Protocol Number: HLAB-003

Human Laboratory Study of ASP8062 for Alcohol Use Disorder

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STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CRF Part 46, 21 CFR Part 50, 21 CFR Part 56 and 21 CFR Part 312)
- International Conference on Harmonisation (ICH) E6

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

1. Protocol Synopsis

Name of Sponsor: National Institute on Alcohol Abuse and Alcoholism (NIAAA)	
Name of Investigational Product: ASP8062	
Name of Active Ingredient: ASP8062	
Protocol Number: HLAB-003	
Study Title: Human Laboratory Study of ASP8062 for Alcohol Use Disorder	
Sponsor's Representative: Raye Litten, Ph.D.	
Clinical Centers/PIs: Three clinical sites will participate in this study.	
Study Period: Approximately 1 year	**Phase of Development:** 2a

Objectives:

Primary: The primary objective of this study is to evaluate the effects of ASP8062, 25 mg once a day and matched placebo, on alcohol cue-elicited alcohol craving during a human laboratory paradigm after 2 weeks of daily dosing among subjects with moderate to severe alcohol use disorder (AUD) as confirmed by the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5™).

Secondary: Secondary objectives include evaluation of ASP8062, 25 mg once a day, and matched placebo on reduction of alcohol consumption, alcohol craving, cigarette smoking (among smokers) and nicotine use (among nicotine users), mood, sleep, alcohol use negative consequences, study retention, and safety and tolerability throughout the last 4 weeks of the treatment phase of the study.

Methodology: This study is a 2-arm, double-blind, randomized, placebo-controlled, parallel group, 3-site study designed to assess the effects of ASP8062 as compared with placebo on responses to *in vivo* alcohol cue exposure in the human laboratory setting. After signing informed consent, subjects will be screened for eligibility and have other baseline assessments. Screening is permitted over a 14-day period and most baseline assessments will be performed on the day of randomization. Assessments include alcohol breathalyzer test (before signing consent), medical history, physical examination, weight, vital signs, electrocardiogram (ECG), drinking history by the timeline follow-back (TLFB) method, Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-AR), prior medication use, MINI neuropsychiatric interview, urine drug test, smoking quantity frequency and nicotine use interview, clinical laboratory tests including chemistry, hematology, medical urinalysis, alcohol craving responses during a baseline cue reactivity session, Columbia Suicide Severity Rating Scale (C-SSRS), drinking goal, Penn Alcohol Craving Scale (PACS), Pittsburg Sleep Quality Index (PSQI), PROMIS Alcohol Negative Consequences short form, Profile of Moods State (POMS), Hyperkatifeia Scale and confirmation that subjects are treatment seeking and desire a reduction or cessation of drinking. Women of child-bearing potential will have a pregnancy test.

If eligible for the study, 60 subjects will be randomized using a stratified permuted block randomization procedure with "clinical site" as the stratification variable in an approximate 1:1 ratio (targeting 30 subjects per group) to receive either ASP8062 25 mg once daily or matched placebo for 6 weeks.

Subjects will be seen in the clinic at screening, at randomization and 5 other times during the study. A final follow-up telephone interview will occur ~2 weeks after the end of study in-clinic visit. Two cue reactivity sessions will be conducted. The first will be during screening (named pretreatment session) and the second will be after two weeks of investigational product administration at Study Week 3. During these cue sessions, subjects will be presented with water, followed by alcohol and will be asked to respond to 4 individual visual analog scales (VAS) items assessing alcohol craving and 1 item assessing beverage liking. Other assessments during the treatment period include TLFB, clinical laboratory tests, blood for serum levels of study drug for determining medication compliance, vital signs, ECG, concomitant medications, CIWA-AR, C-SSRS, pregnancy test, male and female birth control methods, adverse events (AEs), PACS, smoking quantity/frequency, PSQI, and POMS. The end of study visit will include the other assessments performed during the treatment phase and an Exit Interview, PROMIS questionnaire, and a treatment referral.

Number of Subjects (Planned): 60

Main Inclusion/Exclusion Criteria: Subjects will be male and female at least 21 years of age with 4 or more DSM-5™ symptoms of AUD (moderate to severe AUD). They must also be seeking treatment for AUD and if male, report drinking an average of at least 28 drinks per week or if female report drinking an average of at least 21 drinks per week prior to consent, and have at least 1 heavy drinking day (4 or more drinks per day for women/5 or more drinks per day for men) during the 7-day period prior to randomization.

Investigational Product, Dosage and Mode of Administration:

The target doses are 25 mg tablet of ASP8062 by oral administration once daily at bedtime for 6 weeks.

Reference Therapy, Dosage and Mode of Administration: Subjects in the placebo group will take an equivalent number of identically matched placebo tablets (one per day) by oral administration once daily at bedtime for 6 weeks.

Duration of Study: Each subject will participate in the study for up to 11 weeks, including up to 2 weeks of screening, 6 weeks of treatment, one end-of-study visit during the week following the last treatment dose, and a final telephone contact ~2 weeks after completing treatment for a safety follow-up.

Criteria for Evaluation:

Primary: The primary efficacy endpoint is the "strength" of alcohol craving Visual Analog Scale (VAS) score (item 1 below) upon presentation of the alcohol during the cue session at Week 3 – after two weeks of investigational product treatment.

Confirmatory secondary endpoints include the VAS scores for the other 3 VAS scales (items 2 through 4 below) and the average score of the 4 VAS craving items; and the difference score (alcohol cue VAS score minus water cue VAS score) for all 4 of the individual VAS craving items and their average score. The beverage liking VAS item is also a confirmatory secondary endpoint. The 4 VAS craving items in order of appearance are:

1. How strong is your craving to drink alcohol? - note this is the primary efficacy endpoint
2. Having a drink would make things just perfect.
3. If I could drink alcohol now, I would drink it.
4. It would be hard to turn down a drink right now.

The beverage liking item is: How much did you like the beverage just shown to you?

Secondary: Secondary efficacy endpoints will be analyzed over the last 4 weeks of the treatment period.

1. Percentage of subjects with no heavy drinking days. A "heavy drinking day" is 4 or more drinks per drinking day for women and 5 or more drinks per drinking day for men.
2. Percentage of subjects abstinent from alcohol.
3. Percentage of subjects with at least a World Health Organization (WHO) 2-level decrease in alcohol consumption.
4. Percentage of subjects with at least a WHO 1-level decrease in alcohol consumption.
5. Percentage of days abstinent per week.
6. Percentage of heavy drinking days per week.
7. Percentage of very heavy drinking days per week. A "very heavy drinking day" is 8 or more drinks per drinking day for women and 10 or more drinks per drinking day for men.
8. Weekly mean number of drinks per week.
9. Weekly mean drinks per drinking day.
10. Cigarettes smoked per week among smokers.
11. Percentage of subjects with no nicotine use among those reporting nicotine use at baseline.
12. Alcohol craving score (PACS).
13. Sleep quality (PSQI) score (and subscale scores).
14. Profile of Mood States (POMS) score (and subscale scores).
15. PROMIS Alcohol Negative Consequences score.

Safety Endpoints: Safety endpoints will be analyzed over the entire treatment and follow-up period.

1. Vital signs

2. Body weight
3. Clinical laboratory parameters
4. BAC by breathalyzer
5. Urine drug tests
6. AEs
7. ECG results
8. CIWA-AR scores
9. Frequency of subjects with suicidal ideation at any time during the treatment period (C-SSRS)
10. Concomitant medication use
11. Alcohol Craving Questionnaire – Short Form – Revised (ACQ-SF-SR) score (pre- and post-cue response sessions)

Compliance: Self report of compliance with study drug self-administration is confirmed by digital photography (AiCure software) with investigational products and ASP8062 plasma levels.

Statistical Methods (Data Analysis):

Analysis Populations:

Modified intention-to-treat (mITT) Analysis Set: The mITT set is defined as subjects randomized to participate in the study that took at least one dose of investigational product and had a non-missing VAS craving primary endpoint.

Evaluable Analysis Set: The evaluable analysis set for the secondary endpoints is defined as those subjects randomized to the study who took at least 1 tablet per day for at least 80% of days in Weeks 1-6.

Safety Analysis Set: The safety analysis set includes all subjects who took at least one dose of investigational product.

Analysis of the Primary Efficacy Endpoint: Each subject will have an alcohol cue VAS score for "strength" of alcohol craving score during the treatment alcohol cue session that is the primary endpoint. Analysis of covariance (ANCOVA) with the "strength" of alcohol craving value as the dependent variable and the pretreatment "strength' of alcohol craving score as an independent fixed effect. Clinical site will also be included as an independent factor. The ASP8062 group will be compared to the Placebo group. No imputation for missing endpoint data will be performed.

Analysis of the Secondary Endpoints: There are 3 additional questions asked during the cue session for each beverage cue. Each of these questions will be analyzed in the same manner as the primary endpoint. An overall mean of the 4 questions will also be analyzed in the same manner. The difference between the first alcohol cue and water cue for each VAS item will be computed at both the pre and post treatment time points. The difference values for each VAS item and the average difference will be analyzed similarly to the primary endpoint. Continuous secondary endpoints (percent heavy drinking days, percent very heavy drinking days, percent days abstinent, drinks per week, drinks per drinking day, number of cigarettes smoked per week, PACS, POMS, and PSQI score) during the last 4 weeks of treatment period will be analyzed using a mixed-effects model with site, assessment time, and baseline drinking as fixed factors. PROMIS will be analyzed with analysis of covariance model with baseline and treatment as factors. Models will also include time by treatment group interaction term. Additional covariates may be included that are significantly correlated with outcome and/or if there are differences across the treatment groups.

Analysis of the dichotomous secondary endpoints (percentage subjects with no heavy drinking days, percentage subjects abstinent from alcohol, percentage of subjects achieving at least a one and two-level shift in WHO alcohol consumption, and percentage of subjects with no nicotine use among subjects with any use during the week before randomization) during the last 4 weeks of treatment period will be conducted via logistic regression. Covariates may be included provided there are a sufficient number of events.

No imputation for missing endpoint data will be performed for secondary endpoints.

Safety Analyses: AEs will be coded using the most recent version of the Medical Dictionary of Regulatory Activities (MedDRA) preferred terms and will be grouped by system, organ, and class (SOC) designation. The severity, frequency, and relationship of AEs to investigational product will be presented by preferred term by SOC grouping. Listings of each individual AE including start date, stop date, severity, relationship, outcome, and duration will be provided. Each AE (based on preferred terminology) will be counted once only for a given

study subject. If the same AE occurred on multiple occasions, the highest severity and relationship to investigational product will be assumed. Thus, study participants are not counted multiple times in a given numerator in the calculation of frequencies for a specific AE. Laboratory data, vital signs, ECG results, alcohol breathalyzer results, urine drug test results, and CIWA scores will be reported as summary statistics. The numbers and proportion of subjects who reported CIWA scores ≥ 10 at any time after the start of dosing will be presented. Changes in clinical laboratory tests and vital signs will also be presented as summary statistics of change from baseline. The number and percentage of subjects with a higher ACQ-SF-R score post cue session will be provided by treatment group.

Compliance and Participation Outcomes: Medication compliance is defined as the amount of investigational products taken as a proportion of the total amount prescribed. Compliance will also be evaluated by determining the proportion of subjects who were prescribed ASP8062, reported taking ASP8062 (by AiCure assessment), and had a plasma sample with detectable ASP8062. The participation rate is the percentage of subjects with complete drinking data. Compliance and participation rates will be reported on a weekly basis and across the entire trial duration. Compliance by ASP8062 plasma levels will be reported as number and percentage of subjects with a level above the limit of detection at each time point among subjects who were prescribed ASP8062. Compliance with tablet ingestion will be confirmed by AiCure assessment or subject's self-report, if AiCure data is not available. Descriptive statistics will also be provided.

Baseline Descriptive Statistics: Summaries of the characteristics of the subjects in each of the study groups at baseline will be prepared for the mITT, evaluable, and safety analysis sets. Baseline characteristics will be compared between the ASP8062 group and placebo group using appropriate statistical methods.