A RANDOMIZED CONTROLLED CLINICAL TRIAL OF THE NEUROIMMUNE MODULATOR IBUDILAST FOR THE TREATMENT OF ALCOHOL USE DISORDER

STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

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1. INTRODUCTION

Alcohol use disorder (AUD) is a chronic and relapsing condition for which current pharmacological treatments are only modestly effective (1). The development of efficacious medications for AUD remains a high research priority with recent emphasis on identifying novel molecular targets for AUD treatment and to efficiently screen new compounds aimed at those targets (2, 3). To that end, modulation of neuroimmune function represents a promising novel target for AUD (4). Chronic alcohol consumption produces a sustained inflammatory state, such that individuals with AUD have increased neuroinflammation throughout the brain (5), and alcohol-induced neuroinflammation is thought to contribute to chronic alcohol seeking behavior and to the behavioral and neurotoxic effects of alcohol (6). In rodents, lipopolysaccharide-induced neuroinflammation produces prolonged increases in alcohol consumption (7), and knocking out neuroimmune signaling genes attenuates alcohol preference and self-administration (8). Therefore, a medication that reduces proinflammatory signaling may produce anti-alcohol and neuroprotective effects that may be beneficial for the treatment of AUD.

Ibudilast (IBUD; aka, MN-166, previously AV411) has been advanced as a novel addiction pharmacotherapy that targets neurotrophin signaling and neuroimmune function. IBUD inhibits phosphodiesterases -4 (PDE4) and -10 (PDE10) and macrophage migration inhibitory factor (MMIF) (9). As PDE4 and MMIF are critically involved in proinflammatory signaling (10, 11), and PDE10 negatively regulates neurotrophin expression (12), the inhibition of these molecules by IBUD has been theorized to reduce neuroinflammation and promote neurotrophin expression (9). In support, IBUD enhances neurotrophin expression, reduces pro-inflammatory cytokine release, and attenuates neuronal death (13). In rodents, IBUD has been demonstrated to reduce ethanol intake by approximately 50% both under conditions of maintenance and relapse testing (14). These recent preclinical findings for IBUD support prior studies indicating pharmacological inhibition of PDE4 and PDE10 decreases alcohol intake (15-17).

To advance medications development for AUD, our laboratory has recently completed a randomized, double-blind, placebo-controlled crossover laboratory study of IBUD in non-treatment seeking individuals with AUD (R21 AA022214; NCT02025998) (18). This study tested the safety, tolerability, and initial human laboratory efficacy of IBUD (50mg BID) on measures of subjective response to alcohol, as well as cue- and stress-induced changes in craving and mood. Participants (N = 24) completed two separate 7-day intensive outpatient protocols which included daily visits for medication administration and testing. Upon reaching a stable target dose of IBUD (or matched placebo), participants completed a stress-exposure session, an alcohol cue-exposure session, and an IV alcohol administration session. Results indicated that IBUD was well tolerated and associated with mood improvements during stress- and alcohol-cue exposures, and with reduction in tonic levels of alcohol craving. Exploratory analyses revealed that among individuals with higher depressive symptomatology, IBUD attenuated the stimulant and positive mood-altering effects of alcohol.

Building upon the strong rationale and preclinical findings for IBUD, along with safety data and early efficacy in human testing conducted in our laboratory, this proposal seeks to advance medication development for AUD by conducting a 12-week, double-blind, placebo-controlled

randomized clinical trial of IBUD (50mg BID). We propose to randomize 132 treatment-seeking men and women with current AUD (moderate or severe). To provide a standardized behavioral platform, all participants in the study will complete the NIAAA-developed web-based program Take Control during the study.

2. BACKGROUND AND SIGNIFICANCE

2.1. Better medications for alcoholism are needed and neuroimmune signaling represents a promising novel target.

Pharmacotherapies for alcoholism are used less often than psychosocial interventions (19). The limited use of pharmacotherapy for alcoholism is due, in part, to the relative lack of pharmacological options to treat alcohol use disorders. The only pharmacotherapies currently approved by the Food and Drug Administration (FDA) for the treatment of AUD are disulfiram (Antabuse®), naltrexone, acamprosate, and Vivitrol, an injectable extended-release formulation of naltrexone. Given the dearth of available pharmacotherapies and their limited efficacy (20), medication development to treat AUD remains a top research priority (2). To that end, future directions in medication development emphasize the identification of new molecular targets and the development of novel compounds for these targets (2, 4). This is consistent with the phenotypic complexity of alcoholism, which calls for multiple targets that can effectively address multiple pathways of risk. The proposed study seeks to develop ibudilast (IBUD) for AUD, a novel compound that targets modulation of GDNF, PDE, and MIF.

Neurotrophins, including glial (GDNF) and brain derived neurotrophic factor (BDNF), are essential for synaptic plasticity (21), neuron survival, and basic cell signaling, including midbrain dopamine transmission (22, 23). In rodent models of AUD, reductions in GDNF and BDNF expression underlie dysfunctional striatal dopamine signaling, increased motivation to consume alcohol, and heightened alcohol reward (24-27). Conversely, increases in GDNF and BDNF signaling restores mesolimbic dopamine function, reduces alcohol self-administration, and attenuates relapse to alcohol seeking (27-31). These results suggest that medications that increase GDNF and BDF expression may be useful treatments for AUD.

Chronic alcohol consumption produces a sustained inflammatory state, and in turn, this alcohol-induced neuroinflammation contributes to the behavioral and neurotoxic effects of alcohol (6). Individuals with AUD have increased neuroinflammation throughout the brain (5), and elevated peripheral levels of proinflammatory cytokines have been proposed as a biomarker for AUD (32). In rodents, neuroinflammation produces prolonged increases in alcohol consumption (7), and knocking out neuroimmune signaling genes attenuates alcohol preference and self-administration (8). Proinflammatory signaling also mediates acute alcohol-induced motor impairment (33), and chronic alcohol exposure produces long-lasting neuroinflammation, which in turn is associated with sustained cognitive and behavioral impairment and brain damage (34). Finally, neuroinflammation is thought to increase vulnerability to stress-induced drug seeking and relapse (35). In sum, a medication that reduces proinflammatory signaling may produce anti-alcohol and neuroprotective effects that are beneficial for the treatment of AUD.

2.2. Ibudilast is a neuroimmune modulator with robust safety data and early efficacy signal that warrants clinical investigation.

Ibudilast (IBUD; aka, MN-166, previously AV411) has been advanced as a novel addiction pharmacotherapy that targets neurotrophin signaling and neuroimmune function. IBUD inhibits

phosphodiesterases -4 (PDE4) and -10 (PDE10) and macrophage migration inhibitory factor (MMIF) (9). As PDE4 and MMIF are critically involved in proinflammatory signaling (10, 11), and PDE10 negatively regulates neurotrophin expression (12), the inhibition of these molecules by IBUD has been theorized to reduce neuroinflammation and promote neurotrophin expression (9). IBUD enhances neurotrophin expression, reduces pro-inflammatory cytokine release, and attenuates neuronal death (13). Most important to the present study, IBUD has been demonstrated to reduce ethanol intake by approximately 50% in selectively bred alcohol-preferring (P) and high alcohol drinking (HAD1) rats both under conditions of maintenance and relapse testing (14). These recent preclinical findings for IBUD support prior studies suggesting that pharmacological inhibition of PDE4 and PDE10 is associated with decreases alcohol intake in rodents (15-17). These results suggest IBUD is a promising treatment for AUD, but the safety and efficacy of IBUD in combination with alcohol administration has only recently been studied in humans, as part of an NIAAA-supported R21 to test IBUD (50 mg BID) in the human laboratory.

As shown in our preliminary studies section, results of the safety aim of our human laboratory trial suggested that IBUD (50 mg BID) was generally safe and well tolerated. Specifically, there were no study dropouts directly related to IBUD, as well as no dose reductions over the course of the protocol. Analyses of specific side effects revealed significant differences between IBUD and placebo for headaches and a trend-level effect for general gastrointestinal disorders. Furthermore, the co-administration of IBUD with alcohol (to a target Breath Alcohol Concentration or 0.08 g/dl) was not associated with significant changes in cardiovascular parameters, such as blood pressure and heart rate. A trend-level effect for nausea during alcohol administration suggested that IBUD may increase feelings of nausea at rising BrAC levels, compared to placebo. Together, these findings support the safety of IBUD, at the 50mg BID dose, in samples with mild-to-severe AUD. This is particularly noteworthy given that PDE-4 inhibitors, such as rolipram, have yielded promising preclinical findings for AUD (36) while raising safety concerns during testing in humans. As reviewed elsewhere (37), PDE-4 inhibitors, including rolipram, are often associated with gastrointestinal distress, vertigo, nausea, and vomiting within their therapeutic window (38). These effects are believed to be due to increases in gastric acid secretion (39) as well as central effects in brain areas regulating emesis and the vestibular system (40). Although the effects of IBUD are not limited to PDE-4, and include inhibition of PDE-10 and macrophage migration inhibitory factor (13, 41-43), these results support the potential application of IBUD to AUD treatment in human clinical samples and are consistent with recent safety studies for opiate (44, 45) and methamphetamine (46, 47) use disorders.

As recommended by Litten et al. (2, 3, 48), human laboratory models can be used to guide the identification of promising medications by collecting both safety and alcohol interaction data along with initial demonstration of medication effects on subjective responses to alcohol, cue-reactivity, and alcohol self-administration. Such findings on safety and initial efficacy are vital to deciding whether to invest resources on efficacy testing for a novel AUD medication. Based on the results of our recently completed randomized, double-blind, placebo-controlled crossover laboratory study of IBUD in non-treatment seeking individuals with current AUD (R21 AA022214; NCT02025998), we believe that the safety data are robust and that early efficacy results provide sufficient signal to warrant a clinical trial of IBUD (50 mg/BID) for alcoholism.

2.3. Significance of the proposed project hinges on the development of IBUD for alcoholism, which is grounded on preclinical testing, safety, and initial efficacy in individuals with AUD.

Alcoholism is a chronic and relapsing condition affecting 10 million Americans and causing a host of negative medical, psychosocial, and economic consequences to the individual and to society (49, 50). To date, only four pharmacotherapies are approved by the FDA for the treatment of alcoholism and their efficacy is modest (51). Therefore, medication development for AUD represents a high priority area. The significance of this proposal is grounded on the following recent developments: (A) this study focuses on novel molecular targets for AUD, namely GDNF modulation and PDE inhibition, and will test the clinical efficacy a novel compound targeting these systems (IBUD); (B) it is supported by compelling preclinical data validating its molecular targets and its effects on alcohol phenotypes (i.e., IBUD reduced ethanol intake by approximately 50% in animal models); (C) safety data for IBUD are robust and have been established in our own human laboratory study, as well as recent safety studies for opiate (44, 45) and methamphetamine (46, 47) use disorders; (D) the early efficacy data from our R21 study provides sufficient signal to support additional testing of IBUD in treatment-seeking samples. Specifically, our human laboratory study found that IBUD was associated with mood improvements during stress- and alcohol-cue exposures as well as reductions in tonic levels of alcohol craving compared to placebo; and (E) the translation of findings from preclinical to clinical samples has been challenging in the AUD literature and often promising compounds with compelling preclinical data do not progress to testing in humans (described as the “valley of death” in AUD medication development)(2, 3); thus allowing for promising novel (and safe) compounds to progress to clinical trials represents a significant step forward in medications development for AUD. In sum, significant proposals are those that can have a transformative impact on the field and ultimately improve the standards of care for AUD. To that end, the successful completion of the proposed study will further develop IBUD, a safe and promising novel compound with strong preclinical and safety data for AUD. If IBUD proves superior to placebo in this study, it will set the stage for a confirmatory multi-site trial leading to FDA approval of a novel AUD treatment.

3. STUDY OBJECTIVES

3.1. Primary Aims

Primary Aim 1: To test whether IBUD (50mg BID) will decrease percent heavy drinking days (PHDD; HDD defined as 5+ drinks for men and 4+ for women), as compared to placebo, over the course of the 12-week trial.

Primary Aim 2: To test the efficacy of IBUD (50mg BID) on secondary alcohol consumption endpoints, namely (a) drinks per day, (b) drinks per drinking day, (c) percent days abstinent, (d) percent subjects with no heavy drinking days, and (e) percent subjects abstinent, as well as measures of alcohol craving and negative mood, over the course of the 12-week trial. It is hypothesized that IBUD will decrease drinking, improve mood, and attenuate alcohol craving over the course of the 12-week trial.

3.2. Exploratory Aims

Exploratory Aim 1: To test whether the effects of IBUD (50mg BID) on the primary and secondary endpoints (aims 1 and 2) are moderated by depressive symptomatology. This is based on our finding that IBUD attenuated the stimulant effects of alcohol among individuals with higher levels of depressive symptomatology.

Exploratory Aim 2: To test whether IBUD (50mg BID), compared to placebo, reduces neuroinflammation, as indexed by circulating blood levels of proinflammatory markers over the course of the 12-week trial.

4. STUDY DESIGN

4.1. Design Overview

The study design consists of a 12-week, double-blind, placebo-controlled randomized clinical trial of IBUD (50mg BID) for the treatment of AUD. We will randomize 132 treatment-seekers with current AUD over the course of 4 years. As a behavioral support platform, all participants will complete the NIAAA-developed and computer-delivered program "Take Control" during the study. Participants will complete telephone screening, followed by in-person eligibility assessment, a physical exam for medical eligibility, randomization to study medication or matched placebo, and an in-person follow-up visit at week 4, and in-person or remote follow-up visits at 8 and 12 weeks of treatment. A brain imaging session will take place at week 4 (if participant is eligible). In addition, TLFB assessment of drinking outcomes will occur by telephone on weeks 2, 6, and 10. A final safety check visit will occur on week 16, consisting of repeated clinical labs and ECG.

5. PHARMACOTHERAPY INTERVENTIONS

5.1. Ibudilast (IBUD)

Experimental medication and matched placebo will be supplied by MediciNova (see Letter of Support). The study drug is IBUD (MN-166, previously known as AV411) and the formulation is 10 mg delayed-release Pinatos® capsules, the Japanese generic IBUD product produced by Taisho Pharmaceuticals and imported by MediciNova. The target dose of IBUD will be 50 mg BID (5 x 10 mg capsules twice daily). To minimize nausea, the most common side effect of IBUD, all participants will begin at 20 mg BID for 2 days increasing to 50 mg BID on day 3 and remaining at the 50mg BID dosing until week 12. For the last three days of week 12, participants will reduce the dose (step down procedure) to 20 mg BID prior to stopping the medication at the end of the study. This is consistent with the ongoing trial of IBUD for MAUD; NCT01860807).

5.1.1. IBUD Safety Data

IBUD has been used clinically for 20 years in Asia for the treatment of bronchial asthma, and more recently for post-stroke dizziness and ocular allergies during which it has proven to be safe and well tolerated (90). Of note, IBUD is prescribed without any alcohol use restrictions. As IBUD is not currently clinically available in the US, information concerning possible adverse events come from results of phase I trials conducted by the US developer (Avigen/MediciNova) and from experience with clinical use in Asia. In Avigen phase I trials (AV411-009, -010, -016, -026), doses up to 100 mg of IBUD (as a single 100 mg dose and at 50 mg BID [dose used in this study] for up to 2 weeks in diabetics and healthy controls) were well tolerated. In total, ~425 subjects have been treated in the clinical development of IBUD with no SAEs clearly linked to IBUD and one severe AE of hepatic steatosis (possibly-related) at 30 mg/d IBUD and one moderate hepatotoxicity deemed related to IBUD (at 60 mg/d); both at 20-23 months of treatment. There were no serious adverse events in any of these trials. Frequencies of the most

common mild-moderate severity adverse events were (IBUD vs. Plac): headache (18 vs. 21%), nausea (12 vs. 8%), dyspepsia, diarrhea (12 vs. 8%), and emesis (6 vs. < 1%). According to the package insert for Ketas® (IBUD market name in Asia), the most frequently observed adverse reactions are anorexia (weight loss; <1%), nausea (<1%), increased AST (GOT) levels (<1%), increased ALT (GPT; <1%), and thrombocytopenia (<1%). In addition, there have been no significant drug-drug interactions observed to date in clinical studies of IBUD among patients being treated for diabetes, neuropathic pain, opioid dependence, or multiple sclerosis. To date, over 200 subjects have received the proposed 50 mg BID dose without SAEs (in diabetes, AUD, opiate, and MAUD studies).

5.1.2. Medical Monitoring and Side Effects

The study physician (Dr. Miotto) will be available to the study participants for the entire duration of the study. Participants will have access to her 24-hr pager and will report on adverse events at each monthly visit. Dr. Miotto will call every participant at the end of the first week on the study medication (or placebo) to discuss and manage any adverse events. The study staff will notify Dr. Miotto of any adverse events recorded during the follow-up visits. Side effects will be collected as an open-ended question such as “How have you been feeling since your last visit?” at each follow-up visit. A follow-up safety visit will also be conducted 4 weeks after medication is terminated (Week 16) and will consist of clinical labs and ECG, which will be reviewed and managed by the study physician. Dr. Irwin (Co-I), a licensed physician, will be available to Dr. Miotto for consultation on clinical care issues. Any significant escalation in drinking (defined as ≥ 50% increase in drinking from baseline) will prompt an intervention by the PI and /or study physician, aimed at assessing safety and discussing alternative treatment options (e.g., detoxification programs). Lastly, the C-SSRS assessing for suicidal ideation and behaviors will also be conducted at each in-person visit and clinically significant findings will trigger further evaluation by the PI (psychologist) and/or the study physician (Dr. Miotto) and Co-I (Dr. Irwin).

5.1.3. Medication Compliance

Compliance will be monitored by the study staff using participant self-report verified by the pill count method at each in-person follow-up visit.

5.1.4. Medication Stopping Rules

Pre-specified criteria for discontinuation of study medication are:

(a) development of agitation, hostility, depressed mood, or changes in behavior or thinking not typical of alcohol use or withdrawal (more severe and/or temporally un-related to alcohol use/withdrawal;
(b) severe nausea and vomiting;
(c) systolic blood pressure greater than 160, or a diastolic blood pressure greater than 100 (i.e. cutoffs for stage 2 hypertension), or a heart rate greater than 70% of the maximum heart rate expected for their age [0.70(220-age)];
(d) females who become pregnant;
(e) any circumstances that, in the opinion of the investigators, compromise participant safety. Medication stopping criteria will be evaluated at each follow-up visit (4, 8, and 12-weeks post randomization) and each time a participant calls the study physician to report an adverse event.

5.1.5. Dose Justification

Selecting 100 mg/day (50 mg BID) as the single target dose in this study is based on safety considerations, preclinical, and clinical data. Additionally, all in vitro (13, 94, 95), in-vivo animal (96, 97), and clinical neuropharmacology studies of IBUD, found efficacy to be dose- or concentration-incremental - at least up to 80-100 mg/day doses and plasma concentrations (44, 61). In essence, 'more is better' up to the current clinical maximum safe and well-tolerated high dose of 50 mg bid correlates with ~100 ng/ml or ~0.5 uM steady-state plasma concentration (with daily AUC ~1500 ng*hr/ml) and ~1.5 uM brain concentration. The target dose reflects experience in recent MediciNova safety trials, where 50 mg BID has been well tolerated, adverse events being easily managed and 50mg BID representing the upper limit of what the manufacturer believes is the maximal tolerated and potentially efficacious dose for an addiction indication. The half-life of IBUD is estimated at approximately 19 hours (98) justifying BID dosing. Lastly, discussions with MediciNova have reassured the study team that the 50 mg BID dose represents the best balance between obtaining consistent efficacy in a host of clinical studies (for addition and MS) while producing a manageable side effect profile.

6. BEHAVIORAL INTERVENTIONS

6.1. Take Control Program

Take Control is easy-to-use tool, developed by NIAAA (2009) that helps participants analyze their own drinking. Take Control offers evidence-based information to help participant reduce their risk for alcohol problems. In this study, participants will be asked to complete the Take Control program for 30 minutes at the randomization visit and at all in-person follow-ups. This approach is consistent with that of NCIG6, which used Take Control in computer-delivered format. A recent study comparing computer-delivered Take Control to therapist-delivered platforms (TDP) found comparable drinking outcomes and higher medication adherence in the Take Control trials (81), suggesting that Take Control is cost-efficient behavioral platform for AUD trials. Regarding the role of mutual support groups in the Take Control platform, the "Treatment Options" module reviews various treatment resources including mutual support groups, addiction specialist, and medications commonly used to treat problem drinking.

7. STUDY PROCEDURES

7.1. Recruitment of Subjects

Participants will be recruited from the community through radio, TV, online, and newspaper advertisements. Campaigns in local buses and print publications (e.g., LA Weekly) will also be implemented. Consistent with our efforts to identify treatment-seeking individuals with AUD, all recruitment materials will invite individuals who wish to change their drinking and who indicate they have a drinking problem.

7.2. Eligibility Criteria

7.2.1. Inclusion Criteria

To be included in the study, participants must:
(1) Be between the ages of 18 and 65
(2) Meet current (i.e., past 12 months) DSM-5 diagnostic criteria for alcohol use disorder moderate or severe
(3) Be treatment-seeking for AUD
(4) Report drinking at least 14 drinks per week if male (7 drinks per week if female) in the 28 days prior to consent

7.2.2. Exclusion Criteria

To be included in the study, participants must not:
(1) Have a current (last 12 months) DSM-5 diagnosis of substance use disorder for any psychoactive substances other than alcohol and nicotine
(2) Have a lifetime DSM-5 diagnosis of schizophrenia, bipolar disorder, or any psychotic disorder
(3) Have a positive urine screen for narcotics, amphetamines, or sedative hypnotics;
(4) Have clinically significant alcohol withdrawal symptoms as indicated by a score ≥ 10 on the Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-R)
(5) Be pregnant, nursing, or planning to become pregnant while taking part in the study; and must agree to one of the following methods of birth control (if female), unless she or partner are surgically sterile:
- Oral contraceptives
- Contraceptive sponge
- Patch
- Double barrier
- Intrauterine contraceptive device
- Etonogestrel implant
- Medroxyprogesterone acetate contraceptive injection
- Complete abstinence from sexual intercourse
- Hormonal vaginal contraceptive ring

(6) Have a medical condition that may interfere with safe study participation (e.g., unstable cardiac, renal, or liver disease, uncontrolled hypertension or diabetes)
(7) Have AST, ALT, or GGT ≥ 3 times upper normal limit
(8) Have attempted suicide and/or have had serious suicidal intention or plan in the past month
(9) Currently be on prescription medication that contraindicates use of IBUD, including alpha or beta agonists, theophylline, or other sympathomimetic
(10) Currently be on any medications for AUD or any psychotropic medications (e.g., psychostimulants and benzodiazepines) with the exception of stable antidepressants (stable dose for ≥4 weeks)
(11) Have any other circumstances that, in the opinion of the investigators, compromises participant safety.

7.3. Screening Period

7.3.1. Telephone Screen

Individuals who call the lab (in response to flyers and advertisements) expressing interest in the study will receive detailed information about the study procedures, and if they remain interested they will complete a telephone screen performed by a trained research assistant for self-reported inclusion and exclusion criteria. Those who appear eligible will be invited to the laboratory for an initial in-person screening session.

7.3.2. Initial Screening Visit

Prior to conducting any research related procedures, research staff will conduct the informed consent process which details the procedures to take place during the screening visit. Informed consent will be a three-part process. First, participants will be asked to read and provide verbal consent for breathalyzer. If the breathalyzer is above 0.000, the visit will be stopped and the participant will not be compensated. The participant will be given an opportunity to reschedule the visit for another day. If the breathalyzer test is negative, the written informed consent form will be reviewed and signed by the participant and study staff outlining procedures for the initial screening visit. A second written consent form will be reviewed and signed in the presence of the study physician at the medical screening visit if the participant is found eligible to continue to that visit.

At the initial screening visit, subjects will be asked to provide a urine to test for drugs of abuse and pregnancy (if female), and will complete a series of individual differences measures (described in detail below). This visit should take 1 to 2 hours.

Following the initial in-person screening, the study coordinator will meet with the PI to determine if the participant is eligible to continue to the medical screening based on study inclusion/exclusion criteria.

7.3.3. Medical Screening Visit

Those participants who appear to be eligible after the initial screening visit, will then be scheduled for a second screening visit, which will be conducted with the study physician. The visit will start with a breathalyzer test. If the breathalyzer is above 0.000, the visit will be stopped and the participant will not be compensated. The participant will be given an opportunity to reschedule the visit for another day. If the breathalyzer test is negative, the physician will meet with the participant in-person or via telemedicine to conduct the second written (experimental) consent, medical history interview, and physical exam. The participant will then be walked to the UCLA Clinical and Translational Research Center (CTRC) for blood specimen collection including Comprehensive Metabolic Panel and Complete Blood Count to evaluate overall health; and EKG to screen for medical conditions that contraindicate taking ibudilast. In addition, urine drug screen test and pregnancy test (if female) will be repeated. The study physician will review each participant's medical history, vital signs, weight, review of systems, and laboratory tests, including liver function tests (LFTs), drug screen, chemistry screen, and urine pregnancy screen to determine if it is medically safe for the participant to take the study medication.

Any subject who is excluded from the study will be compensated for their time in the screening session and will be offered referrals for alcohol treatment in the community.

7.4. Randomization Visit

Participants who are eligible after the medical screening visit will be scheduled to come into the lab to be randomized and start study medication. Randomization will be done in a 1:1 ratio, to either IBUD or placebo using a stratified block randomization procedure, gender and drinking status (moderate drinking defined as ≥ 14 drinks/week for men and ≥ 7 drinks/week for women versus heavy drinking defined as ≥ 28 drinks/week for men and ≥ 21 drinks/week for women) as the stratification factors. Participants will be asked to provide a urine specimen for drug testing and pregnancy for female participants, perform an alcohol breathalyzer test, and complete measures as described in the Schedule of Assessments below. In addition, blood will be drawn to collect baseline neuroinflammation data. Participants will be dispensed enough medication to last until the next scheduled visit.

7.5. Follow Up Period

Follow-up visits will occur at the UCLA Addictions Lab on weeks 4, 8, 12, and 16. Data collection for the week 8 and week 12 follow-up visits may be conducted remotely if needed. Telephone follow-up interviews will be conducted at weeks 2, 6 and 10 to collect Timeline Follow Back data as described below. At each in-person follow up visit, participants will be asked to provide a urine specimen for drug testing and pregnancy for female participants, perform an alcohol breathalyzer test, and complete measures as described in the Schedule of Assessments below. In addition, blood will be drawn to monitor participant safety (week 16) and collect neuroinflammation data (all in-person visits through week 12). Participants will be asked to bring all study medication and used packaging to each visit to assess for medication compliance and will be dispensed study medication to last until the next scheduled visit.

7.5.1. Brain Imaging Session

Participants found to be eligible for an MRI, as determined by the MRI Safety Screening form, will be asked to complete a brain imaging session as part of the week 4 in-person visit.

Participants will be asked to abstain from drinking alcohol prior to coming into the lab for the brain imaging session, which will be verified through a breathalyzer. Only participants with a blood alcohol concentration of zero will be allowed to complete the scanning visit. Female participants will be given a pregnancy test to make sure that they are not pregnant. We will also collect a urine sample on that day to verify compliance with the study medication. We will then ask participants to fill out a few questionnaires including information about your use of alcohol and tobacco.

After the initial questionnaires, participants will receive some training on how to complete questionnaires in the scanner. The scanning will be performed at the Brain Mapping Center or at the Center for Cognitive Neuroscience, both located on the UCLA campus. They will be asked to lie down on a padded table, with their head placed in the center of a large, metal doughnut-shaped magnet. While the machine is running, the participant will hear loud banging noises and will be offered earplugs to reduce the noise made by the magnet. Head and back support will also be provided to minimize discomfort. In the scanner, participants will view alcohol and neutral cues and will be asked to rate their urge drink. Additionally, in the scanner, participants will complete the Montreal Imaging Stress Task. In this task participants are asked

to solve mental arithmetic problems of varying degrees of difficulty and are given feedback on their performance. Subjective and biological measures of stress will be administered before and after the stress task.

7.6. Compensation for Participation

Participants will be compensated up to a total of $385 for their time and effort according to the following schedule:

Initial Screening Visit:	$40
Medical Screening Visit:	$40
Randomization:	$40
Follow Up Week 4:	$40
Brain Imaging Session:	$50 (if eligible)
Follow Up Week 8:	$40
Follow Up Week 12:	$45
Follow Up Week 16:	$40
Completion Bonus:	$50

All participants will be provided with free parking validation or bus fare for attendance to each study visit. Participants are free to discontinue participation at any time and will receive compensation for the amount of time they participated.

8. SAFETY MONITORING PLAN

Safety monitoring will be conducted throughout the study; therefore safety concerns will be identified by continuous review of the data by the PI and study physician, internal quality assurance monitor, and DSMB.

8.1. PI and Study Physician Safety Monitoring

Participants will be given a 24-hour telephone number for calling the physician to discuss side effects, and physician office hours will be available as needed. Adverse events, including side effects will be collected in an open-ended way at each in-person study visit. In the event that an adverse event is spontaneously reported during a telephone interview at weeks 2, 6, or 10, research staff will note general information to provide to the study physician and will have the physician follow up with the participant via phone to gather more information and address safety issues as needed. Vital signs, weight, and neuropsychiatric side effects, including depression and suicidal ideation, will be monitored at each study visit. Alcohol withdrawal will be monitored at each visit through administration of the CIWA, and any significant withdrawal, as indicated by a score of 10+ on the CIWA will be reported to the study physician immediately. The study physician will repeat all the clinical labs at the week 16 follow-up in order to verify that there were no changes associated with the 12-week medication regimen (+ 2 week titration/ stabilization period). In the event that significant medical problems are encountered, the blind will be broken and appropriate medical treatment will be provided.

8.2. Internal Quality Assurance Monitoring

The PI will designate appropriately qualified personnel to periodically perform quality assurance checks at mutually convenient times during and after the study. These monitoring visits provide the opportunity to evaluate the progress of the study and to obtain information about potential problems. The monitor will assure that data are accurate and in agreement with any paper source documentation used, verify that subjects' consent for study participation has been properly obtained and documented, confirm that research subjects entered into the study meet inclusion and exclusion criteria, verify that study procedures are being conducted according to the protocol guidelines, monitor review AEs and SAEs, perform drug accountability, and assure that all essential documentation required by Good Clinical Practices (GCP) guidelines are appropriately filed. At the end of the study, they will confirm that the site has the appropriate essential documents on file, advise on storage of study records, and inspect the return and destruction records for unused study medication.

8.3. Data and Safety Monitoring Board (DSMB)

An independent DSMB of external advisors will meet prior to the start of the study, annually during enrollment and follow-up and at trial end to review safety data. The Board will be blinded to subjects' actual randomized group assignments but may request at any time that the blind be broken by the data center, if concerns arise from the blinded data. In addition to annual meetings, the DSMB will meet after half of the subjects (66) have been randomized to review safety data and the integrity of the study (i.e., an evaluation of the dropout rate and impact on the planned statistical analysis of the data) and make a formal recommendation to the PI on the continuation or early stopping of the study due to safety concerns. *Ad hoc* meetings will be convened if SAEs occur that are considered at least possibly related to the study medication.

9. ASSESSMENTS

9.1. Schedule of Assessments Table

Procedure / Study Visit:	Initial Screen	Med Screen	Rand. Visit	Wk 4 F/U	Wk 8 F/U	Wk 12 F/U	Wk 16 F/U
Informed Consent: Initial Screen	x						
Informed Consent: Experimental/Medical		x					
Adverse Childhood Experience Questionnaire (ACE)			x				
Adverse Events/Serious Adverse Events (AE/SAE)		x	x	x	x	x	
Alcohol Breathalyzer	x	x	x	x	x	x	
Alcohol Dependency Scale (ADS)			x	x	x	x	
Alcohol Purchase Task (APT)			x	x	x	x	
Alcohol Use Disorders Identification Test (AUDIT)			x				
Beck Anxiety Inventory (BAI)			x	x	x	x	
Beck Depression Inventory (BDI-II)	x		x	x	x	x	
Birth Control Assessment	x						
Brain Imaging (if eligible)				x			
Brief Trauma Questionnaire (BTQ)			x				
Brief AUD Severity Scale (BASS			x				
Clinical Institute W/D Assessment for Alcohol (CIWA-AR)	x		x	x	x	x	
Columbia Suicide Severity Rating Scale (C-SSRS)	x		x	x	x	x	
Safety Labs CMP/CBC (blood sample)		x					x
Concomitant Medications	x	x	x	x	x	x	
Cannabis Use Disorder Identification Test (CUDIT)			x				
Demographics	x						
Drinking Goal			x				
Drug Compliance/Accountability				x	x	x	
Drug Screen (urine sample)	x	x	x	x	x	x	
Electrocardiogram (ECG)		x					x
Fagerstrom Test for Nicotine Dependence (FTND)			x				
Family Tree Questionnaire (FTQ)			x				
Graded Chronic Pain Scale (GCPS)			x	x	x	x	
ImBIBe			x	x	x	x	
Inflammation and Behavior Questionnaire			x	x	x	x	
Insomnia Severity Index (ISI)			x	x	x	x	
Locator Form	x						
Medical History		x					
NIH Toolbox			x			x	
Neuroimmune assays (blood sample)*			x	x	x	x	
Penn Alcohol Craving Scale (PACS)			x	x	x	x	
Physical Exam		x					
Pregnancy Test (urine sample)	x		x	x	x	x	
Profile of Mood States (POMS)			x	x	x	x	
Readiness to Change (RTC) Ladder			x				
Reward-Relief Drinking Scale			x				
Risky Families Questionnaire			x				
Salivary Cortisol Testing				x			
Spielberger State-Trait Anxiety Scale (STAI)				x			
Structured Clinical Interview for DSM-5 (SCID-5)	x						
Subjective Distress Units Scale (SUDS)				x			
Take Control (Computer-delivered)			x	x	x	x	

Timeline Follow Back (TLFB)**	x	x	x	x	x	x	x
Vital Signs (including weight)	x	x	x	x	x	x	x

*RNA sample collected only at Randomization and Week 12 visits.

**TLFB assessment will also be conducted by phone at weeks 2, 6, and 10.

9.2. Adverse Childhood Experiences Questionnaire (ACE)

The Adverse Childhood Experiences Questionnaire (ACE) is a 10-item self-report measure developed to identify childhood experiences of abuse and neglect. The ACE will be completed electronically at the randomization visit.

9.3. Adverse Events (AE) and Serious Adverse Events (SAE)

The study physician and study site staff are responsible for the detection, documentation, classification, reporting, and follow up of events meeting the definition of an AE or SAE. Adverse Events will be assessed at the medical screening visit and at each subsequent visit through the week 12 follow up visit. However, SAEs will be collected from the time of informed consent onward. General symptoms will be collected via an open ended question: “How have you been feeling since your last visit or the last time we spoke?”

Adverse Events will be recorded on the AE Log using accepted medical terms and/or the diagnoses that accurately characterize the event. When a diagnosis is known, the AE term recorded on the eCRF will be the diagnosis rather than a constellation of symptoms. The study physician will assess all AEs for seriousness, relationship to study medication, and severity. When an event has not resolved by study closure, it will be documented on the AE Log as “ongoing”.

If a woman has a positive or borderline pregnancy test after enrollment, the pregnancy will be recorded as an AE. The site will contact the subject at least monthly and document the subject’s status until the pregnancy has been terminated or completed. The outcome of the pregnancy (e.g., normal birth, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn) will be recorded.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by study physicians until satisfactory resolution (the event either resolved or stabilized and is not expected to resolve in the near term). All SAE’s will be reported per requirements.

9.3.1. Adverse Event (AE) Definition

An AE is any untoward medical occurrence in a participant who has been administered a pharmaceutical product and may not necessarily have a causal relationship with the administered treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant laboratory abnormality), symptom, or disease temporally associated with the use of the study medication, whether or not related to the medication. Pre-existing conditions, diseases, or disorders are not considered AEs unless there is a change in severity or frequency.

9.3.1.1. Classification of Adverse Event Intensity and Relationship to Study Medication

For each recorded AE or SAE, the physician must make an assessment of severity based on the following criteria:

- Mild: An event that is usually transient, requiring no special treatment, and does not generally interfere with the subject's daily activities.
- Moderate: An event that interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject. The event is usually ameliorated with additional specific therapeutic intervention.
- Severe: An event that interrupts usual activities of daily living or significantly affects clinical status. The event poses a significant risk of harm to the subject and hospitalization may be required, and typically requires intensive therapeutic intervention.
- Life-threatening: An event that puts the subject into imminent risk of death without intervention.

The physician must also make an assessment of relationship to the investigational product based on the following criteria:

- Unrelated: The subject did not receive the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is not reasonable, or there is another obvious cause of the AE/SAE.
- Unlikely: There is evidence of exposure to the investigational product but there is another more likely cause of the AE/SAE.
- Possible: There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, but the AE/SAE could have been due to another equally likely cause.
- Probable: There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, and the AE/SAE is more likely explained by the investigational product than by any other cause.
- Definite: There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, the AE/SAE is more likely explained by the investigational product than by any other cause, and the AE/SAE shows a pattern consistent with previous knowledge of the investigational product or investigational product class.

9.3.1.2. Outcomes and Actions Taken

All unresolved AEs will be followed for a minimum of 14 days (unless the AE is an ongoing pregnancy which must be followed to conclusion) after the subject's final study visit, unless the investigator's judgment dictates otherwise, the event has resolved or stabilized prior to the 14-day period, or the subject is lost to follow-up. Investigators are not obligated to actively seek AEs or SAEs in former study subjects that occur following the follow-up period.

For each recorded AE or SAE, the investigator must make an assessment of outcome at the time of last observation, as follows:

- Fatal: The subject died.
- Resolved without Sequelae: The AE or SAE has ended.

- Resolved with Sequelae: The AE or SAE has ended but changes are noted from baseline.
- Unresolved – Ongoing: The AE has not ended and is ongoing at the end of the reporting period (i.e., 14 days after the final Follow-up visit) and the investigator deems that further follow up is not medically required
- Unknown – Lost to Follow-up: Lost to follow-up after repeated unsuccessful attempts to contact the subject.

Actions taken with respect to study medication (discontinuation or not) will also be recorded. In addition, if the AE was treated (medications or other physical measures), this will also be recorded.

9.3.2. Serious Adverse Event (SAE) Definition

An SAE is any untoward medical occurrence that meets one of the following:

- Results in death
- Is life-threatening (at the time of the event)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

A serious and unexpected AE is an SAE that is not identified in nature, intensity, or frequency in the risk information included in the Product Label for the drug. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the study subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

9.4. Alcohol Breathalyzer

An alcohol breathalyzer will be administered at consent, and at every in-clinic visit as a safety measure. BrAC must be equal to 0.000 prior to performing any study assessments. Results will be recorded on the paper checklist, and later entered into the database.

9.5. Alcohol Dependency Scale (ADS)

The Alcohol Dependency Scale is a 25-item scale that measures alcohol dependence symptoms over the past 12-months. The ADS assesses problems that are relevant for alcohol dependent drinkers. The ADS is a self-report measure that will be completed by the participant electronically at the randomization visit, and at each follow-up visit.

9.6. Alcohol Purchase Task (APT)

The Alcohol Purchase Task is a 16-item scale that uses hypothetical situations regarding alcohol purchases and consumption at varying prices in order to generate several indices of alcohol-related reinforcement. The APT is a self-report measure that will completed by the participant electronically at the randomization visit, and at each follow-up visit.

9.7. Alcohol Use Disorders Identification Test (AUDIT)

The Alcohol Use Disorders Identification Test is used to identify persons with hazardous and harmful patterns of alcohol consumption. The AUDIT was developed by the World Health Organization (WHO) as a simple method of screening for excessive drinking. The AUDIT is a self-report measure that will be completed by the participant electronically at the randomization visit.

9.8. Beck Anxiety Inventory (BAI)

The Beck Anxiety Inventory (BAI) surveys anxiety symptomatology including physical and cognitive indicators of anxious mood. The BAI will be completed electronically at randomization, and all follow up visits.

9.9. Beck Depression Inventory (BDI-II)

The Beck Depression Inventory, Revised (BDI-II) captures depressive symptomatology (and is needed to test exploratory aim #1). The BDI-II will be completed at the initial screening, randomization, and all follow up visits.

9.10. Birth Control Assessment

The Birth Control Assessment is designed to confirm a female subject's compliance with the birth control specifications detailed in the inclusion criteria. Birth Control Assessment information will be recorded on the checklist at the initial screening visit for participant safety purposes.

9.11. Brief Trauma Questionnaire (BTQ)

The Brief Trauma Questionnaire (BTQ) is a 10-item questionnaire derived from the Brief Trauma Interview (BTI) and is used to assess traumatic exposure according to Criterion A in the PTSD module of the DSM-V. The BTQ will be administered electronically at the randomization visit.

9.12. Brief AUD Severity Scale (BASS)

The Brief AUD Severity Scale (BASS) is a 9-item self-report measure used to assess alcohol use disorder severity. The BASS will be completed at the randomization visit.

9.13. Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)

The CIWA-AR is a brief 10-item measure used to provide a quantitative index of the severity of the alcohol withdrawal syndrome. The CIWA-AR has been used both in clinical and research applications and has demonstrated both reliability and validity. This questionnaire will be administered on paper by appropriately trained staff during screening, at the randomization visit, and at each follow-up visit. Participant responses will then be entered electronically.

9.14. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a 4-page form asking questions about suicidal ideation, intensity of ideation, and suicidal behavior developed by Posner and collaborators at the New York State Psychiatric Institute. This scale is intended for use by trained administrators. The questions contained in the C-SSRS are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment. Training is required before administering the C-SSRS through a 30-minute interactive slide presentation followed by a question-answer session through the Columbia University Medical Center. Those completing the training are certified to administer the C-SSRS, and will receive a training certificate. This scale will be used to assess current suicidal ideation at screening, randomization, and at each follow up visit and will be administered by a trained staff member with responses recorded on paper first, then entered electronically.

9.15. Comprehensive Metabolic Panel/Complete Blood Count

Blood will be drawn for a comprehensive metabolic panel and complete drug count during the medical screening and follow up visit at week 16 to assess for participant safety. The total blood volume to be collected is approximately 8 mL. Additional laboratory samples may be taken at the discretion of the study physician if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure safety.

9.16. Concomitant Medications

All medications taken by the participant 2-weeks prior to the start of screening and through the final follow-up at week 12, collected via participant self-report will be recorded recorded on a source document and later entered electronically.

9.17. Cannabis Use Disorder Identification Test (CUDIT)

The Cannabis Use Disorders Identification Test is used to identify persons with hazardous and harmful patterns of cannabis consumption. The CUDIT was developed a simple method of screening for excessive cannabis use. The CUDIT is a self-report measure that will be completed by the participant electronically at the randomization visit.

9.18. Demographics

Demographics data include the participant's age, gender, race/ethnicity, marital status, education, employment pattern, occupation, and income level. These data will be collected electronically at the initial screening visit.

9.19. Drinking Goal

Drinking Goal is 1-item questionnaire that assesses for the subject's treatment goal in regards to alcohol. The responses are categorized into a controlled drinking goal, complete abstinence, or conditional abstinence. This questionnaire will be completed electronically at the randomization visit.

9.20. Drug Compliance/Accountability

Drug Accountability and Compliance will be monitored by the study staff using participant self-report verified by the pill count method at each follow-up visit. Participants will be asked to bring all unused medication and any packaging, including used blister-packs, to each in-person visit.

9.21. Drug Screen

An FDA cleared, CLIA waived urine drug test card will be used at all visits to assess for recent use of opioids, cocaine, amphetamines, methamphetamine, THC, buprenorphine, methadone or benzodiazepines. Subjects must be negative for all substances except THC. Results will be recorded on the visit checklist first and then entered into the database.

9.22. Electrocardiogram (ECG)

A 12-lead resting ECG will be obtained at the medical screening visit and repeated at week 16. Any abnormalities will be noted and an assessment of clinical significance will be made by the study physician.

9.23. Fagerström Test for Nicotine Dependence (FTND)

The Fagerström Test for Nicotine Dependence will be used to assess smoking status and motivation to change smoking behavior. This questionnaire will be completed by the subject electronically at the randomization visit.

9.24. Family Tree Questionnaire (FTQ)

Information on family history of alcohol problems will be collected using the Family Tree Questionnaire. The questionnaire provides subjects with a family tree listing of relatives to identify blood relatives with alcohol problems. This questionnaire will be completed by the subject electronically at the randomization visit.

9.25. Graded Chronic Pain Scale

The Graded Chronic Pain scale is a 7-item measure used to evaluate an individual's overall severity of chronic pain if they have suffered from chronic pain that has lasted at least six months. The measure assesses on two dimensions: pain severity, and pain-related disability. This questionnaire will be completed by participants electronically at the randomization visit, and at each follow-up visit.

9.26. ImBIBe

ImBIBe is a 15-item questionnaire in which the subject responds on a 5-point scale responses to questions on the consequences of alcohol use. This scale was adapted from the Drinker Inventory of Consequences (Drinc) questionnaire based on FDA recommendations on patient reported outcomes. This questionnaire will be completed by the participant electronically at randomization and at each follow-up visit.

9.27. Inflammation and Behavior Questionnaire

The Inflammation and Behavior Questionnaire will be used to collect relevant inflammatory information, including if the subject has recently been ill, had any vaccinations, taken any anti-

inflammatory medications, consumed caffeine, and exercised. This questionnaire will be completed in conjunction with the blood draw for neuroimmune markers, and will be completed at the randomization and all in-person follow up visits.

9.28. Insomnia Severity Index (ISI)

The Insomnia Severity Index ISI) is a 7-item measure used to assess symptoms of insomnia. The questionnaire probes for the participant's perception and severity of their quality of sleep. This questionnaire will be completed electronically at randomization, and all follow up visits.

9.29. Locator Form

The Locator Form asks participant to provide his/her name, address, and phone number and to provide names, addresses, and phone numbers of friends and family members who can be contacted if the subject cannot be located. This information is essential and will be collected during the initial screening, and will be updated throughout the study as necessary.

9.30. Medical History

A Medical History interview will be conducted by the study physician at the medical screening visit and will screen for medical conditions that contraindicate the study medication, Ibudilast.

9.31. NIH Toolbox

The NIH Toolbox is a platform that provides comprehensive assessment tools for researchers, providing measures that assess from four primary batteries – cognition, sensation, motor and emotion. This platform was developed by HealthMeasures and the NIH. The participants will complete questionnaires electronically from the cognition domain at the randomization visit, and at the 12-week follow-up visit (if visit is completed in-person).

9.32. Neuroimmune Assays

Identifying the effects of IBUD on inflammatory marker levels has the potential to elucidate the biological mechanisms of action of this neuroimmune modulator. Blood samples will be collected at randomization and at in-person follow-ups to address exploratory aim #2. Two lavender EDTA tubes will be collected for plasma to identify markers including innate immune receptors (TLR2, TLR4), cytokines (TNF-α, IL-1α, IL-1β, IL-2, IL-6, IL-10, IL12p70, GM-CSF, IFNγ), chemokines (MCP-1, MIP-1α, and MIP-1β), and other inflammatory signaling molecules (reactive oxidative species, NO, substance P, C-reactive protein). In addition, one RNA PAXgene tube will be collected at randomization and week 12 (if visit is completed in-person) to identify transcription factors that code for cytokines. Due to the diurnal rhythm of cytokine production (117), attempts will be made to collect samples in the early afternoon for all subjects.

9.33. Penn Alcohol Craving Scale (PACS)

The PACS is a five-item, self-report measure that includes questions about the frequency, intensity, and duration of craving, the ability to resist drinking, and asks for an overall rating of craving for alcohol for the previous week. Each question is scaled from 0 to 6. Participants will complete this scale at randomization, and at each follow up visit.

9.34. Physical Exam

A physical examination of the oral cavity, head, eyes, ears, nose, and throat, cardiovascular system, lungs, abdomen, extremities, skin, neuropsychiatric mental status and sensory/motor status, musculoskeletal system and general appearance will be performed during the medical screening visit. Abnormal findings will be reported as AEs, if appropriate.

9.35. Pregnancy Test

An FDA approved rapid result urine pregnancy test will be used (i.e., dipstick test) to assess for pregnancy in female participants at the initial screening, randomization, and in-person follow-up visits. If applicable, participants will be asked to sign a release of information form for study personnel to access medical records to obtain information regarding the outcome of a pregnancy that occurred during the study.

9.36. Profile of Mood States (POMS)

The POMS measures dimensions of mood and will be completed electronically at randomization, and follow up visits.

9.37. Readiness to Change (RTC) Ladder

The Readiness to Change Ladder is a measure with 11 response items designed to assess motivation to reduce or cut back on drinking. This assessment will be completed at the randomization visit.

9.38. Reward-Relief Drinking Scale

The Reward-Relief Drinking Scale is a 4-item scale that measures an individual's reward drinking tendencies. This measure was adapted from the Inventory of Drinking Situations. The participants will complete this measure electronically at randomization.

9.39. Risky Families Questionnaire

The Risky Families Questionnaire is a 13-item self-report that assesses the relation of childhood experiences to mental and physical health outcomes in adulthood. This measure was adapted from the Adverse Childhood Experiences (ACE). This questionnaire will be completed electronically at the randomization visit.

9.40. Salivary Cortisol Testing

Saliva samples will be collected for testing of cortisol levels as a biological measure of stress response at 3 time points during the week 4 follow up visit (at the beginning of the visit, immediately before the fMRI stress task, and immediately after the fMRI stress task).

9.41. Spielberger State-Trait Anxiety Inventory (STAI)

The STAI is a commonly used measure of trait and state anxiety. For this study, the short form, which has 6 items for assessing state anxiety will be completed before and after the stress task, which takes place during the fMRI session at week 4.

9.42. Structured Clinical Interview for DSM-5 Disorders (SCID-5)

The SCID is a semi-structured interview for making the major DSM-5 diagnoses. It will be performed by a master's level clinician under the supervision of the PI. The SCID-5 will be used to assess current (past 12-month) AUD diagnosis (moderate or severe) as well as exclusionary diagnoses (e.g., lifetime psychosis) at the initial screening visit.

9.43. Subjective Units of Distress Scale (SUDS)

The SUDS is a scale of 0-10 for measuring the subjective intensity of disturbance or distress currently experienced by an individual. This measure will be collected before and after the stress task, which takes place during the fMRI session at week 4.

9.44. Take Control Behavioral Platform

The behavioral platform "Take Control" will consist of a series of 11 computerized modules. Participants will view 2 modules of "Take Control" at randomization and at each in-person follow up visit. If a visit is missed, missed modules will be reviewed at the next visit. The intervention is derived from a self-help approach developed by NIAAA that provides evidence-based, field tested information for individuals with alcohol problems, and suggestions for making changes in their drinking. The NIAAA material is publicly available in a NIAAA booklet entitled "Rethinking Drinking" and on a NIAAA website http://rethinkingdrinking.niaaa.nih.gov. Delivering these materials in a computerized method in this trial has the advantage of standardizing the amount of educational material received by the subject.

9.45. Timeline Follow Back (TLFB)

The Time Line Follow Back will be administered to assess quantity and frequency of alcohol, cigarette and marijuana use and will be completed at the initial screening (for the 30 days prior to that visit) and at each subsequent visit to gather data for every day prior to and including the last visit. The TLFB interview will be conducted at all in-person visits and by telephone on weeks 2, 6, and 10 (and any other remote visits) to shorten the duration between drinking outcomes assessment. Information obtained in this interview will be recorded on the TLFB Calendar and transcribed to the database.

9.46. Vital Signs

Vital signs assessed at each visit include sitting blood pressure and pulse rate (after sitting for at least 3 minutes) and weight. Values will be recorded on the visit checklist and entered into the database.

10. STATISTICAL METHODS AND POWER CONSIDERATIONS

The experimental design is a two-arm Phase II, randomized, double-blind, placebo-controlled 12-week clinical trial of IBUD (50mg BID) for the treatment of AUD. We plan to randomize 132 treatment-seekers with current moderate-to-severe AUD. Participants will complete telephone screening, followed by in-person eligibility assessment, a physical exam for medical eligibility assessment, randomization to study medication or matched placebo, and in-person follow-up visits at 4, 8, and 12 weeks and telephone interviews for drinking outcomes (i.e., TLFB) at 2, 6,

and 10 weeks. Randomization will be done in a 1:1 ratio, to either IBUD or placebo using a stratified block randomization procedure, gender and drinking status (moderate drinking defined as ≥ 14 drinks/week for men and ≥ 7 drinks/week for women versus heavy drinking defined as ≥ 28 drinks/week for men and ≥ 21 drinks/week for women) as the stratification factors.

Data analysis will utilize a modified Intention-to-Treat (mITT) population that includes all randomized patients who took at least one dose of medication and provided valid post-randomization outcome data. The primary tests of hypotheses will use percent heavy drinking days (4+ drinks for women/ 5+ drinks for men) measured by the TLFB at weeks 2, 4, 6, 8, 10, and 12 as a-priori primary efficacy endpoint. Other outcomes will also be analyzed as described in the secondary and exploratory aims. Prior to statistical analyses, the data will be inspected to determine the advisability of scale transformations and to identify missing data, outliers, or other unusual features that may be influential. Preliminary analyses will also be performed to compare treatment groups on descriptive and clinical characteristics at baseline to ensure that randomization has succeeded. If confounding variables are found, they will be included as covariates in follow-up analyses. Power analyses have been performed to ensure that the study has sufficient power to detect a small to medium effect size for testing the primary hypothesis using a mixed effects model that takes into account of the repeated measures design. Strategies for handling missing data and performing sensitivity analyses are outlined below.

10.1. Statistical Power

We performed power analyses using the PASS 14 software for the primary hypothesis under the mixed effect model design. Because the lack of preliminary data on IBUD for the primary outcome, we used a similarly designed clinical trial of varenicline (125) as a reference for the anticipated effect size in our power calculations. Specifically, the varenicline study (125) showed that the percent heavy drinking days was 39.6 (SE=3.7) for the varenicline versus 50.2 (SE=3.6) for placebo (difference=10.6; Cohen's d=0.31). With a total of 132 participants (66 subject/group * 2 groups), our repeated measures mixed effect model design will have 93.73% power to detect an effect size of 0.3 (between a small effect size of 0.2 and medium effect size of 0.5 (126)) for the treatment group difference with 12 repeated measurements assuming a compound symmetry covariance structure when the standard deviation is 35.0, the correlation between observations on the same subject is 0.2, and the alpha level is 0.05. We also investigated the power under a variety of other scenarios by varying the covariance structure (Compound Symmetry, Simple, AR(1), and Banded(1)) and the within-subject correlation (from 0.1 to 0.4), all yielded satisfactory power (ranging from 79% to 99%). Importantly, power analyses have been performed to ensure that the study has sufficient power to detect a small to medium effect size for testing the primary hypothesis using a mixed effects model that takes into account of the repeated measures design. The varenicline trial by Litten et al. (2013) was used merely as a reference point and no effect sizes from that trial were used in our analyses.

10.2. Aim 1: To test the primary hypothesis that IBUD (50mg BID) will reduce percent heavy drinking days, as compared to placebo, over the course of the 12-week trial

The a priori primary efficacy endpoint will be percent heavy drinking days, defined as 4+ drinks for women/5+ drinks for men, measured bi-weekly during the maintenance phase of the study

(Weeks 1-12). Patients who discontinued medication will be allowed to remain in the study and participate in study assessments. The primary efficacy analysis will be performed using a repeated measures mixed effects model (GLIMMIX with PROC GLIMMIX in SAS) that includes treatment, time, treatment x time interaction, a random intercept and a random slope, and adjusts for other covariates such as demographic and baseline variables as appropriate. The mixed effects model approach permits testing of between-group differences, within-group changes, and performance trends over time. It also uses all observed repeated measurements data, treating the missing data mechanism as ignorable (see the discussion of attrition below). In addition to testing the treatment effects, a summary of least-square means, standard errors, and 95% confidence intervals (CIs) will be presented for each treatment and will be derived from fully adjusted models on untransformed outcomes averaged across the maintenance period.

10.3. Missing Data and Sensitivity Analysis

The intent to treat (ITT) principle requires all randomized participants to be included in the analyses, but one has to deal with missing outcome measures due to loss to follow-up. First of all, we will minimize the extent of missing data by attempting to follow up all randomized participants event if they withdraw from allocated treatment, and to collect information on reasons of loss to follow-up which can help to determine whether it is related to the outcome. Secondly, we plan to perform sensitivity analyses to explore the effect of departures from the missing data assumptions made in the efficacy analyses. Our primary efficacy model, the linear mixed effects model, assumes missing at random (MAR), which is plausible if the reason for missing data is administrative but implausible if missing data is outcome related. Sensitivity analyses choices will include, but are not limited to, imputation methods as well as the joint modeling approach. Imputation will be done in different ways including a) imputing missing values as heavy drinking days and b) multiple imputation similar to Litten et al. (2013) (125). In addition, we will consider joint models that permits non-ignorable intermittent and monotone missing values (127). Dr. Li is an expert on joint modeling of longitudinal data with non-ignorable missing data and co-author of a recent monograph on joint models (Elashoff, Li, and Li, 2016). All randomized participants will be accounted for in the sensitivity analyses.

10.4. Aim 2: To test the efficacy of IBUD (50mg BID) on secondary alcohol consumption endpoints

In this secondary aim, we plan on traditional analyses of the effects during the maintenance phase of the study (Weeks 1-12) on the following secondary alcohol consumption endpoints: (1) drinks per day, (2) drinks per drinking day, (3) percent days abstinent, (4) percent subjects with no heavy drinking days (PSNHDD), and (5) percent subjects abstinent. The analytical plan for the secondary outcomes with repeated measures are similar to that for the primary efficacy endpoint as discussed above for aim 1. For the dichotomous outcomes (PSNHDD and percent subject abstinent), logistic regression models will be used. Further, in light of recent research on AUD endpoints, we will examine secondary outcomes when allowing an optimal grace period of first 4 weeks and will evaluate the efficacy of IBUD over the maintenance period (Weeks 5-12) (128).

10.5. Exploratory Aim 1: To test whether the effects of IBUD (50mg BID) on the primary and secondary endpoints (aims 1 and 2) are moderated by depressive symptomatology.

Based on our finding that IBUD attenuated the stimulant effects of alcohol among individuals with higher depressive symptomatology, we will examine if the effects of IBUD on the efficacy outcomes are moderated by depressive symptomatology. A moderator identifies for whom or under what conditions a treatment works. It may suggest which participants will respond most to treatment or identify subgroups with possibly different causal pathways. We will study moderators based upon criteria given in Kraemer et al (2002) (129). For the repeated measured efficacy outcomes, we will include depressive symptomatology in the analyses, using the mixed effects analysis designs described above, and testing the interactions of (depressive symptomatology) x treatment as well as (depressive symptomatology) x treatment x time. For the dichotomous outcomes (PSNHDD and percent subject abstinent), we will include depressive symptomatology in the logistic regression analyses, and testing the interactions of depressive symptomatology x treatment. To reduce confounding of main effects with these interaction terms and increase the interpretability of the regression coefficients, the variables will be centered as recommended by Kraemer and Blasey (2004) (130). If interactions are significant, we will estimate treatment effects at low, middle and high values of the moderator (Littell et al., 1996, p. 175) (131). Further, as recommended by the reviewer, we will test whether physiological dependence (marked by tolerance and withdrawal) serves as a moderator of medication effects in this trial, using the framework proposed herein.

10.6. Exploratory Aim 2

In this exploratory aim, we will test whether IBUD (50mg BID) reduces neuroinflammation, as indexed by circulating blood levels of proinflammatory markers over the course of the 12-week trial, using the mixed effect model design. The statistical considerations are similar to aim 1 and thus not repeated here.

11. ETHICS

11.1. IRB Review

The study will be conducted under a protocol reviewed by the UCLA IRB; the study is to be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the study will ensure that the hazards do not outweigh the potential benefits; the results to be reported will be accurate; subjects will give their informed consent and will be competent to do so and not under duress; and all study staff will comply with the ethical principles in 21 Code of Federal Regulations (CFR) Part 50 and the Belmont Principles.

11.1.1. Protocol Modifications

All necessary protocol changes will be submitted in writing as protocol amendments to the IRB by the PI for approval prior to implementation.

11.1.2. Protocol Deviation Reporting Procedures

All subject-specific deviations from the protocol are to be documented. The PI or designee will be responsible for identifying and reporting all deviations, which are occurrences involving a procedure that did not follow the study protocol. Any protocol deviation that adversely affects the

safety or rights of a subject or scientific integrity of the study is considered a major deviation and will be reported immediately to the UCLA IRB.

11.2. Ethical Conduct of the Study

This study will be conducted in accordance with all applicable Federal human research protections requirements and the Belmont Principles of respect for persons, beneficence, and justice. The procedures set out in this study are designed to ensure that all study personnel abide by the principles of the ICH GCP Guideline and the Code of Federal Regulations (CFR). The PI confirms this by signing FDA Form 1572.

11.2.1. Confidentiality of Data and Subject Records

To maintain subject confidentiality, all laboratory specimens, eCRFs, reports and other records will be identified by a subject number only. Research and clinical records will be stored in a locked cabinet. Only research staff, sponsor officials, and other required regulatory representatives will have access to the records. Subject information will not be released without written permission. The PI has received a Certificate of Confidentiality for this study.

11.2.2. Compensation for Participation

Subjects will be compensated for travel expenses and for time contributed to this research study in the form of cash. Compensation will be provided at each subject visit and is detailed in the informed consent form.

11.2.3. Written Informed Consent

The informed consent process and document will be reviewed and approved by the IRB and prior to initiation of the study. The consent document contains a full explanation of the possible risks, advantages, and alternate treatment options, and availability of treatment in the case of injury, in accordance with 21 CFR Part 50. The consent document indicates that by signature, the subject, permits access to relevant medical records as described above. A written informed consent document, in compliance with 21 CFR Part 50, 32 CFR Part 219, and the Belmont Principles, and HIPAA Authorization will be signed by the subject before any study-related procedures are initiated for each subject. All potential subjects for the study will be given a current copy of the Informed Consent Form to read. All aspects of the study and informed consent will be explained in lay language to the subject by either the investigator, or a medically trained designee. Any subject who is unable to demonstrate understanding of the information contained in the informed consent will be excluded from study participation.
All study subjects will be given a copy of the signed informed consent.

11.2.4. Delegation of Responsibilities and Adequate Resources

The PI should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study. The term “investigator” used throughout this protocol refers to the PI and/or qualified Sub-investigators. The PI may delegate responsibilities to other study site personnel. The PI shall delegate tasks only to individuals qualified by education, training, and experience to perform the delegated tasks. The PI shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The PI is responsible for ensuring all delegated staff has been properly trained on the protocol

and their assigned study responsibilities. A delegation log identifying all delegated duties and the individual to whom they have been delegated will be maintained at the study site.

11.2.5. Financial Disclosure

Clinical investigators are required to provide financial disclosure information for the submission of certification or disclosure statements required under 21 CFR § 54. As defined in 21 CFR §54.2, a clinical investigator is a listed or identified investigator or sub-investigator who is directly involved in the treatment or evaluation of research subjects. The term also includes the spouse and each dependent child of the investigator. In addition, investigators must promptly update financial disclosure information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

12. DATA HANDLING AND RECORD KEEPING

Source documents include but are not limited to original documents, data and records such as hospital/medical records (including electronic health records), clinic charts, laboratory results, data recorded in automated instruments, and pharmacy records, etc. This study will use an electronic data capture (EDC) eCRF system (Qualtrics) and paper source documents. Data will be transcribed from source documentation directly into a statistical program such as SPSS. Only questionnaire data will be entered directly into eCRF (i.e., without prior written or electronic record of data). Paper copies of the eCRFs will be available in the event that the EDC is not accessible at the time the questionnaire is being completed. The transcribed data will be consistent with the source documents or the discrepancies will be explained. All entries, corrections, and alterations will be made by the investigator or other authorized study personnel. The EDC system maintains a full audit trail of data entry, data corrections, and data queries.

12.1. Subject Identification and Confidentiality

Subjects will be identified on eCRFs and paper source documents by a unique subject number. No personal identifier will be used in any publication or communication used to support this research study. The subject number will be used if it becomes necessary to identify data specific to a single subject. Regulatory bodies, such as the study sponsor, FDA, and IRB, are eligible to review medical and research records related to this study as a part of their responsibility to protect human subjects in clinical research. Personal identifiers will be removed from photocopied or electronic medical and research records.

12.2. Retention of Records

The investigator is responsible for creating and/or maintaining all study documentation required by Title 21 Code of Federal Regulations (21CFR) Parts 50, 54, 56, and 312, ICH E6 section 8, as well as any other documentation defined in the protocol. The investigator must provide key documents to the Sponsor prior to start of the study. Federal and local regulations require that the investigator retain a copy of all regulatory documents and records that support the data for this study for whichever of the following is the longest period of time:

- A period of 2 years following the final date of approval by the FDA or other regulatory agency of the study drug for the purposes that were the subject of the investigation; or
- A period of 5 years following the date on which the results of the investigation were submitted to the FDA or other regulatory agency in support of, or as part of, an

application for a research or marketing permit for the study drug for the purposes that were the subject of the investigation.

If the investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Study records should not be destroyed without consultation with the Sponsor.

12.3. Trial Registration

The PI will register the trial on the National Library of Medicine's Clinical Trials Registry at http://www.clinicaltrials.gov.

13. REFERENCES

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