for that visit. Follow-up visit data outside this window will only be used for LOCF imputations and for the last postdose visit analyses.
- If the visit after the subject's last scheduled visit is to be performed 28 days later, and the follow-up visit occurs within 22 to 35 days, then the data from the follow-up visit will be used as data for the next scheduled visit. For example, if a subject discontinues after Day 224, and the follow-up visit occurs 33 days after Day 224, then data from the follow-up visit will be used as Day 252 assessments. Follow-up visit data outside this window will only be used for LOCF imputations and for the last postdose visit analyses.

In addition, all follow-up visit data, irrespective of the window of occurrence, will be used for LOCF and last postdose analyses, where applicable.

7. ANALYSIS OF TREATMENT GROUP COMPARABILITY

7.1. Subject Disposition

Subject enrollment, study drug administration, and study discontinuations will be summarized overall and by treatment group. Number and percent of subjects discontinued will be presented by the reason for discontinuation during the double-blind period and overall study period. Distribution of time to discontinuation by treatment group will be displayed in Kaplan-Meier plots.

7.2. Demographic and Baseline Characteristics

The following demographic and clinically relevant baseline characteristics will be summarized for all subjects and by treatment group:

- Age
- Sex
- Race
- Weight
- Height
- Body Mass Index
- Hip circumference
- Waist circumference
- Investigational site
- Duration of opioid dependence
- Number of inpatient treatments for opioid detoxification during the past 12 months (excluding the most recent one)
- Duration of the most recent inpatient treatment for opioid detoxification
- Liver function tests (ALT, AST and bilirubin)
- Opioid craving score
- Percent of self-reported opioid-free days during the 30-day period prior to hospitalization for detoxification
- Beck Depression Inventory (BDI) total score
- Severity of depression as categorized by BDI total score
- Montgomery-Asberg Depression Rating Scale (MADRS) score

7.3. Medical History

Medical history data will be coded using the Medical Dictionary of Regulatory Activities (MedDRA) and summarized by System Organ Class and Preferred Term, for all subjects and by treatment group.

8. ANALYSIS OF EFFICACY

8.1. Analysis of Primary Endpoint

8.1.1. Derivation Rules for Primary Endpoint

During the double-blind phase, urine samples for drug tests are collected at all scheduled weekly visits. Therefore, each subject should provide 20 test results (Visit 7 through Visit 26) during the last 20 weeks of the 24-week double-blind period, which will be used as the denominator to calculate the percent of opioid-free urine tests. Should fewer than 20 test results be available for a subject, all missing test results for this subject will be considered positive. Each urine drug test result reported as negative will be adjudicated by examining the self-reported opioid use within the week prior to the urine sample. If the previous urine sample was collected less than 7 days before the corresponding test, then the days since the previous test will be considered. If TLFB data indicate opioid use during this period, the negative result will be counted as positive. The total number of negative tests during the 20-week period will be the number of unchanged negative results. The rate of opioid-free drug tests will be calculated as follows:

$$Rate\ of\ Opioid\ Negative\ Tests = 100 \times \frac{(Total\ Number\ of\ unchanged\ Negative\ Tests)}{20}$$

For each treatment group, the response profile will be generated by calculating the cumulative percent of subjects at each observed value of the rate of negative drug tests ($\geq$0%, $\geq$5%, $\geq$10%, $\geq$15%... $\geq$95%, =100%).

8.1.2. Primary Analysis of the Primary Endpoint

The primary analysis of the primary endpoint will be the ITT analysis using the FAS. Response profiles for two treatment groups will be displayed graphically by plotting cumulative percent of subjects at each observed rate on the same plot and will be statistically compared with a two-sided Van der Waerden test. Since the desired outcome is to have more abstinence from opioids, the separation of response profiles at the higher end (right-hand side of the X-axis) will be considered clinically meaningful. Descriptive statistics (including 95% confidence intervals for the mean) of the rate (percent) of opioid-negative urine drug tests will be tabulated by treatment group.

8.1.3. Secondary Analyses of the Primary Endpoint

The above analysis of the primary endpoint will be performed using data for PPS.

Proportion of subjects with total abstinence from opioid use (rate of negative tests = 100%) in each treatment group will be compared with a Chi-Square test.

To explore the influence of stratification factors and other clinically relevant baseline characteristics, the rate of opioid negative urine drug tests will be analyzed with an analysis of covariance (ANCOVA) model. The ANCOVA model will contain factors for treatment group, sex, and sex by treatment interaction. Age, duration of opioid dependence, and duration of last pre-study inpatient detoxification treatment period will be included as continuous covariates.

Least square mean estimates for each treatment and for the treatment difference will be displayed along with 95% confidence intervals to demonstrate the robustness of the results of the primary analysis. This analysis will be performed for both FAS and PPS data.

Treatment effect within centers will be explored with descriptive statistics on the rate of opioid negative urine drug tests by treatment group and center. This analysis will be performed for FAS data only.

A sensitivity analysis will be performed by calculating the rate of opioid-negative drug test results using all 24 scheduled drug tests (Visit 3 though Visit 26) during the 24-week double-blind treatment period. This analysis will use the methods described for the primary analysis.

8.1.4. Subgroup Analyses

ITT analyses using FAS data will be performed to explore whether the treatment effect within various subgroups is consistent. Response profiles by treatment group will be graphically displayed for the subgroups defined by the following baseline characteristics:

- Sex (male vs. female)
- Age (between 3 categories formed with tertiles)
- Duration of opioid dependence (between 3 categories formed with tertiles)
- Duration of recent pre-study inpatient detoxification (between 3 categories formed with tertiles).

Treatment by factor interaction will be assessed with analysis of variance (ANOVA) models of the rate of opioid-negative urine drug tests. Least square mean difference between two treatment groups along with 95% confidence intervals by subgroup will be presented. Separate ANOVA models including fixed effects for treatment, subgroup factor and treatment by factor interaction will be used for each baseline characteristic.

8.2. Analysis of Secondary Efficacy Endpoints

This section provides VIVITROL versus placebo comparative analyses of the secondary endpoints derived using data collected during the 24-week, double-blind, placebo-controlled period of the study. All these analyses will be ITT using data for FAS.

8.2.1. Study Retention

Study retention during the double-blind period will be evaluated using time to dropout and the proportion of subjects who completed the double-blind period.

For subjects who discontinue during the double-blind period (Part A), the time to dropout will be calculated as the number of days from the first dose to the dropout date. Those who continue to the open-label period of the study (Part B) will be censored at the date of first open-label injection, and the duration will be calculated as the number of days from the first dose to the date of first open-label injection. The distribution of time to dropout will be estimated and graphically displayed by treatment group using Kaplan-Meier methods. Treatment difference will be tested with a log-rank test. A Cox proportional hazard model will be used to explore the

treatment comparison adjusted for the baseline factors: sex as a fixed effect, age, duration of opioid dependence and the duration of inpatient detoxification as continuous covariates.

All subjects who receive at least one open-label injection will be counted as having completed the double-blind phase. The number and percent of such subjects who completed the double-blind phase will be tabulated by treatment group. The difference between two treatment groups will be tested by Chi-square test.

8.2.2. Opioid Craving Score

Opioid craving scores are collected from subjects' responses on a visual analog scale (0-100) at screening, Day 0, and weekly visits during the double-blind period. Descriptive statistics of observed data and the change from baseline will be presented by treatment group and scheduled visit. Mean (SD) will be graphically displayed by scheduled time point. A generalized estimation equation (GEE) model will be used to compare two treatment groups with on-study results during the double-blind period. Baseline results will be included in the model as a covariate. Normal distribution will be assumed for the built-in probability distribution and Autoregressive [AR(1)] correlation structure will be used for the working correlation matrix.

8.2.3. Incidence of Physiologic Dependence

Incidence of physiologic dependence will be calculated for each treatment group as the proportion of subjects who had a positive naloxone challenge during the double-blind period (Part A). Subjects who discontinue before the end of Part A will be imputed as having positive tests.

Number and percent of subjects who relapsed to physiologic dependence during the double-blind period will be tabulated by treatment group. The difference between two treatment groups will be tested by Chi-square test.

8.2.4. Percent of Self-Reported Opioid-Free Days

Subject-reported opioid use data will be collected by TLFB method[2]. At screening, data for 60 pre-screening days is collected. At every subsequent visit, opioid use data is collected for the period since the previous visit. Percent of self-reported opioid-free days will be calculated for baseline and postdose (Part A and Part B) periods. The baseline rate will be calculated using data for the 30-day period immediately prior to the most recent pre-study hospitalization for detoxification treatment. For the VIVITROL versus placebo comparison, the rate during the double-blind period will be calculated using data from the day of first double-blind dose to the day before the first open-label dose.

For subjects who continue to the open-label period, and for those who provide TLFB data on or beyond Day 168, the rate during the double-blind period will be calculated as:

$$Percent\ opioid\ free\ days = 100 \times \frac{(Number\ of\ reported\ opioid\ free\ days)}{(Number\ of\ days\ with\ TLFB\ data)}$$

For subjects who discontinue within Part A before Day 168, missing data after the dropout date will be imputed using the baseline rate as follows:

First, number of opioid-free days after dropout will be imputed as:

$$No.of\ imputed\ days = Round\left[\frac{(Baseline\ percent\ days\ with\ opioid)}{100} \times (168 - Day\ of\ last\ data\ po\ \text{int})\right]$$

Then, the rate of opioid-free days will be calculated as:

$$Percent\ opioid\ free\ days = 100 \times \left[\frac{(No.of\ reported\ reported\ opioid\ free\ days) + (No.of\ imputed\ days)}{168}\right]$$

The rate during the open-label period will be calculated for subjects who continue to Part B. Since the scheduled length of the 13-dose open-label period is 365 days, for subjects who discontinue early, the rate of opioid-free days will be calculated with above formulae using 365 as the denominator.

Descriptive statistics of the percent of self-reported opioid-free days and the change from baseline will be presented by treatment group for each study period. Treatment group comparisons for the double-blind period will be performed with Van der Waerden test.

8.3. Efficacy Analysis of Part B

One purpose of the single-arm, open-label Part B is to assess the long-term (up to 1.5 years) durability of treatment effect. Since the duration of exposure to VIVITROL depends on the treatment group in Part A, descriptive statistics for efficacy endpoints will be presented by study period and by the treatment in Part A, to facilitate comparisons between periods within treatment groups and between treatment groups during Part B. For period comparisons, Part B results will be compared with Part A results within each treatment group. It is expected that continuation to the open-label VIVITROL treatment will be related to the treatment subjects received during the double-blind period. Therefore, statistical tests for group comparisons with Part B efficacy data will not be performed.

The original baseline data (last assessment conducted prior to first double-blind dose in Part A) will be used as baseline assessments.

The rate of negative opioid urine drug tests will be calculated for this period as a percent of negative drug tests per subject with test results during Part B. During Part B, each subject is scheduled to provide at least 13 urine samples, thus 13 will be used as the denominator; missing test results will be imputed as positive.

Study retention will be assessed by estimating the distribution of time from first open-label dose to study discontinuation by Kaplan-Meier methods. Subjects who complete the study will be censored at the day of the follow-up visit.

Opioid craving scores will be summarized with descriptive statistics by scheduled visit and treatment group in Part A.

Incidence of physiologic opioid dependence will be assessed by the number and percent of subjects with positive naloxone challenge test results. Subjects who discontinue during Part B will be considered as having positive test results.

The rate of self-reported opioid-free days will be calculated for each subject as a percent of days without opioid use as reported by TLFB data during Part B. Descriptive statistics will be presented by study period and treatment group.

9. SAFETY ANALYSIS

Safety endpoints will be assessed with available data using the safety population that will consist of all randomized subjects who receive at least one injection of study drug.

The main parameters for evaluating safety will be the incidence of TEAEs and abnormal laboratory test results. Any reported AE with start or stop date before the first injection of study drug will not be counted as a TEAE. An event with missing information on timing will be excluded if it can be determined explicitly that the event started or stopped prior to the first injection of study drug, using the available information of start and stop dates. All AE terms will be coded using MedDRA. A study period will be assigned for each TEAE by comparing the date of onset against the date of first open-label injection. All the events of a subject who did not continue to Part B will be counted as occurring during Part A. For others, any event with date of onset prior to first open-label injection will be counted as occurring during Part A, and all others will be counted as occurring during Part B.

Incidence of TEAEs will be presented by tabulating the number and percent of subjects by MedDRA System Organ Class and Preferred Term by treatment group and overall. To assess the safety of VIVITROL versus placebo, incidence rates during Part A will be presented. For exploratory purposes, P-values from 2-tailed Fisher's Exact test (unadjusted for multiple comparisons) will be displayed for each event. To assess the long-term safety, incidence rates during each study period (Part A and Part B) will be tabulated by treatment group in Part A.

Serious adverse events (SAEs) and events judged by the investigator to be related to study drug will be summarized. Adverse events judged by the investigator as possibly related, probably related, or definitely related will be counted as related events. Frequency of events by severity and relationship to study drug will also be presented.

Laboratory test results and changes from baseline will be summarized by treatment group throughout scheduled visits. For selected laboratory tests, changes in lab abnormalities will be presented as shift tables. Descriptive summaries of vital sign data at each scheduled visit will be presented.

ECG findings will be displayed in data listings.

10. ANALYSIS OF EXPLORATORY ENDPOINTS

Health economics and QOL outcomes following monthly VIVITROL administration as a treatment for opioid dependence will be explored using 5 questionnaires. The degree of severity of the illness and the improvement with treatment will be assessed by the investigator's response to CGI score.

10.1. Social Functioning and Healthcare Utilization Questionnaire

Data from subjects' responses to SFHUQ will be collected at each scheduled visit. The following information will be collected:

1. Number of psychosocial therapy visits
2. Number of self-help group visits
3. Number of emergency room visits
4. Number of days in a hospital
5. Number of doctor visits (other than hospitalizations, ER, or study participation)
6. Number of missed days at work, school, or other responsibilities

The total number for each item for each subject will be calculated by study period and summarized as continuous variables by treatment group. The number and percent of subjects with values >0 will be tabulated for each study period (Part A and Part B). Treatment comparisons of the actual number of events will be made using Van der Waerden test for data collected during the double-blind period. Summary statistics by month will also be produced to explore trends over time on treatment.

10.2. Addiction Severity Index

The ASI is a questionnaire designed to measure the severity of seven potential problem areas in substance-dependent patients. Subject responses to ASI questions are collected at baseline, the end of Part A (or early termination), and the end of Part B (or early termination). The following composite scores are derived for each subject at each visit, using the calculation methods detailed in the ASI Composite Score Manual[3]:

1. Medical status
2. Employment/support status
3. Alcohol use
4. Drug use
5. Legal status
6. Family/social status
7. Psychiatric status.

Composite scores and changes from baseline will be summarized with descriptive statistics. Changes at the end of Part A data will be compared using Van der Waerden test to assess the differences between treatment groups.

10.3. SF-36v2 Health Survey

SF-36v2 is administered prior to study drug administration at the first dosing visit and every 12 weeks thereafter during both study periods. Composite scores will be calculated for physical component summary, mental component summary, general health, physical functioning, role-physical, bodily pain, mental health, role-emotional, social functioning and vitality. Standard methodologies[4] will be used to calculate composite scores.

Descriptive statistics for each composite score will be tabulated by treatment group at each scheduled time point. Part A data (Visit 14 and Visit 26 assessments) for VIVITROL and placebo groups will be compared using Van der Waerden test by visit.

10.4. Euro-Qol Health Questionnaire

EQ-5D is a measure used to characterize the current health status using 5 domains (mobility, self-care, usual activities, pains/discomfort and anxiety/depression) and a visual analog scale[5]. For each of the 5 domains, subjects can select one out of three ordinal responses. This self-assessment questionnaire is administered prior to study drug administration at the first dosing visit, and at the end of each study period (Visit 26 and 39).

Each domain will be summarized by tabulating the number and percent of subjects who select each possible response, by treatment group and scheduled time point. Part A data for VIVITROL and placebo groups will be compared using Mantel-Haenszel Chi-Square test. Subjects' assessments of their health state using the visual analog scale will be summarized with descriptive statistics by treatment group and time point. End of Part A results (Visit 26 assessment) for VIVITROL and placebo groups will be compared using Van der Waerden test.

10.5. Risk Assessment Battery

The RAB questionnaire is administered prior to study drug administration at the first dosing visit, at the end of Part A, and at the end of Part B (or at the early termination visit). Three composite scores per subject will be calculated out of subject responses to 24 questions at each timepoint:

1. Drug Risk Total is the sum of responses to questions 1, 2, 3, 8, 12, 13, 14 and 15. This score can range from 0 to 22.
2. Sex Risk Total is the sum of responses to questions 9, 16, 17, 18, highest score out of (19, 20 and 21) and 22. This score can range from 0 to 18.
3. RAB Scale score will be the standardized (0–1 scale) average of the above two scores, Drug Risk Total and Sex Risk Total. ie,

$$RAB\ Scale\ Score = \frac{(Drug\ Risk\ Total) + (Sex\ Risk\ Total)}{40}$$

RAB scale scores at each visit and the change from baseline will be summarized with descriptive statistics by treatment group. Part A data for VIVITROL and placebo groups will be compared using Van der Waerden test.

10.6. Revised Clinical Global Impression Scale

Investigator's measure of the degree of severity of opioid addiction and improvement following study enrollment is assessed using the CGI scale, collected prior to study drug administration at the first dosing visit and at the end of each study period. The number and percent of subjects counted for each response category will be tabulated by treatment group and visit. With the ordinal rating categories, VIVITROL versus placebo comparisons of Part A data will be made using the Mantel-Haenszel Chi-Square test.

11. REFERENCES

1. Holm, S. (1979). A simple sequentially rejective multiple test procedure. Scandinavian Journal of Statistics 6, 65-70

2. Sobell L, Sobell M. Timeline Follow-Back, a technique for assessing self-reported alcohol consumption. In: Litten RZ, Allen J, eds. *Measuring alcohol consumption: Psychosocial and Biological Methods*. Totowa, NJ: The Humana Press; 1992:41-72.

3. Peggy L. McGahan et. al. Addiction Severity Index Composite Score Manual, The University of Pennsylvania/Veterans Administration Center for Studies of Addiction; 1986.

4. Ware J, Kosinski M, Dewy J: How to score version 2 of the SF-36®. Lincoln, RI: QualityMetric Incorporated; 2000

5. Gunther, O. et. al. The EQ-5D in alcohol dependent patients: Relationships among health-related quality of life, psychopathology and social functioning. Drug and Alcohol Dependence. 86(2007);253-264

10.5. Additional Data Tables

Table 18: Response Profiles Based on the Rate of Opioid-Free Weeks during the Last 20 Weeks of the Double-blind Period

Opioid-Free Weeks during the Last 20 Weeks of Double-Blind Period		Cumulative N (%) of Patients	
		Full Analysis Set	
Number	Rate (%)	Placebo (n = 124)	VIVITROL (n = 126)
20	100	28 (22.6)	45 (35.7)
≥ 19	≥ 95	36 (29.0)	60 (47.6)
≥ 18	≥ 90	39 (31.5)	65 (51.6)
≥ 17	≥ 85	45 (36.3)	68 (54.0)
≥ 16	≥ 80	47 (37.9)	70 (55.6)
≥ 15	≥ 75	49 (39.5)	74 (58.7)
≥ 14	≥ 70	52 (41.9)	75 (59.5)
≥ 13	≥ 65	52 (41.9)	75 (59.5)
≥ 12	≥ 60	53 (42.7)	75 (59.5)
≥ 11	≥ 55	58 (46.8)	81 (64.3)
≥ 10	≥ 50	60 (48.4)	83 (65.9)
≥ 9	≥ 45	60 (48.4)	84 (66.7)
≥ 8	≥ 40	61 (49.2)	85 (67.5)
≥ 7	≥ 35	66 (53.2)	87 (69.0)
≥ 6	≥ 30	67 (54.0)	90 (71.4)
≥ 5	≥ 25	69 (55.6)	94 (74.6)
≥ 4	≥ 20	70 (56.5)	98 (77.8)
≥ 3	≥ 15	74 (59.7)	102 (81.0)
≥ 2	≥ 10	77 (62.1)	105 (83.3)
≥ 1	≥ 5	79 (63.7)	109 (86.5)
≥ 0	≥ 0	124 (100.0)	126 (100.0)
P-value from Van der Waerden test for the treatment for difference			**0.0002**

Source: ALK21-013 CSR Table 14.2.1.1

Table 19: Days to Discontinuation during Part A (Full Analysis Set)

Estimate	Placebo	VIVITROL	P-Value[1]
25th percentile (95% CI)	24.0 (20.0, 30.0)	81.0 (52.0, 118.0)	0.0042
Median (95% CI)	96.0 (63.0, 165.0)	>168	
75th percentile (95% CI)	>168	>168	
Number censored[2]	47	67	

Source: ALK21-013 CSR Table 14.2.2.1
Note: CI = confidence interval
[1] P-value from the log-rank test for the difference between two distribution curves of time to dropout
[2] Patients who continued to Part B were censored at the day of the first open-label dose

Table 20: Opioid Craving Scores during the Double-Blind Period—Summary by Visit with LOCF (FAS)

Week	Statistic	Craving Score			Change from Baseline		
		Placebo	VIVITROL	P-Value[1]	Placebo	VIVITROL	P-Value[1]
Baseline	N	124	126	0.0824			
	Mean (SD)	21.8 (24.2)	18.2 (22.8)				
1	N	124	126	0.0006	124	126	0.0357
	Mean (SD)	26.3 (27.6)	15.5 (20.5)		4.5 (22.7)	-2.8 (19.5)	
2	N	124	126	0.0273	124	126	0.1488
	Mean (SD)	21.5 (26.1)	12.0 (18.3)		-0.3 (22.2)	-6.2 (18.7)	
3	N	124	126	0.0037	124	126	0.1272
	Mean (SD)	20.1 (25.8)	10.8 (17.5)		-1.6 (25.8)	-7.5 (16.8)	
4	N	124	126	0.0106	124	126	0.3291
	Mean (SD)	20.5 (25.9)	12.2 (18.7)		-1.3 (27.5)	-6.0 (18.6)	
5	N	124	126	0.0014	124	126	0.0730
	Mean (SD)	20.1 (26.4)	9.9 (18.0)		-1.6 (27.5)	-8.3 (17.5)	
6	N	124	126	0.0016	124	126	0.0759
	Mean (SD)	19.7 (26.1)	10.2 (18.9)		-2.1 (25.8)	-8.0 (20.9)	
7	N	124	126	0.0005	124	126	0.0109
	Mean (SD)	19.4 (26.7)	7.9 (14.6)		-2.4 (27.0)	-10.3 (18.4)	
8	N	124	126	<0.0001	124	126	0.0048
	Mean (SD)	21.2 (27.4)	8.5 (15.5)		-0.5 (27.5)	-9.7 (19.2)	
9	N	124	126	0.0003	124	126	0.0104
	Mean (SD)	20.4 (27.2)	8.3 (15.2)		-1.4 (26.9)	-9.9 (20.2)	

Table 20: Opioid Craving Scores during the Double-Blind Period—Summary by Visit with LOCF (FAS) (continued)

Week	Statistic	Craving Score			Change from Baseline		
		Placebo	VIVITROL	P-Value[1]	Placebo	VIVITROL	P-Value[1]
10	N	124	126	0.0003	124	126	0.0061
	Mean (SD)	20.5 (27.0)	7.7 (14.8)		-1.2 (26.5)	-10.5 (20.9)	
11	N	124	126	<0.0001	124	126	0.0024
	Mean (SD)	20.6 (27.5)	6.8 (13.4)		-1.1 (27.5)	-11.4 (19.4)	
12	N	124	126	<0.0001	124	126	0.0019
	Mean (SD)	22.4 (29.2)	7.4 (15.8)		0.7 (28.9)	-10.8 (20.9)	
13	N	124	126	<0.0001	124	126	0.0011
	Mean (SD)	21.5 (27.9)	7.1 (14.5)		-0.2 (27.7)	-11.1 (20.6)	
14	N	124	126	<0.0001	124	126	0.0032
	Mean (SD)	21.5 (27.6)	8.3 (17.4)		-0.2 (28.1)	-9.9 (23.5)	
15	N	124	126	<0.0001	124	126	0.0029
	Mean (SD)	21.2 (27.6)	8.0 (17.4)		-0.5 (27.6)	-10.2 (24.2)	
16	N	124	126	<0.0001	124	126	0.0049
	Mean (SD)	21.1 (27.2)	8.5 (18.1)		-0.7 (27.6)	-9.7 (24.6)	
17	N	124	126	<0.0001	124	126	0.0057
	Mean (SD)	21.4 (27.5)	8.9 (18.4)		-0.3 (27.2)	-9.3 (24.0)	
18	N	124	126	<0.0001	124	126	0.0061
	Mean (SD)	22.0 (27.9)	9.0 (17.7)		0.3 (28.1)	-9.2 (24.1)	
19	N	124	126	<0.0001	124	126	0.0017
	Mean (SD)	22.0 (28.2)	8.0 (17.1)		0.3 (27.9)	-10.3 (23.7)	
20	N	124	126	<0.0001	124	126	0.0015
	Mean (SD)	22.5 (28.6)	8.2 (17.0)		0.7 (28.0)	-10.0 (23.5)	
21	N	124	126	<0.0001	124	126	0.0017
	Mean (SD)	22.6 (28.7)	8.0 (17.0)		0.8 (28.3)	-10.3 (24.1)	
22	N	124	126	<0.0001	124	126	0.0028
	Mean (SD)	21.9 (28.3)	8.3 (17.4)		0.2 (27.8)	-9.9 (24.7)	
23	N	124	126	<0.0001	124	126	0.0023
	Mean (SD)	22.6 (28.7)	8.5 (17.4)		0.9 (27.6)	-9.7 (24.7)	
24	N	124	126	<0.0001	124	126	0.0029
	Mean (SD)	22.5 (28.9)	8.8 (18.2)		0.8 (28.0)	-9.4 (25.5)	

[1] P-value from Van der Waerden test for the treatment difference at the visit (without adjusting for multiplicity).
Source: ALK21-013 CSR Table 14.2.3.1

Table 21: Incidence of Relapse to Physiologic Dependence (Part A)

Group	Relapsed to dependence n (%) of Patients			RR[1] (95% CI)	P-Value[2]
	No	Yes	All		
Placebo	47 (37.9)	77 (62.1)	124 (100)		
VIVITROL	67 (53.2)	59 (46.8)	126 (100)	0.75 (0.60, 0.95)	0.0154

Source: ALK21-013 CSR Table 14.2.4.1
Note: Physiologic dependence was defined as a patient having a positive naloxone challenge or terminated during Part A
[1] Relative risk (VIVITROL/placebo) of relapse to dependence
[2] Chi-square test P-value for treatment difference

Table 22: Patients with a Positive Naloxone Challenge during the Double-Blind Period

Group	N (%) of Patients			RR[1] (95% CI)	P-Value[2]
	Positive Naloxone Challenge				
	No	Yes	All		
Placebo	107 (86.3)	17 (13.7)	124 (100)		
VIVITROL	125 (99.2)	1 (0.8)	126 (100)	0.06 (0.01,0.43)	<0.0001

Source: ALK21-013 CSR Table 14.1.1
[1] Relative risk (VIVITROL/placebo) of relapse to dependence
[2] Chi-square test P-value for treatment difference

Table 23: SF-36v2 Composite Scores

Composite Score	Visit	Statistic	All (n=250)	Placebo (n=124)	VIVITROL (n=126)	P-Value[1]
Physical Component Summary	Baseline	N	247	122	125	0.6784
		Mean (SD)	50.55 (5.75)	50.73 (5.51)	50.37 (5.99)	
	End of Part A	N	167	76	91	0.9463
		Mean (SD)	54.45 (4.91)	54.09 (5.83)	54.75 (4.00)	
Mental Health	Baseline	N	250	124	126	0.6373
		Mean (SD)	37.09 (9.63)	37.35 (9.90)	36.83 (9.39)	
	End of Part A	N	167	76	91	**0.0011**
		Mean (SD)	48.98 (10.24)	46.04 (10.75)	51.43 (9.16)	
Role Emotional	Baseline	N	249	123	126	0.8571
		Mean (SD)	38.04 (10.74)	38.13 (11.37)	37.95 (10.14)	
	End of Part A	N	167	76	91	**0.0128**
		Mean (SD)	46.92 (8.89)	45.09 (9.19)	48.45 (8.37)	
Social Functioning	Baseline	N	250	124	126	0.9002
		Mean (SD)	37.69 (10.71)	37.67 (10.56)	37.72 (10.90)	
	End of Part A	N	167	76	91	**0.0069**
		Mean (SD)	50.22 (8.10)	48.52 (8.52)	51.63 (7.49)	
Vitality	Baseline	N	250	124	126	0.4306
		Mean (SD)	46.26 (9.09)	46.70 (8.69)	45.82 (9.47)	
	End of Part A	N	167	76	91	**0.0133**
		Mean (SD)	56.48 (8.99)	54.51 (9.30)	58.13 (8.43)	

Table 23: SF-36v2 Composite Scores (Continued)

Composite Score	Visit	Statistic	All (n=250)	Placebo (n=124)	VIVITROL (n=126)	P-Value[1]
Mental Component Summary	Baseline	N	247	122	125	0.7564
		Mean (SD)	35.19 (10.53)	35.40 (10.80)	34.98 (10.29)	
	End of Part A	N	167	76	91	**0.0043**
		Mean (SD)	48.05 (10.08)	45.28 (10.47)	50.37 (9.18)	
Physical Component Subscale – General Health	Baseline	N	249	124	125	0.1837
		Mean (SD)	44.24 (7.92)	44.88 (8.02)	43.60 (7.80)	
	End of Part A	N	167	76	91	0.0575
		Mean (SD)	47.09 (9.00)	45.66 (9.79)	48.29 (8.16)	

[1] p-Value from Van der Waerden test for treatment difference without adjusting for multiplicity
Source: ALK21-013 CSR Table 14.3.3

Table 24: RAB Scale Scores

Visit	Statistic	RAB Scale Score[1]				Change from Baseline			
		All (N=250)	Placebo (n=124)	VIVITROL (n=126)	P-Value[2]	All (N=250)	Placebo (n=124)	VIVITROL (n=126)	P-Value[2]
Baseline	N	250	124	126	0.1008				
	Mean (SD)	0.292 (0.152)	0.281 (0.162)	0.303 (0.141)					
End of Part A	N	136	65	71	0.5180	136	65	71	**0.0212**
	Mean (SD)	0.119 (0.076)	0.130 (0.096)	0.108 (0.051)		-0.160 (0.166)	-0.130 (0.173)	-0.187 (0.156)	

[1] 0 = Low risk assessment, 1 = High risk assessment
[2] P-Value from Van der Waerden test for treatment difference without adjusting for multiplicity
Source: ALK21-013 CSR Table 14.3.5

Table 25: CGI Scale Scores

Assessment	Visit	Score and Response	N (%)[1] of Patients			P-Value[2]
			All (N=250)	Placebo (n=124)	VIVITROL (n=126)	
Severity of Opioid dependence	**Baseline**	Patients Assessed	245 (100.0)	120 (100.0)	125 (100.0)	0.5431
		1 Normal, not at all ill	2 (0.8)	0 (0)	2 (1.6)	
		2 Borderline ill	9 (3.7)	5 (4.2)	4 (3.2)	
		3 Mildly ill	41 (16.7)	19 (15.8)	22 (17.6)	
		4 Moderately ill	130 (53.1)	63 (52.5)	67 (53.6)	
		5 Markedly ill	57 (23.3)	31 (25.8)	26 (20.8)	
		6 Severely ill	6 (2.4)	2 (1.7)	4 (3.2)	
	End of Part A	Patients Assessed	137 (100.0)	66 (100.0)	71 (100.0)	**0.0092**
		1 Normal, not at all ill	39 (28.5)	14 (21.2)	25 (35.2)	
		2 Borderline ill	38 (27.7)	17 (25.8)	21 (29.6)	
		3 Mildly ill	31 (22.6)	16 (24.2)	15 (21.1)	
		4 Moderately ill	18 (13.1)	11 (16.7)	7 (9.9)	
		5 Markedly ill	9 (6.6)	6 (9.1)	3 (4.2)	
		6 Severely ill	2 (1.5)	2 (3.0)	0 (0)	
Global Improvement	**End of Part A**	Patients Assessed	137 (100.0)	66 (100.0)	71 (100.0)	**0.0011**
		1 Very much improved	42 (30.7)	15 (22.7)	27 (38.0)	
		2 Much improved	57 (41.6)	23 (34.8)	34 (47.9)	
		3 Minimally improved	21 (15.3)	16 (24.2)	5 (7.0)	
		4 No change	13 (9.5)	9 (13.6)	4 (5.6)	
		5 Minimally worse	2 (1.5)	1 (1.5)	1 (1.4)	
		6 Much worse	1 (0.7)	1 (1.5)	0 (0)	
		7 Very much worse	1 (0.7)	1 (1.5)	0 (0)	

[1] 0 = Percent is out of the number of patients assessed at the visit

[2] P-Value from Mantel-Haenszel Chi-Square test (using scores for responses) for the treatment difference without adjusting for multiplicity

Source: ALK21-013 CSR Table 14.3.6

Table 26: EQ-5D Health Questionnaire Responses to Five Domains

Domain	Visit	Score and Response	N (%)[1] of Patients			P-Value[2]
			All (N=250)	Placebo (n=124)	VIVITROL (n=126)	
Mobility	Baseline	Patients responded	249 (100.0)	124 (100.0)	125 (100.0)	0.5261
		1. No problems in walking about	205 (82.3)	104 (83.9)	101 (80.8)	
		2. Some problems in walking about	44 (17.7)	20 (16.1)	24 (19.2)	
		3. Confined to bed	0 (0)	0 (0)	0 (0)	
	End of Part A	Patients responded	136 (100.0)	65 (100.0)	71 (100.0)	0.5494
		1. No problems in walking about	128 (94.1)	62 (95.4)	66 (93.0)	
		2. Some problems in walking about	8 (5.9)	3 (4.6)	5 (7.0)	
		3. Confined to bed	0 (0)	0 (0)	0 (0)	
Self-Care	Baseline	Patients responded	249 (100.0)	124 (100.0)	125 (100.0)	0.8153
		1. No problems with self-care	232 (93.2)	116 (93.5)	116 (92.8)	
		2. Some problems washing or dressing myself	17 (6.8)	8 (6.5)	9 (7.2)	
		3. Unable to wash or dress myself	0 (0)	0 (0)	0 (0)	
	End of Part A	Patients responded	136 (100.0)	65 (100.0)	71 (100.0)	0.4168
		1. No problems with self-care	131 (96.3)	62 (95.4)	69 (97.2)	
		2. Some problems washing or dressing myself	4 (2.9)	2 (3.1)	2 (2.8)	
		3. Unable to wash or dress myself	1 (0.7)	1 (1.5)	0 (0)	

Table 26: EQ-5D Health Questionnaire Responses to Five Domains (Continued)

Domain	Visit	Score and Response	N (%)[1] of Patients			P-Value[2]
			All (N=250)	Placebo (n=124)	VIVITROL (n=126)	
Usual Activities	Baseline	Patients responded	249 (100.0)	124 (100.0)	125 (100.0)	0.9452
		1. No problems with performing my usual activities	152 (61.0)	75 (60.5)	77 (61.6)	
		2. Some problems with performing my usual activities	91 (36.5)	47 (37.9)	44 (35.2)	
		3. Unable to perform my usual activities	6 (2.4)	2 (1.6)	4 (3.2)	
	End of Part A	Patients responded	136 (100.0)	65 (100.0)	71 (100.0)	**0.0372**
		1. No problems with performing my usual activities	114 (83.8)	50 (76.9)	64 (90.1)	
		2. Some problems with performing my usual activities	22 (16.2)	15 (23.1)	7 (9.9)	
		3. Unable to perform my usual activities	0 (0)	0 (0)	0 (0)	

[1] Percent is out of the number of patients responded at the visit

[2] P-Value from Mantel-Haenszel Chi-Square test (using scores for responses) for treatment difference without adjusting for multiplicity

Source: ALK21-013 CSR Table 14.3.4.1 (Note: if zero (0) patients indicated a response, then the response was not collected in the source table)

Table 26: EQ-5D Health Questionnaire Responses to Five Domains (Continued)

Domain	Visit	Score and Response	N (%)[1] of Patients			P-Value[2]
			All (N=250)	Placebo (n=124)	VIVITROL (n=126)	
Pain/ Discomfort	Baseline	Patients responded	249 (100.0)	124 (100.0)	125 (100.0)	0.9446
		1. No pain or discomfort	142 (57.0)	70 (56.5)	72 (57.6)	
		2. Moderate pain or discomfort	105 (42.2)	54 (43.5)	51 (40.8)	
		3. Extreme pain or discomfort	2 (0.8)	0 (0)	2 (1.6)	
	End of Part A	Patients responded	136 (100.0)	65 (100.0)	71 (100.0)	0.1978
		1. No pain or discomfort	103 (75.7)	46 (70.8)	57 (80.3)	
		2. Moderate pain or discomfort	33 (24.3)	19 (29.2)	14 (19.7)	
		3. Extreme pain or discomfort	0 (0)	0 (0)	0 (0)	
Anxiety/ Depression	Baseline	Patients responded	249 (100.0)	124 (100.0)	125 (100.0)	0.6741
		1. Not anxious or depressed	97 (39.0)	48 (38.7)	49 (39.2)	
		2. Moderately anxious or depressed	143 (57.4)	70 (56.5)	73 (58.4)	
		3. Extremely anxious or depressed	9 (3.6)	6 (4.8)	3 (2.4)	
	End of Part A	Patients responded	136 (100.0)	65 (100.0)	71 (100.0)	0.1326
		1. Not anxious or depressed	86 (63.2)	36 (55.4)	50 (70.4)	
		2. Moderately anxious or depressed	47 (34.6)	28 (43.1)	19 (26.8)	
		3. Extremely anxious or depressed	3 (2.2)	1 (1.5)	2 (2.8)	

[1] Percent is out of the number of patients responded at the visit

[2] P-Value from Mantel-Haenszel Chi-Square test (using scores for responses) for treatment difference without adjusting for multiplicity

Source: ALK21-013 CSR Table 14.3.4.1 (Note: if zero (0) patients indicated a response, then the response was not collected in the source table)

Table 27: EQ-5D Visual Analog Scale Assessment of Own Health State[1]

Visit	Statistic	VAS Score				Change from Baseline			
		All (N=250)	Placebo (n=124)	VIVITROL (n=126)	P-Value[2]	All (N=250)	Placebo (n=124)	VIVITROL (n=126)	P-Value[2]
Baseline	N	249	124	125	0.6302				
	Mean (SD)	69.3 (18.0)	69.9 (17.4)	68.7 (18.6)					
End of Part A	N	136	65	71	**0.0283**	136	65	71	**0.0005**
	Mean (SD)	77.6 (16.3)	73.9 (18.6)	81.0 (13.2)		8.7 (19.7)	2.7 (18.7)	14.1 (19.1)	

[1] 0 = Worst imaginable health, 100 = Best imaginable health
[2] P-Value from Van der Waerden test for treatment difference without adjusting for multiplicity
Source: ALK21-013 CSR Table 14.3.4.2

Table 28: ASI Composite Scores

Composite Score	Visit	Statistic	All (n=250)	Placebo (n=124)	VIVITROL (n-126)	p-Value[1]
Medical Status	Baseline	N	250	124	126	0.7161
		Mean (SD)	0.279 (0.253)	0.284 (0.258)	0.275 (0.249)	
	End of Part A	N	134	65	69	0.9018
		Mean (SD)	0.142 (0.187)	0.140 (0.179)	0.143 (0.196)	
Employment Status	Baseline	N	250	124	126	0.3227
		Mean (SD)	0.737 (0.275)	0.753 (0.275)	0.720 (0.275)	
	End of Part A	N	135	65	70	0.0848
		Mean (SD)	0.590 (0.311)	0.636 (0.314)	0.547 (0.305)	
Alcohol Use	Baseline	N	250	124	126	0.8857
		Mean (SD)	0.108 (0.125)	0.107 (0.121)	0.109 (0.130)	
	End of Part A	N	134	65	69	0.6605
		Mean (SD)	0.131 (0.121)	0.133 (0.123)	0.129 (0.119)	
Drug Use	Baseline	N	250	124	126	0.9027
		Mean (SD)	0.242 (0.076)	0.241 (0.081)	0.243 (0.070)	
	End of Part A	N	134	65	69	**0.0003**
		Mean (SD)	0.056 (0.066)	0.078 (0.079)	0.034 (0.041)	
Legal Status	Baseline	N	250	124	126	0.8438
		Mean (SD)	0.083 (0.108)	0.089 (0.124)	0.078 (0.091)	
	End of Part A	N	135	65	70	0.4931
		Mean (SD)	0.054 (0.082)	0.061 (0.093)	0.048 (0.071)	
Family/Social Status	Baseline	N	250	124	126	0.6553
		Mean (SD)	0.307 (0.204)	0.314 (0.206)	0.301 (0.203)	
	End of Part A	N	135	65	70	**0.0474**
		Mean (SD)	0.167 (0.174)	0.202 (0.202)	0.135 (0.137)	
Psychiatric Status	Baseline	N	250	124	126	0.6227
		Mean (SD)	0.132 (0.165)	0.135 (0.170)	0.129 (0.161)	
	End of Part A	N	135	65	70	0.1827
		Mean (SD)	0.042 (0.114)	0.058 (0.149)	0.028 (0.066)	

[1] P-Value from Van der Waerden test for treatment difference without adjusting for multiplicity
Source: ALK21-013 CSR Table 14.3.2

Table 29: Percent of Opioid-Free Weeks, Weeks 5–24

Site Number	Statistic	Placebo	VIVITROL
101	N	24	23
	Mean (SD)	51.0 (39.2)	78.7 (34.2)
	Median	45.0	95.0
	Min – Max	0 – 100	0 – 100
102	N	20	19
	Mean (SD)	44.5 (46.7)	74.7 (34.3)
	Median	20.0	95.0
	Min – Max	0 – 100	0 - 100
104	N	19	17
	Mean (SD)	57.9 (39.5)	47.9 (42.2)
	Median	70.0	25.0
	Min – Max	0 – 100	0 – 100
106	N	19	18
	Mean (SD)	35.8 (45.6)	55.3 (43.1)
	Median	0.0	65.0
	Min – Max	0 – 100	0 – 100
105	N	12	12
	Mean (SD)	34.6 (45.8)	51.3 (48.8)
	Median	0.0	60.0
	Min – Max	0 – 100	0 – 100
107	N	11	11
	Mean (SD)	40.5 (44.6)	61.8 (36.4)
	Median	20.0	55.0
	Min – Max	0 – 100	0 – 100
103	N	6	8
	Mean (SD)	30.0 (46.6)	95.6 (8.6)
	Median	0.0	100.0
	Min – Max	0 – 95	75 – 100
108	N	3	4
	Mean (SD)	91.7 (14.4)	95.0 (7.1)
	Median	100.0	97.5
	Min – Max	75 – 100	85 – 100
109	N	2	4
	Mean (SD)	45.0 (63.6)	40.0 (34.9)
	Median	45.0	40.0
	Min – Max	0 – 90	0 – 80
112	N	4	4
	Mean (SD)	38.8 (48.4)	18.8 (24.6)
	Median	27.5	10.0
	Min – Max	0 – 100	0 – 55
113	N	3	3
	Mean (SD)	85.0 (26.0)	71.7 (49.1)
	Median	100.0	100.0
	Min – Max	55 – 100	15 – 100
110	N	1	2
	Mean (SD)	0.0	50.0 (70.7)
	Median	0.0	50.0
	Min – Max	0 – 0	0 – 100

Table 29: Percent of Opioid-Free Weeks, Weeks 5–24 (Continued)

Site Number	Statistic	Placebo	VIVITROL
111	N		1
	Mean (SD)		95.0
	Median		95.0
	Min – Max		95 – 95

Source: ALK21-013 CSR Table 14.2.1.7

11. REFERENCES

Reference List

American Psychiatric Association (2000) Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision (DSM-IV-TR). Washington, DC

Birnbaum HG, White AG, Reynolds JL, Greenberg PE, Zhang M, Vallow S, Schein JR, Katz NP (2006) Estimated costs of prescription opioid analgesic abuse in the United States in 2001: A societal perspective. Clin J Pain 22:667-676

Brown LS, Jr., Kritz S, Goldsmith RJ, Bini EJ, Robinson J, Alderson D, Rotrosen J (2007) Health services for HIV/AIDS, HCV, and sexually transmitted infections in substance abuse treatment programs. Public Health Rep 122:441-451

Center for Substance Abuse Treatment (CSAT) (2004) A national assessment of methadone-associated mortality: Background briefing report. In: Curie CG, Clark HW eds. Substance Abuse and Mental Health Services Administration (SAMHSA) / US Department of Health and Human Services, Rockville, MD

Center for Substance Abuse Treatment (CSAT) (2005) Medication-assisted treatment for opioid addiction in opioid treatment programs: Treatment Improvement Protocol (TIP) Series #43. DHHS Publication No. (SMA) 05-4048. In: Batki SL, Kauffman JF, Marion I, Parrino MW, Woody GE eds. Substance Abuse and Mental Health Services Administration (SAMHSA) / US Department of Health and Human Services, Rockville, MD

Cornish JW, Metzger D, Woody GE, Wilson D, McLellan AT, Vandergrift B (1997) Naltrexone pharmacotherapy for opioid dependent federal probationers. J Substance Abuse Treat 14:529-534

Crits-Christoph P, Siqueland L, Blaine J, Frank A, Luborsky L, Onken LS, Muenz L, Thase ME, Weiss RD, Gastfriend DR, Woody G, Barber JP, Butler SF, Daley D, Bishop S, Najavits LM, Lis J, Mercer D, Griffin ML, Moras K, Beck AT (1997) The National Institute on Drug Abuse Collaborative Cocaine Treatment Study. Rationale and methods. Arch Gen Psychiatry 54:721-726

Curran S, Savage C (1976) Patient response to naltrexone: issues of acceptance, treatment effects, and frequency of administration. NIDA Res Monogr 9:67-69

Dijkstra BA, De Jong CA, Bluschke SM, Krabbe PF, van der Staak CP (2007) Does naltrexone affect craving in abstinent opioid-dependent patients? Addict Biol 12:176-182

Drug Abuse Warning Network (DAWN) (2010) Detailed tables: Drug-related emergency department visits for 2004-08 [website: https://dawninfo.samhsa.gov/data/default.asp].

Substance Abuse & Mental Health Services Administration (SAMHSA) / US Department of Health & Human Services,

Dunbar J, Turncliff R, Hayes S, Farrell C (2007) Population pharmacokinetics of extended-release injectable naltrexone (XR- NTX) in patients with alcohol dependence. J Studies Alcohol Drugs 68:862-870

Dunbar JL, Turncliff RZ, Dong Q, Silverman BL, Ehrich EW, Lasseter KC (2006) Single- and multiple-dose pharmacokinetics of long-acting injectable naltrexone. Alcohol Clin Exp Res 30:480-490

DURAMED (1984) REVIA: NDA No. 018932. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/index.cfm?fuseaction=Search.DrugDetails.

Fishman MJ, Winstanley EL, Curran E, Garrett S, Subramaniam G (2010) Treatment of opioid dependence in adolescents and young adults with extended release naltrexone: Preliminary case-series and feasibility. Addiction [Epub ahead of print]:

Ghany MG, Strader DB, Thomas DL, Seeff LB (2009) Diagnosis, management, and treatment of hepatitis C: An update. Hepatology 49:1335-1374

Gonzalez JP, Brogden RN (1988) Naltrexone. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of opioid dependence. Drugs 35:192-213

Guo S, Jiang Z, Wu Y (2001) Efficacy of naltrexone hydrochloride for preventing relapse among opiate-dependent patients after detoxification. Hong Kong J Psychiatry 11:2-8

Hollister LE, Bearman JE, Duster TS, Freedman DX, Gallant DM, Harris LS (1978) Clinical evaluation of naltrexone treatment of opiate-dependent individuals. Report of the National Research Council Committee on Clinical Evaluation of Narcotic Antagonists. Arch Gen Psychiatry 35:335-340

Hulse GK, Morris N, rnold-Reed D, Tait RJ (2009) Improving clinical outcomes in treating heroin dependence: randomized, controlled trial of oral or implant naltrexone., pp. 1108-1115

Hyman SM, Fox H, Hong KI, Doebrick C, Sinha R (2007) Stress and drug-cue-induced craving in opioid-dependent individuals in naltrexone treatment. Exp Clin Psychopharmacol 15:134-143

Johansson BA, Berglund M, Lindgren A (2006) Efficacy of maintenance treatment with naltrexone for opioid dependence: A meta-analytical review. Addiction 101:491-503

Jones ES, Moore BA, Sindelar JL, O'Connor PG, Schottenfeld RS, Fiellin DA (2009) Cost analysis of clinic and office-based treatment of opioid dependence: Results with methadone and buprenorphine in clinically stable patients. Drug Alcohol Depend 99:132-140

Joseph H, Stancliff S, Langrod J (2000) Methadone maintenance treatment (MMT): A review of historical and clinical issues. Mt Sinai J Med 67:347-364

Koob GF (2008) Neurobiology of addiction. In: Galanter M, Kleber HD eds. The American Psychiatric Publishing Textbook of Substance Abuse Treatment. American Psychiatric Press, Arlington, VA, p. 9

Korvick J (2008) Relistor™ (methylnaltrexone bromide) NDA #21-964: Summary Basis of Approval. Progenics Pharmaceuticals, Inc., Tarrytown, NY

Krupitsky EM, Zvartau EE, Masalov DV, Tsoi MV, Burakov AM, Egorova VY, Didenko TY, Romanova TN, Ivanova EB, Bespalov AY, Verbitskaya EV, Neznanov NG, Grinenko AY, O'Brien CP, Woody GE (2004) Naltrexone for heroin dependence treatment in St. Petersburg, Russia. J Subst Abuse Treat 26:285-294

Krupitsky EM, Zvartau EE, Masalov DV, Tsoy MV, Burakov AM, Egorova VY, Didenko TY, Romanova TN, Ivanova EB, Bespalov AY, Verbitskaya EV, Neznanov NG, Grinenko AY, O'Brien CP, Woody GE (2006) Naltrexone with or without fluoxetine for preventing relapse to heroin addiction in St. Petersburg, Russia. J Subst Abuse Treat 31:319-328

Ladewig D (1990) [Naltrexone--an effective aid in the psychosocial rehabilitation process of former opiate dependent patients]. Ther Umsch 47:247-250

Lerner A, Sigal M, Bacalu A, Shiff R, Burganski I, Gelkopf M (1992) A naltrexone double blind placebo controlled study in Israel. Isr J Psychiatry Relat Sci 29:36-43

Martin WR, Jasinski DR, Mansky PA (1973) Naltrexone, an antagonist for the treatment of heroin dependence. Effects in man. Arch Gen Psychiat 28:784-791

Mason BJ, Kocsis JH, Melia D, Khuri ET, Sweeney J, Wells A, Borg L, Millman RB, Kreek MJ (1998) Psychiatric comorbidity in methadone maintained patients. J Addict Dis 17:75-89

Mathers BM, Degenhardt L, Phillips B, Wiessing L, Hickman M, Strathdee SA, Wodak A, Panda S, Tyndall M, Toufik A, Mattick RP (2008) Global epidemiology of injecting drug use and HIV among people who inject drugs: A systematic review. Lancet 372:1733-1745

McAleer SD, Mills RJ, Polack T, Hussain T, Rolan PE, Gibbs AD (2003) Pharmacokinetics of high-dose buprenorphine following single administration of sublingual tablet formulations in opioid naive healthy male volunteers under a naltrexone block. Drug Alcohl Depend 72:75-83

Metzger DS, Navaline HA, Woody GE (2001) Assessment of substance abuse: HIV risk assessment battery (RAB). In: Carson-DeWitt R, Macmillan-Thomson G eds. Encyclopedia of Drugs, Alcohol, and Addictive Behavior.

Miller NS, Mahler JC, Gold MS (1991) Suicide risk associated with drug and alcohol dependence. J Addict Dis 10:49-61

Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A (2006) Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database Syst Rev 1:i-23

Narcotics Anonymous World Services Inc. (2007) NA groups and medication (Pamphlet No. 2205). Chatsworth, CA

National Institute on Drug Abuse (NIDA) (1976) Narcotic antagonists: The search for long-acting preparations. In: Willette RE ed. Research Monograph Series #4. National Institutes of Health (NIH) / US Department of Health and Human Services, Rockville, MD

National Institute on Drug Abuse (NIDA) (1986) Urine testing for drugs of abuse. In: Hawks RL, Chiang CN eds. Research Monograph Series #73. Alcohol, Drug Abuse, and Mental Health Administration / US Department of Health and Human Services, Rockville, MD

National Institute on Drug Abuse (NIDA) Treatment Workgroup (1997) Naltrexone: An antagonist therapy for heroin addiction. In: Tai B, Blaine J eds. National Institutes of Health (NIH) / US Department of Health and Human Services, Rockville, MD

National Institutes of Health (NIH) (2002) Management of hepatitis C. NIH Consens State Sci Statements 19:1-46

National Survey on Drug Use and Health (NSDUH) (2005) NSDUH Report: Nonmedical oxycodone users--A comparison with herion users. Substance Abuse and Mental Health Services Administration (SAMHSA) / US Department of Health and Human Services / Office of Applied Studies, Rockville, MD

Nestler EJ, Malenka RC (2004) The addicted brain. Sci Am 290:78-85

O'Brien CP, Greenstein RA, Mintz J, Woody GE (1975) Clinical experience with naltrexone. Am J Drug Alcohol Abuse 2:365-377

O'Connor PG (2005) Methods of detoxification and their role in treating patients with opioid dependence. JAMA 294:961-963

Obama BH (2010) 2010 National Drug Control Strategy. White House Office of National Drug Control Policy, Washington, DC

Rawson RA, Glazer M, Callahan EJ, Liberman RP (1979) Naltrexone and behavior therapy for heroin addiction. NIDA Res Monogr 25:26-43

Reckitt Benckiser Pharmaceuticals Inc. (2002) Suboxone® [buprenorphine HCL/naloxone HCl dihydrate sublingual tablets] package insert.

Resnick RB, Volavka J, Freedman AM, Thomas M (1974) Studies of EN-1639A (naltrexone): A new narcotic antagonist. Am J Psychiatry 131:646-650

Roxane Laboratories, Inc. (2002) Dolophine® Hydrochloride CII [Methadone hydrochloride tablets, USP] package insert. Columbus, OH

San L, Pomarol G, Peri JM, Olle JM, Cami J (1991) Follow-up after a six-month maintenance period on naltrexone versus placebo in heroin addicts. Br J Addict 86:983-990

Sandelowski M, Voils CI, Chang Y, Lee EJ (2009) A systematic review comparing antiretroviral adherence descriptive and intervention studies conducted in the USA. AIDS Care 21:953-966

Schottenfeld RS, Chawarski MC, Mazlan M (2008) Maintenance treatment with buprenorphine and naltrexone for heroin dependence in Malaysia: A randomised, double-blind, placebo-controlled trial. Lancet 371:2192-2200

Shufman EN, Porat S, Witztum E, Gandacu D, Bar-Hamburger R, Ginath Y (1994) The efficacy of naltrexone in preventing reabuse of heroin after detoxification. Biol Psychiatry 35:935-945

Smyth B, Hoffman V, Fan J, Hser YI (2007) Years of potential life lost among heroin addicts 33 years after treatment. Prev Med 44:369-374

Sobell LC, Sobell MB (1992) Timeline Follow-Back: A technique for assessing self-reported alcohol consumption. In: Litten RZ, Allen JP eds. Measuring Alcohol Consumption: Psychosocial and Biological Methods. The Humana Press, Totowa, NJ, pp. 41-72

Stella L, D'Ambra C, Mazzeo F, Capuano A, DelFranco F, Avolio A, Ambrosino F (2005) Naltrexone plus benzodiazepine aids abstinence in opioid-dependent patients. Life Sci 77:2717-2722

Stinson FS, Grant BF, Dawson DA, Ruan WJ, Huang B, Saha T (2005) Comorbidity between DSM-IV alcohol and specific drug use disorders in the United States: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. Drug Alcohol Depend 80:105-116 [Epub 2005 Apr 18]

Substance Abuse and Mental Health (SAMHSA) Data Archive (2007) Guidelines for the accreditation of opioid treatment programs. Department of Health and Human Services / Office of Applied Studies / Center for Substance Abuse Treatment (CSAT), Rockville, MD

Substance Abuse and Mental Health (SAMHSA) Data Archive (2009) Results from the 2008 national survey on drug use and health: National findings (NSDUH Series H-36, HHS Publication No. SMA 09-4434). Department of Health and Human Services / Office of Applied Studies, Rockville, MD

Substance Abuse and Mental Health Services Administration (SAMHSA) (2002) Report to Congress on the prevention and treatment of co-occurring substance abuse disorders and mental disorders. US Department of Health and Human Services, pp. 1-175

Substance Abuse and Mental Health Services Administration (SAMHSA) (2004) Mandatory guidelines and proposed revisions to mandatory guidelines for Federal workplace drug testing programs--Notices (Part III). Federal Register 69:19643-19673

Substance Abuse and Mental Health Services Administration (SAMHSA) (2007) National Survey of Substance Abuse Treatment Services (N-SSATS): 2007. Data on substance abuse

treatment facilities. DASIS Series: S-44, DHHS Publication No. (SMA) 08-4348 . Department of Health and Human Services / Office of Applied Studies, Rockville, MD

Substance Abuse and Mental Health Services Administration (SAMHSA), JBS International Inc. (2006) Diversion and abuse of buprenorphine: A brief assessment of emerging indicators [Final Report]. Department of Health and Human Services / Office of Applied Studies / Center for Substance Abuse Treatment, Rockville, MD

Verebey K, Volavka J, Mule SJ, Resnick RB (1976) Naltrexone: Disposition, metabolism, and effects after acute and chronic dosing. Clin Pharmacol Ther 20:315-328

Volavka J, Resnick RB, Kestenbaum RS, Freedman AM (1976) Short-term effects of naltrexone in 155 heroin ex-addicts. Biol Psychiatry 11:679-685

Warner M, Chen LH, Makuc DM (2009) Increase in fatal poisonings involving opioid analgesics in the United States, 1999-2006. National Center for Health Statistics (NCHS)Data Brief. US Department of Health and Human Services / Center for Disease Control and Prevention, pp. 1-8

White AG, Birnbaum HG, Mareva MN, Daher M, Vallow S, Schein J, Katz N (2005) Direct costs of opioid abuse in an insured population in the United States. J Manag Care Pharm 11:469-479