CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-897
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Indication(s):	Treatment of alcohol dependence
Applicant:	Alkermes, Incorporated
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Table of Contents

1 EXECUTIVE SUMMARY 3

1.1 CONCLUSIONS AND RECOMMENDATIONS 3
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES 3
1.3 STATISTICAL ISSUES AND FINDINGS 4

2. INTRODUCTION 6

2.1 OVERVIEW 6
2.2 DATA SOURCES 6

3. STATISTICAL EVALUATION 7

3.1 EVALUATION OF EFFICACY 7
3.2 EVALUATION OF SAFETY 20

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS 21

4.1 GENDER, RACE AND AGE 21
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS 21

5. SUMMARY AND CONCLUSIONS 23

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE 23
5.2 CONCLUSIONS AND RECOMMENDATIONS 24
5.2.1 Labeling 24

APPENDICES 27

DYNAMIC RANDOMIZATION ALGORITHM 28
SUMMARY OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS 31
STATISTICAL FORMULATION OF MODEL 35
RE-RANDOMIZATION ANALYSIS RESULTS 37
EXPLORATION OF PATIENT DISCONTINUATION 38
ANALYSES REPEATED USING ALTERNATE DEFINITION OF A HEAVY DRINKING DAY 40

1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Alkermes, Incorporated proposes Medisorb Naltrexone for the treatment of alcohol dependence. Based on an evaluation of the event rate of heavy drinking over 24 weeks, the applicant claims that Medisorb Naltrexone 380 mg reduces heavy drinking. My review of the statistical evidence suggests support for the claim. However, I believe that several additional factors warrant consideration when assessing Medisorb Naltrexone. First, protocol violations were identified at two of the three sites inspected by the Division of Scientific Investigations. Alkermes' failure to identify these violations prior to the submission of the NDA diminished my confidence in the overall conduct of the study and resulting data. Furthermore, analyses of the data including and excluding the sites with violations resulted in inconsistent findings further adding to my concern. Since support for Medisorb Naltrexone was derived from a single study, there was no replication of the findings to provide additional assurance. Lastly, multiple safety concerns, such as elevated transaminases and severe allergic reactions, were identified by the review team. While there is statistical evidence that the drug is active, the previously mentioned factors must be assessed collectively by the review team in order to evaluate the risks and benefits of Medisorb Naltrexone. In my opinion, this task is further complicated by the uncertainty surrounding the overall conduct of the study and resulting data.

1.2 Brief Overview of Clinical Studies

Oral naltrexone is approved for the management of alcohol dependence. Alkermes proposes an injectable depot formulation of naltrexone, namely Medisorb Naltrexone. The applicant asserts that Medisorb Naltrexone provides continued exposure for at least a month and may reduce the potential for hepatotoxicity associated with the oral formulation. The drug was introduced to the Division of Anesthesia, Analgesia, and Rheumatology Products via IND 61,138. The clinical development plan, endpoints, and statistical analyses were discussed during several meetings between the applicant and the division.

Prior to submission of the NDA, the applicant sought input from the division regarding the needed number of studies. At that time, the applicant proposed a single study to support the use of the drug. The division stated that two adequate and well-controlled studies were necessary unless the application was submitted under Section 505(b)(2) of the Food, Drug, and Cosmetic Act. On 31 March 2005, Alkermes submitted NDA 21-897 (pursuant to Section 505(b)(2)) in support of Medisorb Naltrexone. The application included a single, double-blind, placebo-controlled, multi-center study and relied on the agency's previous findings of efficacy for oral naltrexone. In the study, patients were randomized to intramuscular injections of Medisorb Naltrexone 190 mg, Medisorb Naltrexone 380 mg, or placebo. Patients randomized to placebo received a matching volume of Medisorb microspheres (i.e. 2 mL or 4 mL) without naltrexone.

Moreover, patients were allocated to treatment for balance on four baseline characteristics using a dynamic randomization scheme. Treatment was administered, along with biopsychosocial support therapy (using the BRENDA approach), during clinic visits occurring every four weeks for the duration of 24 weeks. Patients recorded their alcohol consumption using the timeline follow-back method (TLFB). The primary measure of efficacy was the event rate of heavy drinking over 24 weeks of treatment where a heavy drinking day was defined as a day on which a man consumed at least five drinks or a woman consumed at least four drinks. The applicant defined the event rate as the number of heavy drinking days divided by the number of days at risk for heavy drinking. Additionally, an alcoholic drink was defined as 13.6 grams of absolute ethanol. The applicant employed a stratified Andersen-Gill model for the primary analysis.

1.3 Statistical Issues and Findings

Since the event of interest (i.e. heavy drinking) could potentially occur on multiple days, the applicant employed an Andersen-Gill model to assess the overall effect of treatment. In general, the results produced by the model may be influenced by the non-proportionality of the hazard functions and/or by patient withdrawal that is treatment related. Thus prior to the submission of the NDA, the Division recommended that the applicant consider and propose methodology for use in the event that the proportional hazards (PH) assumption was seriously violated. Moreover, the applicant was urged to conduct a re-randomization test to validate the model inferences. The division additionally suggested the applicant justify and specify how missing data would be handled. To address the former recommendation regarding the PH assumption, the applicant used a stratified Andersen-Gill model. According to the applicant, "A stratified analysis adjusted for different baseline 'hazards' of the prespecified stratification factors. In this way, the treatment effect was not subject to the distortion that a covariate-by-time interaction would induce by inclusion of such a covariate in the model." The applicant additionally proposed a nonparametric Wilcoxon test as an alternative method of analysis if the PH assumption was violated. Alkermes formally tested the assumption by inclusion of an interaction term in the model. To address potential missing data concerns, Alkermes assessed the randomness of the missing data via evaluations of the event rate of heavy drinking by the number of doses received, the Kaplan-Meier curves, and a pattern mixture model.

According to the applicant, there was evidence of a severe violation of the proportional hazards assumption, both overall and for some strata. Additionally, the applicant stated that the re-randomization test based on the stratified Andersen-Gill model produced unstable results because of the small sizes of some of the strata. Based on the evaluation of drop-outs, the applicant concluded that study discontinuations were comparable across treatment groups and were therefore less likely to affect conclusions. I was not convinced that the violation of the proportional hazards could be ignored, nor was I convinced that the missing data occurred randomly. Thus, I focused significant attention on the nonparametric analysis. The nonparametric analysis conducted by the applicant essentially employed a last observation carried forward strategy for missing data. Since I had some concern regarding the possibility that patients withdrew for treatment-related reasons, I performed an additional analysis imputing heavy drinking days for all missing data days. My collective evaluation of the analyses and results suggested the existence of a treatment effect for the 380 mg dose of Medisorb Naltrexone.

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