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ALK21-002 SYNOPSIS

Study Title:	A Phase Ib Evaluation of the Safety and Pharmacokinetics of Repeat Dose Administration of Medisorb® Naltrexone in Alcohol Dependent Patients	
Study Number:	ALK21-002	
Product Name:	Medisorb® Naltrexone	
Active Ingredient:	naltrexone	
Indication:	alcohol dependence	
Name of Sponsor:	Alkermes, Inc. 88 Sidney Street, Cambridge, MA 02139 USA	
Investigators:	<u>Principal Investigators:</u> Bankole A. Johnson, MD, PhD; Richard V. Guzzetta, MD; Willen (Wim) Van den Brink, MD, PhD; Prof. Henri-Jean Aubin This study was conducted at 2 sites in the United States and 2 sites in Europe.	
Publication:	Johnson BA, Ait-Daoud N, Aubin HJ, Van Den Brink W, Guzzetta R, Loewy J, Silverman B, Ehrich E. Alcohol Clin Exp Res. 2004 Sep;28(9):1356-61.	
Study Period:	First Dose Administered: 15 March 2001 Last Dose Administered: 16 August 2001	Clinical Phase: Ib
Objectives:	<u>Primary Objective:</u> To evaluate the safety and tolerability of repeat intramuscular (IM) administration of Medisorb Naltrexone over a 4-month period in DSM IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) alcohol dependent adults. <u>Secondary Objectives:</u> (1) To assess repeat-dose trough concentrations (predose) of naltrexone and 6 β -naltrexol; and (2) To assess data collection methodology including outcome measures related to drinking activity.	

METHODS

Study Design: This was a multi-center, randomized, double-blind, placebo-controlled, study in which DSM IV alcohol dependent subjects received an IM injection of study drug every 28 days. A total of 4 injections were administered over the course of the study. Subjects received either Medisorb Naltrexone (400 mg) or placebo. Treatments were randomly assigned in a 5:1 (active:placebo) ratio. Psychosocial support was offered to subjects in both treatment groups; US sites used the BRENDA approach, European sites used the best common practice.

Potential subjects were screened within 7 days prior to Day 0. At Day 0, eligible subjects were administered the first dose of study drug; additional doses were administered on Days 28, 56, and 84. Blood samples for determination of trough concentrations of naltrexone and 6 β -naltrexol, the primary metabolite, were collected predose on Days 0, 28, 56, and 84. Subjects returned for 2 additional visits, 1 and 2 months after the final dose of study drug; safety and pharmacokinetic assessments were performed at these 2 follow-up visits. Psychosocial support was offered at each study visit.

Number of Subjects: 30 subjects were randomized and received study drug; 21 completed the study.

Diagnosis and Criteria for Inclusion: The study population included adults with a diagnosis of DSM IV alcohol dependence, who had a stable address and telephone number, and who provided written informed consent to participate in all aspects of this study. Qualified subjects did not have any clinically significant medical condition or laboratory abnormality at the screening visit, and had not participated in a clinical trial within the previous 90 days. Subjects dependent on benzodiazepines, opiates or cocaine (by DSM IV criteria) were excluded, as were those with psychosis. Pregnant or nursing women were excluded. Women of childbearing potential were required to use an approved method of contraception.

Test Product, Dose, Mode of Administration, Lot No(s): Medisorb Naltrexone, 400 mg, administered as a dorsogluteal IM injection every 28 days. The lot numbers for Medisorb Naltrexone were: 192-2570A, 192-2630A, 192-3000A, and 192-3050A.

Reference Therapy, Dose, Mode of Administration, Batch No(s): Placebo for Medisorb Naltrexone was administered as a dorsogluteal IM injection every 28 days. The lot number for Placebo was 198-2800A

Duration of Treatment: Subjects received 400 mg Medisorb Naltrexone or a matching volume of placebo every 28 days for a total of 4 doses, administered over a 3 month period. Because of the extended release nature of the study drug, duration of exposure for the entire study period is anticipated to be approximately 4 months. In addition, follow-up visits occurred 1 and 2 months after the final dose. The period from first dose to final follow up visit was approximately 5 months.

Criteria for Evaluation:

Safety:

The main parameters for evaluating safety were the incidence of adverse events, injection site assessment findings, physical examination findings, and abnormal laboratory tests from all subjects.

Pharmacokinetics:

Pharmacokinetic parameters were based on trough plasma concentrations of naltrexone and 6 β -naltrexol.

Efficacy / Data Collection on Drinking Outcomes:

There was no formal efficacy evaluation in this study. However, an analysis of outcome measures related to drinking activity was conducted. Outcome measures included the Social Functioning Health Survey Questionnaire (SF-36™) and drinking data obtained using Time Line Follow-Back (TLFB) methodology.

Statistical Methods: The analysis was descriptive; no formal statistical tests were performed. In general, summary statistics by treatment were provided for all variables. Source data for the summary tables and figures are provided in subject data listings.

RESULTS

A total of 107 injections were administered to 30 subjects. 24 subjects received all 4 injections (20 in the Medisorb Naltrexone group; 4 in the placebo group).

Safety and Tolerability:

No serious adverse events occurred. Incidence of the most common adverse events was similar for Medisorb Naltrexone and placebo.

The most common adverse events considered related to Medisorb Naltrexone were headache (4), nausea (6), and dry mouth (6). Headache (1) and nausea (1) were considered related to placebo.

Two subjects, both in the Medisorb Naltrexone group, discontinued the study due to an adverse event (injection site induration, angioedema).

Pharmacokinetics:

Prior to injection #2, the mean trough plasma naltrexone concentration was 1.23 ng/mL, which remained relatively constant for the remainder of the study.

Trough 6 β -naltrexol concentrations were slightly higher than observed for naltrexone (mean concentration prior to injection #2 = 2.91 ng/mL), and did not increase significantly with subsequent doses.

Efficacy / Data Collection on Drinking Outcomes:

Drinking data collected during this study were compatible with data previously reported in the literature. There was no significant missing data, and subject retention rates were within expected ranges.

Conclusions:

- Medisorb Naltrexone 400 mg was safe and generally well tolerated over a 4-month treatment period.
 - Mean trough naltrexone and 6 β -naltrexol concentrations were approximately 1 and 3 ng/mL, respectively.
 - The ability to capture drinking information using the TLFB instrument was confirmed. The methods used in this study can be applied to a larger, pivotal trial.
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GCP Compliance: Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. The Alkermes commitment is compliance with this standard to provide assurance that the rights, safety and well being of trial subjects will be protected, consistent with the principles that have their origin in the Declaration of Helsinki.

Date of the Report: January 15, 2004
