CLINICAL STUDY DISCLOSURE: APPROVAL OF REDACTED DOCUMENTS

Product: VIVITROL

Study No.: ALK21-014

Title: Efficacy and Safety of VIVITROL® in Adults Completing Inpatient Treatment for Alcohol Dependence

Redacted Documents: CSR Synopsis (06 Jul 2011)

Documents redacted by: Synchrogenix LLC

Functional Area	Signature	Date
Craig Hopkinson Chief Medical Officer and Executive Vice President, R&D	DocuSigned by: Signer Name: Craig Hopkinson Signing Reason: I approve this document Signing Time: 23-May-2022 | 8:48:55 PM EDT 053193E167294AB2B07FDCF8958E2AEF	23-May-2022
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Ling Wang Vice President, Biostatistics	DocuSigned by: Signer Name: Ling Wang Signing Reason: I approve this document Signing Time: 25-May-2022 | 8:17:22 AM EDT 5A2AAD7D06C84CAE80F3456C30D0FE8B	25-May-2022

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Margaret Caulfield Senior Director, R&D Counsel	DocuSigned by: Margaret A. Caulfield Signer Name: Margaret A. Caulfield Signing Reason: I approve this document Signing Time: 25-May-2022 | 9:01:01 AM EDT 8D25BF2ADA614B2E8ADA4B118EAD6EC9	25-May-2022
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Adam Simmons Senior Director, Clinical Program Management, Clinical Operations	DocuSigned by: Adam Simmons Signer Name: Adam Simmons Signing Reason: I approve this document Signing Time: 26-May-2022 | 2:02:29 PM EDT 9B219E09AC94400FBEA52A0D3D503805	26-May-2022

2. SYNOPSIS

Name of Sponsor/Company: Alkermes, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: VIVITROL® (naltrexone for extended-release injectable suspension)		
Name of Active Ingredient: naltrexone		

Study Title: Efficacy and Safety of VIVITROL® in Adults Completing Inpatient Treatment for Alcohol Dependence

Participating Investigators:

This was a multi-center study at 20 sites in Germany and Austria. A list of participating investigators is provided in Section 16.1.4.

Publications (reference):

none

Studied Period (years)	**Phase of Development:**
First subject dosed: 10 August 2007 Last subject out: 11 February 2011 (deemed lost to follow-up)	3b

Objectives

Primary:

- To evaluate the clinical efficacy of 12 weeks of treatment with VIVITROL (naltrexone for extended-release injectable suspension, 380 mg) vs. placebo administered to adults every 4 weeks upon discharge from inpatient treatment for alcohol dependence.

Secondary:

- To evaluate the clinical safety and efficacy of VIVITROL administered every 4 weeks in the treatment of alcohol dependent adults as assessed by secondary and exploratory endpoints.
- To assess longer-term safety, durability of effect, and health economic measures.

Endpoints

Primary Efficacy Endpoint

- Response rate based on percent heavy drinking days during the blinded treatment period.

Secondary Efficacy Endpoints

- Response profiles for the percent days abstinent
- Percent days with heavy drinking
- Percent of subjects with no heavy drinking
- Days to first drinking day
- Days to first heavy drinking day
- Obsessive Compulsive Drinking Scale (OCDS) scores

- Gamma glutamyl-transferase (GGT) levels
- Re-admittance to hospital during treatment for drinking

Exploratory Efficacy Endpoints

- Number of drinks per day
- Number of drinks per drinking day
- Adrenocorticotropic hormone (ACTH) levels
- Cortisol levels
- Responses to questionnaires:
  - Global Assessment of Functioning (GAF)
  - Fagerstrom Test for Nicotine Dependence (FTND)
  - EuroQol Health Outcomes (EQ-5D)
  - SF-36v2® Health Survey (SF-36)
  - Short Inventory of Problems (SIP)

Safety Endpoints

- Treatment emergent adverse events (TEAEs)
- Changes in laboratory test results
- Vital signs
- Electrocardiogram (ECG) results

Methodology

This was a Phase 3b randomized, placebo-controlled, multi-center study conducted in two parts—Part A and Part B. All subjects were in the process of inpatient treatment for alcohol dependence prior to entering the study.

Part A was a double-blind, placebo-controlled assessment of safety and efficacy. Subjects were administered VIVITROL 380 mg or placebo by intramuscular (IM) injection every 4 weeks for a total of 3 injections. Randomization was 1:1 (VIVITROL:placebo) and stratified by site.

Part B was an open-label extension to assess longer-term safety, durability of effect, and health economics during which subjects received an injection of VIVITROL 380 mg every 4 weeks for an additional nine months of treatment.

Over the course of the entire study, subjects were to attend 16 scheduled visits over approximately 12 months. Subjects who discontinued from the study prematurely were encouraged to return for an early termination visit. If, in the opinion of the investigator, it was necessary to monitor the subject beyond the early termination visit for safety reasons, provisions were made to extend the follow-up period accordingly. Subjects who discontinued treatment prematurely were also encouraged to continue providing drinking data (via Timeline FollowBack (TLFB) method [Sobell and Sobell 1992]) and answers to health economic questions monthly (by telephone) throughout the planned duration of the study.

Number of Subjects (planned and analyzed):

Planned for enrollment: approximately 300 subjects

Number of Subjects	Part A	Part B
Randomized	303	not applicable
Dosed	300	189
Analyzed	300	189

Main Criteria for Subject Inclusion:

- Diagnosis of alcohol dependence, meeting at least 5 of the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision (DSM-IV-TR) criteria.
- Aged 18 to 65 years, inclusive, at the time of consent.
- Expected to complete inpatient treatment for alcohol dependence within 24 hours of randomization.
- Seven to 21 days, inclusive, inpatient treatment for alcohol dependence prior to first dose.
- Free of symptoms and/or signs of acute alcohol withdrawal at the time of randomization.

Study Treatment (including dose, mode of administration, and batch numbers)

VIVITROL (naltrexone for extended-release injectable suspension) 380 mg or placebo by IM injection. The VIVITROL batch numbers used during Part A of the study were 422-1156BA, 422-2276AA, 422-0097AA, 422-3098AA; batch numbers used during Part B of the study were 402-0158AA and 402-1138AA. Placebo used during Part A of the study was from batch numbers 423-0416BA and 423-2927AA.

Duration of Treatment:

The study duration for each subject was approximately 12 months.

Criteria for Evaluation

Efficacy:

- Self-reported drinking data, collected using the TLFB method
- OCDS
- Alcohol Dependence Scale (ADS)
- Alcohol Severity Index (ASI)—family history component only
- Treatment goal
- Beck Depression Inventory (BDI)
- FTND
- SF-36v2
- EQ-5D
- GAF
- SIP

Safety:

Treatment emergent adverse events (TEAEs), vital signs, laboratory findings (ie, blood chemistry, hematology, urinalysis), physical examinations.

Health Economics:

Productivity loss (indirect costs) was assessed by the days of work lost. Resources used (direct costs) were assessed by:

- Inpatient stays (including rehabilitation inpatient stays)
- Emergency room visits
- Outpatient treatment (including physician visits, psychotherapy)
- Transport
- Medication
- Medical Management

Statistical Methods (data analysis):

Efficacy

The assessment of efficacy was based on the full analysis set (FAS) population, defined for this study as all eligible subjects who were randomized and received at least one dose of study drug.

Primary Endpoint

The primary endpoint to evaluate efficacy was the response rate based on percent heavy drinking days during the blinded treatment period. A heavy drinking day was defined as 4 or more alcohol drinks in one day for females, and 5 or more alcohol drinks in one day for males. Heavy drinking rate was defined as the number of heavy drinking days divided by the number of days with drinking data per subject. Subjects with missing drinking data at the end of the period were assigned their heavy drinking rate at baseline. Intermittent missing drinking data were not imputed. Response profiles were generated for each treatment group. Treatment difference was tested during the double-blind period (ie, Part A) with Van der Waerden test.

Secondary Endpoints

Similar to the analysis of heavy drinking days, response profiles for the percent of days abstinent were generated by treatment group for Part A and Part B and compared for the double-blind period with Van der Waerden test.

The percent of subjects with no heavy drinking days was defined as the percent of subjects who did not indicate any days where the amount of alcohol consumed qualified as a heavy drinking day (ie, heavy drinking day rate of zero). Days to first drinking day and days to first heavy drinking day were presented using a Kaplan-Meier curve and compared using Cox proportional hazard models.

The proportion of subjects without heavy drinking during the 12-week double blind period (ie, subjects with percent heavy drinking days Part A = 0) was tabulated. Relative risk (VIVITROL vs. placebo) was calculated along with 95% confidence limits. Statistical significance of the treatment difference was assessed using a chi square test.

OCDS scores and GGT levels were summarized by visit and compared using the Van der Waerden test.

The rate of patients hospitalized post-baseline for drinking related reasons during either Part A or Part B was summarized by period and treatment group and tested using a chi-squared test for hospitalizations that occurred in Part A. Patients who were hospitalized were included if the terms alcohol and/or relapse were used to describe the hospitalization event. Time to rehospitalization was summarized by treatment for events occurring in Part A using Kaplan-Meier analysis and compared using the log-rank test.

Exploratory Endpoints

Numbers of drinks per day and number of drinks per drinking day were analyzed in a similar fashion as responses to questionnaires (GAF, FTND, EQ-5D, SF-36v2, and SIP) and were summarized by visit using available data and compared using a chi-square and Van der Waerden tests for categorical and

continuous variables, respectively.

Safety

Safety was analyzed using TEAEs, changes in laboratory test results, vital signs, and ECGs. Reported adverse event (AE) terms were coded using MedDRA preferred terms and system organ classes. For European Union safety reporting purposes, serious adverse events (SAEs) were coded using MedDRA lower level terms.

Health Economics

Health economics data has been collected, but has not yet been analyzed. An addendum to this report will be submitted at a later date.

Sample size Considerations:

The power projection of this study was based on the heavy drinking rates in the first 12-week period of the subgroup of subjects with baseline abstinence of the 24-week, double blind, placebo control study, ALK21-003. Assuming similar treatment response, 150 patients per group would provide approximately 90% power to detect the treatment difference with a 2-sided rank-sum test with 5% significance level.

RESULTS SUMMARY

Of the 303 subjects randomized for the double-blind period of the study, 300 received at least 1 dose of study drug. Two subjects PPD were not dosed, because they were randomized in error. One subject was inadvertently randomized twice, receiving 2 subject numbers (but was not dosed as 2 subjects). Of the 300 subjects who received at least 1 dose of study drug, 148 were randomized to receive placebo and 152 were randomized to receive VIVITROL 380 mg.

A total of 99 (66.9%) subjects in the placebo group and 90 (59.2%) in the VIVITROL group completed Part A and entered Part B. Reasons for early study discontinuation during the double-blind period of the study were relatively evenly distributed between treatment groups. Most subjects who discontinued from the study early were withdrawn due to AEs (10.8% for placebo, 15.1% for VIVITROL) or they were lost to follow-up (12.8% for placebo, 13.8% for VIVITROL).

For the purposes of this report, subjects who "switched" from placebo during Part A to VIVITROL in Part B are described as being in the "placebo-to-VIVITROL" group. Subjects who received VIVITROL in both Part A and Part B are described as being in the "VIVITROL-to-VIVITROL" group.

A total of 48 subjects (32.4%) in the placebo-to-VIVITROL group completed the entire study compared with 37 subjects (24.3%) in the VIVITROL-to-VIVITROL group.

Efficacy Results

Primary Efficacy Endpoint--Percent Heavy Drinking Days

There was a marked decrease in percent heavy drinking days during Part A compared with baseline values (mean of 67.7 vs. 18.8%, respectively). There were similar reductions in both placebo and VIVITROL treatment groups (-49.3 vs. -48.4 average decrease, respectively; p=0.334). A decrease in percent heavy drinking days was maintained during Part B compared with baseline values, though the decrease during Part B was not as low when compared to Part A, indicating some return to heavy drinking.

Secondary Efficacy Endpoints

Re-admission to Hospital during Treatment for Drinking

During Part A, a significantly lower rate of rehospitalization was observed for the VIVITROL group, in comparison with the placebo group (13.82 vs 22.97%, respectively; p=0.040). This observation would be consistent with the presence of a treatment effect in the subgroup of patients with more significant drinking. This treatment effect may be obscured in the entire study population of low alcohol consumers is analyzed.

Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints included:

- Percent of days abstinent from drinking
- Percent of subjects with no heavy drinking days
- Days to first heavy drinking day
- Days to first drinking day
- OCDS scores
- GGT values

Overall, subjects in both groups in this study had very low rates of drinking during the study period, with a median of 0.3 drinks per day among all subjects during the double blind period. While changes from baseline were observed for each of these endpoints, they occurred with both VIVITROL and placebo treatment. No meaningful differences between VIVITROL and placebo were observed for any of the secondary endpoints listed above.

Exploratory Endpoints

Exploratory endpoints included:

- Number of drinks per day
- Number of drinks per drinking day
- ACTH and cortisol values
- Questionnaire scores (GAF, EQ-5D, SF-36v2, SIP, and FTND)

While changes from baseline did occur, no meaningful differences from placebo were observed for any exploratory efficacy endpoint.

Safety Results

Safety assessments indicated that VIVITROL was generally well tolerated in this population of adults with alcohol dependence. There were no deaths reported. Most AEs were mild or moderate in intensity, and the type and incidence of AEs appeared to be evenly distributed among the 2 treatment groups. The most common SAE was rehospitalization for alcoholism, which reflects the standard of care in Germany and Austria. The most common AEs during the double-blind phase of the study included: injection site pain, alcoholism, headache, nasopharyngitis, nausea, fatigue, sleep disorder, depression/depressed mood, back pain, dizziness, pain in extremity, diarrhea, arthralgia, and injection site induration. Aside from alcoholism, which was reported for 27% of placebo subjects vs 16% of VIVITROL subjects, the incidence of these common AEs was similar in both treatment groups.

No overall clinically significant changes in hematology values were observed for either treatment group in Part A or Part B. While mean increases in eosinophil counts were observed in VIVITROL-treated subjects in Part A and Part B, only 3 subjects had individual values that were deemed clinically significant by the investigator. These were reported as AEs (1 non-serious AE, and 2 SAEs of eosinophilia). Mean decreases in platelet counts were observed for both placebo- and VIVITROL-treated subjects during the study with no significant differences between treatment groups in Part A or Part B. One AE of thrombocytopenia was reported for a subject in the placebo group. The event was deemed probably not related by the investigator, and no AEs related to bleeding disorders were noted.

No significant differences in ALT or AST were observed between the treatment groups in Part A or Part B of this study. Decreases in ALT were observed to similar degrees in both treatment groups in Part A and Part B. Subjects who entered the study with elevated liver enzymes were unlikely to progress to elevations more than 3 times the upper limit of normal in any treatment group.

While changes in total bilirubin and CPK values were observed for both placebo- and VIVITROL-treated subjects during the study, there were no clinically significant trends. Similar increases in mean

total bilirubin were observed for both treatment groups in Part A and Part B that were not clinically significant. As frequently seen in this patient population, there was a large degree of variability in CPK values at all time points but no clinically significant differences between treatment groups.

OVERALL CONCLUSIONS

There was a significant decrease in all measures of drinking during Part A compared with baseline values. However, there were reductions in both placebo and VIVITROL treatment groups, and measures of drinking behavior were similar in the VIVITROL and placebo groups.

The primary endpoint, the response rate based on percent heavy drinking days during the double blind treatment period, was similar in the VIVITROL-and placebo-treated groups. There was a significant increase in percent days abstinent from drinking during Part A compared with baseline values, but again increases were similar in both placebo and VIVITROL treatment groups.

These results may have been influenced by the overall very low rate of heavy drinking in this study compared to previous VIVITROL clinical trials. For example, the median rate of heavy drinking in Study ALK21-003 was 19.8% for placebo subjects, and 10.2% for VIVITROL subjects, compared to median rates of 1.2% and 2.5% for placebo and VIVITROL subjects in the current study We speculate that this very low rate of heavy drinking contributed to the inability to demonstrate a treatment effect. The long pretrial period of hospitalization (28 days per the protocol) and abstinence, combined with ongoing psychosocial therapy, had a very large effect on drinking behaviors.

Importantly, a significantly lower rate of rehospitalization was observed for the VIVITROL group, in comparison with the placebo group (p=0.040). This would be consistent with a treatment effect for those with more significant drinking, that is obscured in the entire sample of low alcohol consumption during the double blind phase.

As expected from the drinking results, differences between treatment groups were not observed in the exploratory questionnaire responses.

Safety findings in this study were consistent with the overall safety profile seen in previous VIVITROL clinical trials. There were no deaths. The most common serious adverse event was rehospitalization for alcoholism, which reflects the standard of care in Germany and Austria. The most common adverse events reported herein, have been seen in previous clinical trials with VIVITROL, with some more subjective AEs such as nausea being reported at a lower frequency in this study. The observed changes in laboratory values are consistent with those seen in previous VIVITROL clinical trials. Both the adverse event profile and laboratory findings seen in this study are consistent with the current VIVITROL Package Insert.

Date of report: 6 July 2011

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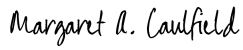
Margaret A. Caulfield Margaret.Caulfield@alkermes.com Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signed by link sent to Margaret.Caulfield@alkermes.com Signature ID: 8D25BF2A-DA61-4B2E-8ADA-4B118EAD6EC9 Using IP Address: 108.49.24.235 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 5/23/2022 9:54:39 AM Viewed: 5/23/2022 11:06:48 AM Signed: 5/25/2022 9:01:05 AM
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