2. Synopsis

MERCK RESEARCH LABORATORIES MK-0594 Serlopitant, Tablet Treatment of Alcohol Dependence in Adults	**CLINICAL STUDY REPORT SYNOPSIS**	
PROTOCOL TITLE/NO.: A Phase II Multicenter, Randomized, Double-Blind, Two-Stage Clinical Trial to Evaluate the Efficacy and Safety of MK-0594 in Patients With Alcohol Dependence		#020
PROTECTION OF HUMAN SUBJECTS: This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research. For study audit information see [16.1.8].		
INVESTIGATOR(S)/STUDY CENTER(S): This study was performed in 11 study centers in the United States and 15 study centers Ex-US. A list of investigators and study centers is provided in [16.1.3.1; 16.1.4].		
PUBLICATION(S): Not applicable.		
PRIMARY THERAPY PERIOD: (11-MAR-2009) – (24-FEB-2010)	**CLINICAL PHASE:**	IIa
DURATION OF TREATMENT: During the Randomization visit (Visit 2), a loading dose equal to 3 times the assigned daily dose of MK-0594 (or placebo) was administered. MK-0594 5 mg or matching placebo was taken orally once a day. Patients returned for follow-up visits at 2, 4, 8, and 12 weeks after randomization [16.1.1]. Study was terminated early for administrative reasons on 05-Feb-2010 and treatment of on-going patients was truncated at the time of study termination.		
PRIMARY OBJECTIVE(S): (1) To evaluate the efficacy of MK-0594 in maintaining absence of heavy alcohol drinking (as defined by consumption of at least 5 standard drinks for men and 4 standard drinks for women; a standard drink is 15 ml absolute alcohol) over weeks 3 to 12 of a 12-week treatment period using the Timeline Follow back Interview (TLFB). (2) To evaluate the safety and tolerability of MK-0594 over a 12-week treatment period. **Hypothesis:** (1) MK-0594 is superior to placebo in maintaining absence of heavy drinking over weeks 3 to 12 of a 12-week treatment period. The criteria for determining superiority in patients with alcohol dependence or in patients with alcohol dependence and high-trait anxiety are found in the Data Analysis Section 3.5 of the protocol. (2) MK-0594 is well tolerated over a 12-week treatment period.		
SECONDARY OBJECTIVE: To evaluate the efficacy of MK-0594 in maintaining abstinence from drinking over weeks 3 to 12 of a 12-week treatment period using the TLFB interview. **Hypothesis:** MK-0594 is superior to placebo in maintaining abstinence from drinking over weeks 3 to 12 of a 12-week treatment period. [16.1.1]		
STUDY DESIGN: This was a multi-center, randomized, double-blind (with in-house blinding), placebo-controlled, outpatient, two-stage, parallel-group trial. Eligible patients with a DSM-IV-TR diagnosis of alcohol dependence (based on the MINI International Neuropsychiatric Interview; MINI 5.0.0) were randomized in a double-blind fashion in a 1:1 ratio to one of two treatments for 12-weeks: A) MK-0594 5 mg or B) matching placebo taken orally once a day. During the Randomization visit (Visit 2), a loading dose equal to 3 times the assigned daily dose of MK-0594 (or placebo) was administered. Patients returned for follow-up visits at 2, 4, 8, and 12 weeks after randomization. [16.1.1]		

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CLINICAL STUDY REPORT SYNOPSIS
-2-

SUBJECT/PATIENT DISPOSITION:

	MK-0594 5 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
SCREENING FAILURES:					100	
RANDOMIZED:	77		85		162	
Male	48	(62.3)	65	(76.5)	113	(69.8)
Female	29	(37.7)	20	(23.5)	49	(30.2)
Age range	22 to 66		23 to 69		22 to 69	
COMPLETED:	29	(37.7)	29	(34.1)	58	(35.8)
DISCONTINUED:	48	(62.3)	56	(65.9)	104	(64.2)
Clinical adverse experience	2	(4.2)	1	(1.8)	3	(2.9)
Withdrew Consent	2	(4.2)	6	(10.7)	8	(7.7)
Lost to Follow Up	6	(12.5)	2	(3.6)	8	(7.7)
Trial Terminated	38	(79.2)	46	(82.1)	84	(80.8)
Physician Decision	0	(0.0)	1	(1.8)	1	(1.0)

Data Source: [16.1.7.1; 16.2.1.1; 16.2.4.1]

DOSAGE/FORMULATION NOS.: MK-0594 1 mg and 5 mg oral tablets and matching placebo. [16.1.1]

DIAGNOSIS/INCLUSION CRITERIA: A patient was eligible to participate in this study if all of the following criteria applied.

1. Patient was male or female at least 21 years of age or older at Screening.
2. Patient had a DSM-IV-TR diagnosis of alcohol dependence (not in remission), and alcohol addiction was the patient's primary complaint among substance use disorders.
3. Patient had at least two heavy drinking days in the previous month, as defined by consumption of at least 5 standard drinks for men and 4 standard drinks for women. A standard drink was 0.5 oz (15 ml) absolute alcohol, equivalent to 10 oz beer (300 ml), 4 oz wine (120 ml), or 1 oz (30 ml) 100-proof liquor.
4. Patient expressed the desire to stop drinking alcohol and had achieved at least 3 days of abstinence from alcohol immediately prior to the randomization visit. If the patient met all inclusion/exclusion criteria except for 3 days of abstinence, then the patient was given the opportunity and additional time to attain abstinence, with provision of medical detoxification if necessary at any time during abstinence.
5. Patients had negative urine toxicological screen for opiates, stimulant, and sedative-hypnotics, unless medically prescribed. Urine toxicology was allowed to be repeated (at the initial screening visit or at a second screening visit).
6. If applicable, dose of medically prescribed daily psychotropic medications had been unchanged for at least four weeks prior to the initial screening visit.
7. Patient was:
   a. of reproductive potential and agreed to maintain true abstinence or used (or their partner used) one of the listed highly effective methods of birth control within the projected duration of the study.
8. Patient understood the study procedures, alternative treatments available, and risks involved with the study, and voluntarily agreed to participate in the study by giving written informed consent.
9. Patient had stable residence in the 2 months prior to screening visit (Visit 1), no unresolved legal problems that would impact participation in the study, had reasonable transportation arrangements to the study site and had no plans to move for the study duration.

10. Patient was willing and able to comply with the study procedures and visits as described in the protocol in the opinion of the investigator.
11. Patient had breath alcohol concentration (BAC) equal to 0.00 when consent was signed. Note: repeat measurements of BAC were permitted at the discretion of the investigator. [16.1.1]

EVALUATION CRITERIA: Primary Endpoint: maintained absence of heavy drinking. Patients were considered to have maintained absence of heavy drinking if they do not have any heavy drinking occasions during weeks 3 to 12 of the 12-week treatment period; a heavy drinking occasion was defined as an occasion on which at least 5 standard drinks of alcohol are consumed for men, or at least 4 standard drinks of alcohol are consumed for women. A drinking occasion was assigned to the day it began if there was no meaningful break across days (e.g., sleep). A standard drink was defined as 0.5 oz absolute alcohol which is equivalent to 10 oz beer, 4 oz wine, or 1 oz 100-proof liquor. Conversions of reported drinks to standard drinks (in terms of alcohol) were made at the investigative site. Secondary Endpoint: maintained abstinence from drinking. Patients were considered to have maintained abstinence from drinking if they did not have any drinks of alcohol during weeks 3 to 12 of the 12-week treatment period. [16.1.1]

STATISTICAL PLANNING AND ANALYSIS: Due to early termination of this study, only summary measures are presented. [16.2.6]

RESULTS:

Safety:

Table 2-1

Adverse Event Summary
All Patients as Treated (APaT)

	MK-0594 5 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	77		85		162	
with one or more adverse events	40	(51.9)	45	(52.9)	85	(52.5)
with no adverse event	37	(48.1)	40	(47.1)	77	(47.5)
with drug-related[†] adverse events	25	(32.5)	26	(30.6)	51	(31.5)
with serious adverse events	3	(3.9)	2	(2.4)	5	(3.1)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	1	(1.2)	1	(0.6)
discontinued[‡] due to an adverse event	2	(2.6)	3	(3.5)	5	(3.1)
discontinued due to a drug-related adverse event	0	(0.0)	2	(2.4)	2	(1.2)
discontinued due to a serious adverse event	2	(2.6)	1	(1.2)	3	(1.9)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be related to the drug.

[‡] Study medication withdrawn.

See also [16.2.7.1].

Efficacy:

Table 2-2

Analysis of Timeline Follow Back (TLFB) MK-0594 5 mg vs Placebo, 3 Months Absence of Heavy Alcohol Drinking Full Analysis Set / Data-as-Observed

Treatment	N	n (%)
MK-0594 5 mg	20	4 (20.0)
Placebo	25	7 (28.0)
N = Number with opportunity to complete three month treatment period.		

CONCLUSIONS: Based on patients who completed the study (N=45, about 10% of the planned sample size of 488), the efficacy of MK-0594 5 mg cannot be determined. (See Table 2-2.) MK-0594 given 5 mg daily with a 15 mg single loading dose was safe and well-tolerated with all AE rates similar to placebo. (See Table 2-1).

AUTHORS: See [16.1.5.1].

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