THE EFFECTS OF THE HISTAMINE-3 RECEPTOR INVERSE AGONIST PITOLISANT ON ALCOHOL SELF-ADMINISTRATION IN HEAVY DRINKERS

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1 List of Abbreviations

Abbreviation	Abbreviation definition
Alcohol Use Disorder	AUD

2 Protocol Summary

Title:	The Effects of the Histamine-3 Receptor Inverse Agonist Pitolisant on Alcohol Self-Administration in Heavy Drinkers
Population:	The present study will involve 72 men and women aged 21 to 55 who exceed safe levels of drinking. Women and minorities who meet the study criteria will be eligible to participate. No vulnerable populations are being targeted for inclusion in this study.
Intervention:	Eligible subjects will receive a dose of 8.9 mg (two 4.45 mg pills) of pitolisant or a matched placebo once daily over a 7-day period and a dose of 17.8 mg (one 17.8 mg pill) of pitolisant or matched placebo once daily over a 5-day period. A 25 mg riboflavin tracer will be added to each 4.45 mg capsule and 50 mg riboflavin tracer will be added to each 17.8 mg capsule to serve as an objective measure of medication adherence. Subjects will take study medication by mouth. Subjects will receive alcohol in the laboratory on day 12 in an alcohol craving challenge. Subjects will be presented with four drinks, each mixed to raise their BAL 0.0125g/dl. They will be told that they can either consume the desired number of drinks over the following 60 minutes or they will receive the equivalent in a cash reward. This procedure will be repeated with an additional 4 drinks after 60 minutes has elapsed. Subjects will serve as their own controls. The intervention will be repeated with a placebo/pitolisant after a washout period. The order of pitolisant and placebo dosing will be randomized.
Objectives:	The specific objective of this study is to determine whether pitolisant, an H-3 receptor inverse agonist that is FDA-approved for treating narcolepsy, has effects on alcohol craving and consumption. Testing the effects of pitolisant on drinking is a compelling opportunity that is consistent with the mission of NIAAA to evaluate the efficacy of re-purposed compounds with novel mechanisms that have the potential to treat AUD. If successful, this study could lead to a phase II randomized controlled trial to test pitolisant as a treatment for AUD. The specific goal of this study is to evaluate the effects of pitolisant on drinking and craving among heavy drinkers in a human laboratory using an alcohol self-administration paradigm.

Design/Methodology:	This is a double-blind, randomized, placebo-controlled, crossover design trial that will test the effect of pitolisant on alcohol self-administration and craving following a priming dose of alcohol. An established human laboratory self-administration procedure will be followed. Each subject will complete 5 clinic visits over a period of up to 66 days of participation. Study participation is comprised of a baseline assessment, randomization visit, alcohol self administration Trial 1, an assessment visit to verify continued eligibility and dispense medication, and a second alcohol self-administration Trial. The volume of alcohol consumed during alcohol challenge trials 1 and 2 will be used to test the effect of pitolisant on alcohol consumption. Craving measures (AUQ and VAS) collected during the self-administration trials will be used to test the effect of pitolisant on alcohol craving.
Total Study Duration:	The entire study will take 24 months to complete.
Subject Participation Duration:	Each subject's length of participation will be up to 66 days.

3 Background/Rationale & Purpose

3.1 Background Information

Current models of care for treating Alcohol Use Disorder (AUD) include both behavioral therapies and pharmacotherapy[1]. Although pharmacotherapy for AUD in the US has been available since 1948 when disulfiram was approved, options for treatment are limited as there are only four medications which have been approved by the FDA for treating AUD. Disulfiram, naltrexone, acamprosate, and long-acting naltrexone have all shown promise as agents to treat AUD[2] but no single medication has proven to be effective across the heterogeneous groups of people with AUD[3]. Movement towards models of personalized care and pharmacogenetic treatment matching[4-5] hold some promise for improving AUD treatment outcomes, but the limited number of unique mechanisms of action of the currently approved drugs presents a challenge to implementing this model of care. Unfortunately, few novel compounds to treat AUD progress to phase II trials, and developing novel compounds is both costly and time-consuming[6]. One pathway of drug development efforts has been focused on re-purposing FDA approved medications that have promising mechanistic effects[7] and some success data has supported the use of H3 receptor antagonists as haing potential to modulate craving and consumption[8]. Identification of additional drugs with unique mechanisms of action that are found to reduce alcohol consumption could expand the treatment options and further the goal of personalized care for AUD. The overarching goal of our research is to identify agents with unique mechanisms that hold promise for treating AUD. The specific objective of this study is to determine whether pitolisant, an H-3 receptor inverse agonist that is FDA-approved for treating narcolepsy, has effects on alcohol craving and consumption.

Alcohol Use Disorder as a national health problem

More than 16 million adults suffer from Alcohol Use Disorder (AUD) in the United States[9]. The economic burden of this is estimated to be 249 billion dollars and approximately 88,000 Americans die from alcohol-related causes each year[10]. Untreated AUD is associated with an increased risk of accidents, injuries, suicide, and worsening of other health comorbidities[11] and it is the third most preventable cause of death in the US[10]. Treating addiction more effectively has become a priority of national importance and the Surgeon General has urged researchers to undertake testing of new treatments to combat addiction[12]. The present study is intended to answer the call for accelerating drug development for AUD by exploring the potential to re-purpose an existing drug as a treatment for AUD[6-7].

Rationale for developing pitolisant as an agent to treat AUD

H-3 histamine receptors are one of the four types of presently known histamine receptors. These G protein-coupled receptors are present predominately in the brain and are implicated in the regulation of a variety of behaviors including those related to cognitive function, locomotor activity and anxiety[13-15]. The finding that the density of binding of an H-3 receptor ligand was lower in insular cortical, accumbal, and hippocampal brain regions in alcohol-preferring rats (AA) as compared to alcohol-avoiding rats provided some of the first evidence that brain H-3 receptors may play an important role in the regulation of alcohol consumption[16]. Further evidence of this includes the observation that H-3 receptor knock-out mice derived from the C57B/6J strain consume less alcohol than wild type mice of this strain[17]. Numerous studies have shown that the administration of either H-3 receptor antagonists or H-3 inverse agonists/antagonists (i.e. ciproxifan clobenpropritor or thioperamide) reduces ethanol consumption in rats[16,18] and mice [18, 19,20]. In contrast, the administration of H-3 receptor agonists increases the self-administration of alcohol by AA rats[16]. Conditioned place preference studies indicate that H-3 receptor antagonists and inverse agonists/antagonists reduce alcohol-related reward[17,19-21]. This may be a factor that explains the reduction of alcohol consumption produced by these agents. It should be noted, however, that the administration of ciproxifan or the H-3 receptor antagonist conessine, failed to block ethanol-induced place preference in certain strains of mice, namely C57BL/6Sca[22] and Swiss mice[23], respectively. Cue-induced reinstatement of responding by mice for alcohol is attenuated by the administration either of the H-3 receptor antagonist JNJ-39220675 or by ciproxifan, suggesting that these agents may decrease alcohol cue-induced craving[24].

While much of the research based on animal studies indicates that pharmacological blockade of H-3 receptors may lead to reductions in the drinking of alcohol, the degree to which these studies will translate to human alcohol consumption in individuals with AUD remains to be determined. Ligand binding studies do indicate that H-3 receptors are located in several areas of the human brain that are linked to the regulation of alcohol consumption including the nucleus accumbens, insular cortex, and anterior cingulate[25-28].

Recently the FDA has approved the H-3 receptor inverse agonist/antagonist pitolisant for the treatment of excessive daytime sleepiness and catalepsy in narcolepsy patients. The Ki of this drug as an antagonist of the recombinant human H-3 receptor is 0.16 nm, and its E50 for its action as an inverse agonist at these receptors is 1.5 nm[13]. In contrast, the Ki for pitolisant at H1, H2, and H4 receptors are in the micromolar range indicating that this drug has a high degree of selectivity for the H-3 receptor. The therapeutic effects of pitolisant in narcolepsy patients may be mediated by the activation of histaminergic neurons resulting from the blockade of presynaptic H-3 receptors. The presynaptic actions of this drug promote the release of

histamine[13]. Increased histamine release in the nucleus accumbens produced by the administration of ciproxifan was found to correlate with reductions in alcohol seeking behaviors[24]. Whether the histamine releasing actions of drugs that counteract H-3 receptor activation can account for their suppressant effects on alcohol consumption in rodents is still being studied. Some authors have postulated that these effects may be related by the blockade of the effects of dopamine resulting from inhibition of H-3/dopamine heteroreceptors in the nucleus accumbens[24]. Pitolisant, in contrast to stimulants such as amphetamine that are abused, has not been found to elevate levels of mesolimbic dopamine[29].

In healthy volunteers who were moderate drinkers, enhanced bold signals in the striatal areas including the nucleus accumbens were found to correlate with stimulation ratings during alcohol infusion[30]. This finding suggests that alcohol-induced stimulation involves activation of the brain linked to the reinforcing effects of many drugs of abuse. One group of investigators has found that heavy drinkers may be more sensitive to the stimulant effects of alcohol than are light drinkers as measured on the ascending limb of the blood alcohol curve[31-33] and suggest that continued sensitivity to the stimulant effects of alcohol may be one of the factors that contributes to the continued alcohol consumption in AUD. Given the possible role of alcohol stimulant effects in facilitating drinking and that pitolisant has what can be construed as stimulant-like properties such as decreasing daytime sleepiness and in enhancing alertness, it is important to determine that this drug will not enhance the stimulating effects of alcohol in drinkers. We hypothesize that it will not for several reasons. Pitolisant as compared to psychomotor stimulants such as amphetamine does not increase the release of dopamine in the nucleus accumbens, which may play a key role in mediating the reinforcing effects of many drugs of abuse[29]. Unlike psychomotor stimulants pitolisant is not self-administered by primates, an established animal model of abuse liability[29]. More importantly, among people who use stimulants, drug liking and willingness to use the drug did not differ significantly between pitolisant and placebo[34]. In this study we will examine whether pitolisant increases the stimulant effects of a priming drink of alcohol as assessed using the biphasic alcohol effects scale (BAES)[35].

In narcolepsy patients, pitolisant is well tolerated but may produce some adverse effects such as insomnia and sleep disturbance that may be related to its activation of the systems that mediate this drug's therapeutic effects. In healthy human subjects, single oral doses of pitolisant at doses several times above those currently recommended for therapeutic use were well tolerated with EEG evidence of increased vigilance and enhanced attention being detected at the end test days[36]. The H-3 receptor antagonist, ABT-288, also has been reported to be well tolerated when it was administered to healthy young adults[37]. Thus, it is anticipated that pitolisant should be well tolerated in subjects who do not have narcolepsy.

3.2 Rationale and Purpose

This proposal holds significant innovation as there is strong evidence that medications that act as inverse agonists at the H-3 receptor decrease alcohol consumption and its rewarding effects. There are currently no published clinical studies concerning the effects of either H-3 receptor inverse agonists/antagonists or of H-3 receptor antagonists on alcohol consumption. This proposed study answers the call for accelerating the development of medications for AUD by testing a commercially-available and well-tolerated agent at a fraction of the cost of developing novel therapies. This proposal is innovative as no other human studies have explored

the H-3 receptor systems as a target for medications to treat alcohol use disorder. Given the compelling preclinical findings that H-3 inverse agonists/antagonists modulate craving and consumption, testing this mechanism in a human laboratory is the next logical step in drug development.

4 Objectives

4.1 Study Objectives

The specific objective of this study is to determine whether pitolisant has effects on alcohol craving and consumption. Testing the effects of pitolisant on drinking is a compelling opportunity that is consistent with the mission of NIAAA to evaluate the efficacy of re-purposed compounds with novel mechanisms that have the potential to treat AUD.

4.2 Study Outcome Measures

4.2.1 Primary Outcome Measures

The primary outcomes are alcohol consumption and cravings during the alcohol self-administration trials. Drinking volume during the alcohol self-administration will be measured to evaluate the effects of pitolisant vs. placebo on the rate of alcohol consumption after a priming drink. Alcohol craving will be measured using the Visual Analog Scale (VAS) and the Alcohol Urge Questionnaire (AUQ)[38] during the alcohol self-administration trial. These self-report measures of craving will be used to evaluate the effect of pitolisant on craving vs. placebo.

4.2.2 Secondary Outcome Measures

Secondary outcome measures for this study include the effect of pitolisant on 1) stimulant effects of alcohol, and 2) alcohol consumption and craving and sleep quality during the medication exposure period**.** The Biphasic Alcohol Effects Scale (BAES)[35] will be used to assess the effects of pitolisant administration on the stimulant effects of alcohol. The Obsessive-Compulsive Drinking Scale (OCDS)[39] and alcohol Visual Analog Scale (VAS) will be used to assess the effects of pitolisant on craving during the medication exposure period. Sleep Diaries will be used to assess the effects of pitolisant on sleep quality during the medication exposure period.

5 Study Design

This is a double-blind, randomized, placebo-controlled, crossover design trial that will test the effect of pitolisant on alcohol self-administration and craving following a priming dose of alcohol. An established human laboratory self-administration methodology developed by O'Malley and her colleagues will be followed[40]. The O'Malley self-administration methodology entails subjects consuming a priming drink of alcohol and subsequently participating in two one-hour self-administration sessions. In each session subjects receive four alcoholic drinks which

they may either drink, or otherwise receive compensation for not consuming. Confirmation of the validity of this approach as a method for screening for medications to treat AUD include the finding that pre-treatment with naltrexone significantly reduced alcohol consumption when the O'Malley methodology was used[40]. Using this method, our group has found that the anticonvulsant zonisamide reduces alcohol consumption in non-treatment seeking social drinkers[41]. We later confirmed that the administration of zonisamide decreases alcohol consumption in subjects with AUD in a double-blind randomized clinical trial[42] as have other investigators[43]. Testing pitolisant using this self-administration methodology is the next logical step in drug development given the strong evidence that the H-3 receptors are located in the pathways that regulate alcohol consumption in humans and that H-3 receptor inverse agonist/antagonists reduce drinking in animal models. The human laboratory-based alcohol self-administration methodology is cost effective and time-efficient for testing novel drug candidates for AUD treatment[44].

Subjects: Heavy-drinking subjects will be enrolled to increase the potential generalizability of these findings to a clinical AUD population. Subjects will be recruited through advertising, study flyers, internet postings, and an established subject registry at Boston Medical Center. Interested subjects will be screened by telephone to determine initial eligibility prior to the baseline assessment.

6 Potential Risks and Benefits

6.1 Risks

Risks of study medication

To minimize the risk of adverse health events we will instruct subjects to contact study staff with any questions or concerns about changes in health effects after initiating study medication/placebo. Trained medical staff will evaluate any reported adverse effects and make a clinical determination about management through dosing methods, dose discontinuation, and/or referral for medical care. If subject cannot tolerate the escalation in dose of study medication during the medication exposure period, their participation in the study will be discontinued and they will be instructed to stop taking the study medication immediately Subjects will be given a wallet card that includes a phone number with 24/7 coverage for medical emergencies. As an added safety precaution, subjects will be contacted three times mid-week of the medication exposure period for an adverse effect assessment.

Adverse events

The following adverse reactions were observed in data collected for 266 patients with narcolepsy, 114 of which received a placebo[45]. The incidence of the following adverse reactions of pitolisant versus placebo were as follows: Headache (18% vs 15%), Insomnia (6% vs 2%), Nausea (6% vs 3 %), Upper respiratory tract infection (5 % vs 3 %), Musculoskeletal pain (5% vs 3%), Anxiety (5 vs 1%), Heart rate increased (3% vs 0%). In post marketing reports, the following adverse effects have been recorded: fatigue, weight gain, epilepsy, abnormal behavior and dreams, bipolar disorder, depression/depressed mood, sleep disorders, nightmares,

suicidality, and pruritus. Post marketing reports of side effects are uncertain in causality and because the population size is unknown, the rates of these effects cannot be determined. Although pitolisant has wakefulness effects, it has not been found to have a strong potential for misuse[29].

Pitolisant can reduce the reliability of hormonal contraceptives, and it's dosing is altered by concomitant use of strong CYP2D6 inhibitors and CYP3A4 inducers. The pharmacodynamic effects of pitolisant may be blocked by the administration sedating histamine-1 receptor antagonists. Use of pitolisant can result in QT interval prolongation, especially when taken with other drugs that prolong the QT interval. Preclinical studies have found a risk of exposure during pregnancy with doses four times greater than the maximum dose. Given that the risk is unknown in humans, pregnant women should avoid exposure to pitolisant.

To protect against the risk of altered drug metabolism for subjects taking strong CYP2D6 inhibitors and CYP3A4 inducers, we will exclude subjects taking any of these medications. Subjects known to be poor CYP2D6 metabolizers (PMs) will also be excluded due to risk of higher pitolisant concentrations. Subjects who need to take sedating H-1 receptor antagonists will be excluded because these drugs may block the CNS effects of pitolisant.

Given that pitolisant is largely metabolized by the liver, subjects will be excluded from this study who have any clinically significant hepatic disease. Because the pharmacokinetics of pitolisant are unknown among people with renal disease, subjects will be excluded for renal insufficiency.

To protect against the risk of QT prolongation, subjects taking other medications which have this adverse effect will be excluded and we will exclude subjects whose have QTc interval > 450 msec. Subjects will also be excluded if they have a history of any clinically significant cardiac disease or a family history of long-QT syndrome.

Risks of Phlebotomy
To minimize the risk of pain, bruising, lightheadedness, and on rare occasions, infection or fainting from a blood draw, we will used trained phlebotomists.

Physical discomforts:

The drawing of blood may cause pain, bruising, lightheadedness, and on rare occasions, infection. Subjects may briefly feel the prick of the needle when it is inserted. Subjects may feel dizzy or faint when blood is drawn. Trained phlebotomists will be used to minimize these risks.

ECGs may cause discomfort and/or irritation of the skin (redness and itching) from the adhesive electrodes. Hair on your chest may need to be removed in order to obtain the best electrical contact between the adhesive electrodes and subjects' skin. Trained staff will be used to minimize these risks.

Risk to a developing fetus

The administration of pitolisant in pregnant women has not established a known risk for major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproductive studies, however, there is a known maternal and embryofetal toxicity in rats and rabbits.

To protect against the risk of potential developmental toxicity to a fetus, women will be excluded from study entry if they have a positive urine pregnancy test or if they are of childbearing age and are either not using appropriate methods of contraception or not practicing abstinence. Pitolisant may reduce the efficacy of oral contraceptives. If the subject's primary method of contraception is oral contraceptive, they will be required to use an approved back-up form of contraception beginning at first dose of pitolisant/placebo and continuing through 21 days following last dose. Urine pregnancy testing will also be completed at each study visit as a protection to the developing fetus. Subjects with positive pregnancy test results will be discontinued form participation.

Risks of alcohol self-administration

Risk to recovery efforts

Treatment-seeking drinkers will be excluded from this study to minimize the risk that drinking in the laboratory could worsen outcomes for a subject trying to reduce or abstain from alcohol. All subjects will undergo a medical screening and we will exclude subjects who have diagnosed medical or mental condition for which alcohol exposure in this study would be contraindicated. All subjects will receive the NIAAA self-help guide *Rethinking Drinking* at the end of study participation.

Risk of overconsumption

To minimize the risk of subjects reaching a level of intoxication that is uncomfortable to them, we will remind subjects that they may discontinue study participation at any time. Subjects will be asked to drink to a target BAL (0.03 g/dl) that is customary for them given the minimum drinking criteria. The alcohol self-administration paradigm that we have chosen does not include any coercion, inducements, or pressure to consume more alcohol than subjects feel comfortable consuming. There are no experimental manipulations that would increase drinking (e.g., heavy drinking confederate, anxiety manipulation). In fact, in this study design there are inducements for subjects to not drink beyond the initial priming dose. Subjects will receive monetary incentives for each drink that they do not consume. Access to medical backup services will be maintained throughout each alcohol challenge session. Subjects will be monitored during the course of the study, both through direct assessment with study staff and by observation through a video camera. Medical staff will evaluate subjects and may make a determination to halt study participation if the subject becomes too behaviorally impaired or if there are emergent safety issues. Subjects who have a BAL greater than 0.04 g/dl or who appear to be too behaviorally impaired to leave our research center will be asked to remain in the clinic until their intoxication is reduced to a level that it is safe to discharge them from the research laboratory. BAL readings will be taken twice to confirm BAL is not greater than 0.04 g/dl prior to release. Subjects will

not be released within 60 minutes of their last drink consumed to ensure that peak BAC has been reached prior to discharge. During the descending BAL period, subjects will have access to a comfortable space with entertainment (streaming media), snacks, non-alcoholic beverages, and a nearby bathroom.

Risks of suicidality

Following consent at screening and during subsequent visits, suicidal ideation and behavior will be assessed using a validated measure (C-SSRS) by trained and credentialed staff including the study PI (PhD, Clinical Psychology), study physician (MD), study nurse (RN, MSN), and project manager (LMHC). All suicidality assessments are completed during in-person visits and are reviewed in real time. Staff who perform suicidality assessments are experienced in managing suicidal ideation and behavior. Clinical staff will work with subjects to ensure a plan for safety, and if this cannot be achieved will escalate to a higher level of care. Subjects will be escorted to the BMC Emergency Department in the case of emergent suicidal ideation. All subjects who have any suicidal ideation will be educated about the Boston Emergency Services Team and will be given the toll-free number for the BEST team.

Risk of loss of confidentiality

There is some risk that health information collected as part of this study could be seen by unauthorized individuals. Every effort will be made to minimize this risk and protect subject confidentiality. Before a subject agrees to allow study staff to mail study materials to their home address, they will be asked to carefully consider the risk of others learning that they are participating in the study in the event that mail containing study materials is intercepted. Electronic data will be housed in the REDCap data management system. REDCap is protected via Secure Sockets Layer (SSL) encryption that provides access restriction options. Exported data from REDCap will be stored on a secure password-protected server behind the BMC firewall. Source and CRF binders will be stored in a double-locked area that is accessible to only study staff. Subjects will be assigned a study identification number and this will be used to code any forms that do not require the subject's direct identifiers (e.g., consent form, laboratory results, and contact information). A linking key that associates study ID with direct identifiers will be stored in a double-locked cabinet accessible only by study team members. Data will be stored on a password-protected computer accessible only to the study team. Video of subjects during the drinking session will be stored on an encrypted drive with password protection. Video files will be deleted at the end of the study. All study staff will receive appropriate training for the protection of human subjects (NIH Protecting Human Research Participants, CITI Training). A certificate of confidentiality will be sought to protect subjects from disclosure under court order or subpoena.

6.2 Potential Benefits

There is no potential direct benefit to participation in this study. This study presents a very strong potential for benefit to science. Drug development for treating AUD is costly and few pharmaceutical companies are testing novel compounds as agents to treat AUD. Re-purposing

compounds with FDA approval for other indications is the most promising route for rapid and cost-effective development of medications to treat AUD. This study will bridge the gap in drug development by providing a test of pitolisant to see if it may be a candidate drug for treating AUD. If successful, this could lead to the expansion of pharmacotherapy options to treat AUD and a broadening of our understanding of the mechanistic approach to treating AUD.

6.3 Analysis of Risks in Relation to Benefits

Given that pitolisant has FDA approval for another indication and is well-tolerated in other populations, the risk to human subjects has been established through pre- and post-marketing data. With the protections we have in place, we believe the risks of this study are well minimized. The study holds significant promise for informing new models of care given the novel mechanism of pitolisant. We believe the risk/benefit ratio is favorable.

7 Study Subject Selection

7.1 Subject Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following inclusion criteria:

1. 21-55 years of age
2. Able to verify age with a state or federal picture ID
3. Exceeds safe weekly drinking limits during the 28 days prior to consent (average of 14 drinks for women or 21 drinks for men per week)
4. Reports at least one episode of binge drinking (>3 drinks for women, >4 drinks for men) in the 28 days prior consent.
5. Meets DSM-5 criteria for mild alcohol use disorder or greater severity.

7.2 Subject Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Does not have a smartphone to complete medication exposure period study assessments
2. Seeking treatment for alcohol problems
3. Clinical Institute Withdrawal Assessment at ≥10
4. DSM-5 diagnosis of current major depression, bipolar disorder, schizophrenia, bulimia/anorexia, insomnia disorder or a substance use disorder other than alcohol, nicotine, marijuana or caffeine
5. If female, pregnant, nursing, have plans to become pregnant
6. If female, does not agree to use an accepted form of birth control
7. Has a medical contraindication to the use of pitolisant
8. Has diagnosed medical or mental condition for which further alcohol exposure at the planned dose range would be contraindicated
9. Current risk of suicidality (MINI suicidality score greater than 8 (low risk) or Yes to the ideation question #4 of the C-SSRS)

10. BMI is greater than 40 or less than 18
11. Impaired renal function (GFR <80 mL/min)
12. Has a history of any clinically significant renal or hepatic disease
13. Child-Pugh Score equal to or greater than Class B (evaluated based on presence or absence of encephalopathy and ascites, INR, bilirubin, and albumin) [https://www.mdcalc.com/child-pugh-score-cirrhosis-mortality]
14. Has a clinically significant ECG as determined by the investigator or abnormal ECG heart rate (<45 or >100 bpm) or QTc interval corrected for heart rate using the Fridericia formula (QTcF) > 450 msec
15. Has a history of cardiac arrhythmias or who for other reasons are at risk for developing Torsade de Pointes including those with bradycardia, hypokalemia, and congenital QT interval prolongation
16. Has a history of dementia
17. Has received alcohol counseling or other non-pharmacologic intervention to treat AUD in the past 90 days
18. Has taken medications that are used to treat AUD in the past 90 days
19. Is currently taking medication that is a sensitive CYP3A4 substrate
20. Is currently taking a QTc prolongation agent
21. Has urine toxicology results positive for cocaine, opioids, amphetamines, buprenorphine, methadone, methamphetamines, oxycontin, barbiturates, or benzodiazepines.
22. Subject is taking a medication which will significantly alter drug metabolism (e.g., strong CYP2D6 inhibitors, strong CYP3A4 inducers, or H1 receptor antagonists that cross the blood barrier (e.g. diphenhydramine or meclizine).
23. Subject has known hypersensitivity to pitolisant and any of its components, riboflavin, and/or lactose.
24. Subject is known to be a poor CYP2D6 metabolizer.
25. Subject is unable to comfortably abstain from nicotine for a period of 8 hours.
26. Has COPD, history of solid organ transplant, sickle cell disease, severe heart disease or other health condition for which exposure to COVID-19 represents an unreasonable risk as determined by the study staff physician using accepted COVID-19 guidance (e.g. Centers for Disease Control, etc.).

8 Study Intervention

Study Medication

Study medication will be packaged by the BMC Investigational Pharmacy Service. Pitolisant 4.45 mg pills will be over-encapsulated with 25 mg of riboflavin and pitolisant 17.8 mg pills will be over-encapsulated with 50 mg of riboflavin which will serve as a tracer of medication compliance using urine obtained on the day of the alcohol challenge. Matching placebo will also be packaged using lactose and 25 mg (4.45 mg pill) or 50 mg (17.8 mg pill) of riboflavin. Medication will be dispensed to each subject in two bottles. One bottle will contain 14 pills of pitolisant (4.45 mg) or placebo and the other bottle will contain 5 pills of pitolisant (17.8 mg) or placebo. Capsule size required will be determined by IPS with the goal of a minimum capsule size needed for over-encapsulation. If a subject reports losing (or destroying) study medication, a replacement prescription will be written by one of the study physicians and the BMC Investigational Pharmacy will dispense additional medication to replace the lost (or destroyed) medicine.

Dosing
Subjects will take an 8.9 mg dose of pitolisant (two 4.45 mg pills) or placebo once per day on day 1 through 7, beginning 12 days prior to the alcohol challenge. Subjects will then take a 17.8 mg dose of pitolisant (one 17.8 mg pill) or placebo once daily on days 8 through 12. This dose was chosen because it is consistent with the clinical dose range of this drug when it is used for treating narcolepsy.

Medication Storage
Medication will be stored in the Investigational Pharmacy at room temperature (within the range of 59°F to 86°F) in a secured area until the time that medication is needed for study subjects. Stability and expiry will be monitored by IPS according to the labelling of the medication from the manufacturer.

Medication Labeling
The study number will be preprinted on each bottle label. The label will include the drug name (e.g., "Pitolisant 4.45 mg**",** "Pitolisant 17.8 mg" or "placebo"). The label will also have a randomization number, the number of tablets contained in the bottle, storage conditions, the 24/7 phone number of the clinical site, and places to record the subject number and the date dispensed. Additional fields may be added to this label to meet any regulatory requirements as determined by IPS.

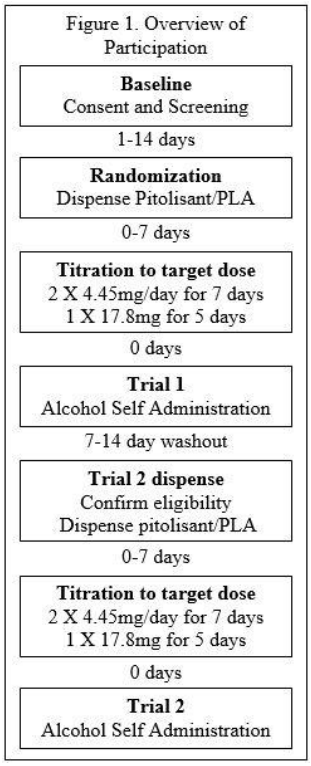
Medication Blinding and Unblinding
Study medication and placebo capsules will be identically matched in appearance and the bottle labels will not reveal the drug identity. The Study PI and study physician(s) will make the decision to un-blind the identity of the study medication in the event that the study blind needs to be broken to make medical decisions regarding subject treatment.

Medication accountability
The site principal investigator (PI) or designated study personnel will maintain a log of all study medication and record of dispensing of all medication to the subject. The site PI or his staff will count the tablets remaining at the end of the study and record the tablet count on the appropriate drug accountability form. Subject compliance with study medication will be assessed by comparing unused capsule count to dispensing logs and dosing records (number of tablets dispensed, number of tablets prescribed, versus the number returned). Subjects will also be asked to account for any missing tablets. If the bottles are not returned, the subject will be asked to report daily drug self-administration.

9 Study Procedures

Study Overview: Each subject will complete 5 clinic visits over a period of up to 66 days of participation. Study participation is comprised of a baseline assessment, randomization visit, alcohol self administration Trial 1, an assessment visit to verify continued eligibility and dispense medication, and a second alcohol self-administration Trial (see figure 1 for an overview of study participation).

Baseline assessment: Consenting subjects will undergo a general medical screen, physical examination, and electrocardiogram. Drinking will be assessed using the TLFB[46], alcohol withdrawal using the Clinical Institute Withdrawal Assessment[47], and suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS)[48]. Exclusionary mental health conditions will be assessed using the MINI Neuropsychiatric Interview and SCISD-R Interview for DSM-5[49]. Subjects will undergo laboratory testing that includes liver function and renal function, complete blood count, electrocardiogram recording, urine toxicology and a urine pregnancy test for women of child bearing potential.



Study randomization (medication visit #1): Qualified subjects will return to the lab within 14 days for randomization to a crossover sequence of drug exposure. Subjects will be assigned to one of 2 groups (n=18), with one group receiving pitolisant prior to the first alcohol challenge trial and the other receiving pitolisant prior to the second alcohol challenge trial. Randomization of subjects will be accomplished using a stratified randomization procedure that will allow for between-group balance for drinking status (heavy vs. very heavy). Heavy drinking is defined as ≥ 21 and < 35 standard drinks per week for men, and ≥ 14 and < 28 standard drinks per week for women. Very heavy drinking is defined as ≥ 35 standard drinks per week for men, and ≥ 28 standard drinks per week for women. This stratified randomization will minimize the possibility that the order of study drug administration seems to influence outcomes when order effects are actually related to differences in severity of drinking between the two groups of subjects who are receiving the study medication in a different order. On the day of randomization, subjects will undergo an alcohol breath test, urine drug screening, urine pregnancy testing, assessment of concomitant medications, and the TLFB to ensure eligibility. Subjects who have purposefully abstained from drinking and achieved 14 days of abstinence prior to the challenge will be discontinued from participation for ethical reasons[50]. Eligible subjects will be randomized and will receive a 12-day supply of over-encapsulated pitolisant or a matched placebo. Subjects will be scheduled for an alcohol challenge trial within 19 days of randomization. Subjects will be contacted to remind them to start taking study medication twelve days prior to the scheduled alcohol challenge trial. Subjects will be allowed to delay start of medication for up to 7 days after randomization in order to accommodate scheduling for the alcohol challenge trial.

Drug exposure period:
Randomized subjects will receive 12 days of study medication at the time of randomization. A riboflavin tracer (25 mg for 4.45 mg pill; 50 mg for 17.8 mg pill) will be added to each capsule to serve as an objective measure of medication adherence using urine obtained on the day of the alcohol challenge[51]. Two bottles will be dispensed to each subject. One bottle will contain 14 pills of pitolisant (4.45 mg) or placebo and the other bottle will contain 5 pills of pitolisant (17.8 mg) or placebo. All pills will be over-encapsulated with 25 mg (4.45 mg pill) or 50 mg (17.8 mg pill) of riboflavin. Subjects will take an 8.9 mg dose (two 4.45 mg pills) of pitolisant or placebo

once per day on day 1 through 7. Subjects will then take a 17.8 mg dose (one 17.8 mg pill) of pitolisant or placebo once per day on day 8 through 12. The 17.8 mg pill will be overencapsulated with 50 mg of riboflavin. Based on the published half-life for pitolisant, subjects should reach steady state levels after 5 days of taking the 17.8 mg dose. This dosing plan is consistent with the FDA approved prescribing information for the treatment of narcolepsy.

During the twelve-day period of drug exposure, subjects will be asked to answer a medication compliance question each day by smartphone using the REDCap data capture App[52]. In addition to assessing medication compliance, subjects will also be asked to rate their craving for alcohol each day using the alcohol VAS. Subjects will receive a $5 reimbursement on each day they complete the VAS and answer the medication compliance question using the REDcap smartphone App. Sleep quality during the drug exposure period will also be assessed by having subjects complete items from the National Sleep Foundation Sleep Diary each day. Items to be completed will include daily reports on the total number of hours slept per night and on the number of times and number of minutes for awakening during the night.

Medication Visit #2
After the 7-14 day washout period subjects will return to the lab to receive study medication prior to the alcohol challenge #2. Subjects will complete the same tests and interviews completed during the randomization visit (See appendix A for schedule of events). Based on the assessments at medication visit #2, subjects be discontinued for the following reasons: pregnancy, recreational drug use except for marijuana, evidence of non-compliance with study medication, suicidal thoughts or behavior, and use of a new medication that would make participation unsafe. Subjects will receive a 12-day supply of study medication and will be scheduled for the alcohol challenge #2. Subjects will be allowed to delay start of medication for up to 7 days after randomization in order to accommodate scheduling for the alcohol challenge trial.

Alcohol Challenge Trials 1 & 2: Subjects will return to the laboratory on day 12 of drug exposure for each medication trial to complete the alcohol challenge. For safety reasons, subjects will be asked to arrange transportation plans (no driving) prior each of the alcohol challenge trials. There will be a 7-14 day washout period between alcohol challenge Trial 1 and medication visit #2. The washout may extend to 14 days to accommodate the scheduling of the medication visit. Concomitant medications, urine drug screening, urine pregnancy testing, blood alcohol level will be assessed to determine eligibility to proceed with the challenge. Blood alcohol level must be 0.000 to continue with the study procedures. Urine collected for drug screening will be exposed to ultraviolet light as an objective test of medication compliance. If no fluorescence is observed in the urine sample the subject will be excluded from continuing with the challenge. Measures of drinking (TLFB) and cravings (OCDS, VAS and AUQ) will be collected to inform secondary outcomes. Subjects will be observed taking the morning dose of pitolisant (or placebo) on the day of the challenge (after compliance is confirmed via a urine screening). The peak plasma concentration of pitolisant should be reached approximately 60 minutes after administration. The alcohol self-administration session will begin no sooner than one hour after the administration of the observed 17.8 mg morning dose. The alcohol self-administration will be conducted in the GCRU. The room will be a carpeted and furnished with

a lounge chair, side table and television which allows access to popular streaming entertainment (e.g., Netflix, YouTube). A small unobtrusive camera is placed in the room to allow for monitoring without study staff being present in the room. The room has ready access to a bathroom. The alcohol self-administration is divided into four segments: 1) a 5-minute segment for the priming dose, 2) a 40-minute segment for observing alcohol's effects, 3) a 60-minute segment of alcohol self-administration (Block1) and, 4) a second 60-minute segment of alcohol self-administration (Block2) [see figure 2 for the alcohol self-administration Procedure].

Figure 2: Alcohol Self-Administration Procedure

Priming Dose	**Observation**	**Self-Administration Blocks 1 & 2**
5 minutes Drink mixed to achieve BAL= 0.03g/dl	40 minutes Craving and intoxication measured in 10-minute intervals	60 minutes each 4 drinks per block Each drink mixed to raise BAL 0.0125 g/dl

Priming dose. Subjects will be given a priming drink designed to increase the subject's blood alcohol level (BAL) to 0.03g/dl, using the alcohol of their choice that is 24% Alcohol By Volume (ABV) or greater. The volume of alcohol will be calculated using an online tool developed by UW-Madison (http://dionysus.psych.wisc.edu/WebCMS/baccalc.htm) based on a formula described by Watson[53]. The subjects will be asked to drink the priming drink over a period of 5 minutes. Part of the purpose of the priming drink is to normalize drinking in the laboratory.

Observation period. Subjects will be observed for 40 minutes following the priming dose of alcohol to allow for absorption of the alcohol. Cravings will be assessed using the AUQ and VAS and effect of pitolisant on stimulant effects of alcohol swill be assessed using the BAES every 10 minutes during the observation period.

Alcohol self administration Blocks 1 and 2. In each of the alcohol self-administration Blocks, subjects will be presented with four drinks, each mixed to raise their BAL 0.0125g/dl. They will be told that they can either consume the desired number of drinks over the following 60 minutes or they will receive the equivalent dollar amount of the cost of each drink ($3.00) they did not consume before leaving the clinic. At the end of each 1 hour session the tray with the remaining drinks will be removed and the amount of alcohol remaining will be measured. Cravings will be assessed using the AUQ and VAS and effect of pitolisant on stimulant effects of alcohol will be assessed using the BAES every 30 min during the self-administration blocks. Based on the rate of alcohol metabolism over the time of the trial, we anticipate that subjects who consumed every drink could reach a BAC of 0.09 to 0.13 g/dl depending upon differences in alcohol metobolism. Safety assessments will be completed (intoxication, sedation, adverse effects) prior to subjects leaving the laboratory. Subjects will be required to have a plan for transportation home that does not involve driving. Subjects will not be released until their blood alcohol level is ≤ 0.04 g/dl and they are not behaviorally impaired. After the second alcohol self-administration trial has been completed subjects will receive a copy of the NIAAA publication *Rethinking Drinking*[54] and will be encouraged to review rethinking drinking materials online.

Subject compensation

Subjects will be compensated up to $543 for completion of all study activities. Subjects will

receive a reimbursement of $50 for the screening visit, $100 for alcohol Challenge Trial #1, $100 for alcohol Challenge Trial #2 and a $75 completion bonus if they complete both challenges. Subjects will also receive $20 on each of the two visits during which medication is dispensed. Subjects will receive a $5 payment each on day during the two drug exposure periods that they respond to the REDcap smartphone app to rate their alcohol craving, medication compliance, and sleep quality. Subjects will also receive a $10 completion bonus in each challenge if they complete the craving scale and medication log on all days. Subjects may receive up to $48 dollars in payments for drinks not consumed during the two alcohol self-administration trials.

In addition to this $543 of compensation, subject may also be reimbursed up to an additional $60 for distributing study recruitment materials to other people who may want to take part in this study. Distributing recruitment materials is completely optional. subjects may take part in the study and decline to hand out flyers to people they know.

Subjects who report no recreational drug use other than marijuana at the time of phone screening but then test positive for recreational drug use other than marijuana at the first in-clinic visit will not be reimbursed. Subjects will be informed of this policy at the time of telephone screening. This measure is in place to prevent subjects from lying about no recreational drug use in order to receive compensation for a single visit in this study.

10 Assessment of Safety and Data Safety Monitoring Plan (DSMP)

10.1 Definitions

The following definitions will be used in the assessment of safety:

Adverse Event (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Serious Adverse Event (SAE) is any adverse event that

(1) results in death;
(2) is life-threatening;
(3) results in inpatient hospitalization or prolongation of existing hospitalization;
(4) results in a persistent or significant disability/incapacity;
(5) results in a congenital anomaly/birth defect; or
(6) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Life-threatening means that the event places the subject at immediate risk of death from the event as it occurred.

Unanticipated Problem is defined as an event, experience or outcome that meets **all three** of the following criteria:

- is unexpected; AND
- is related or possibly related to participation in the research; AND
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research

Unexpected means the nature, severity, or frequency of the event is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

10.2 Safety Review

Both the risks listed in Section 6.1 and unknown risks will be monitored as follows:

Adverse events will be monitored from the time of study enrollment until the end of participation. Adverse events will be monitored by medical staff using the "adverse events" CRF. Adverse event monitoring will be conducted at three mid-week calls during both titration periods. Adverse events will also be assessed on the alcohol self-administration challenge days. Subjects will be given a wallet card with a 24/7 telephone number in the event that there are adverse effects which the subject would like to consult with medical staff prior to the next scheduled visit. Adverse events will be assessed if at any point in the study a subject uses this 24/7 emergency phone contact. If a subject has an ongoing SAE or unanticipated problem at the time that the subject completes all study procedures, Adverse Event assessment will continue until satisfactory resolution (either resolved or stabilized and is not expected to resolve in the near term) of the event or problem.

For each recorded AE or SAE, the study MD staff or study nurse will assess expectedness based on the known published side effect profile for pitolisant. The study MD staff or study nurse will also assess 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

Mild:	An event that is usually transient, requiring no special treatment, and does not generally interfere with the subject's daily activities. 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 study MD staff or study nurse will assess AE/SAE 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 or 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.

10.3 Reporting Plans

The Principal Investigator at BMC/BU Medical Campus will report Unanticipated Problems and Adverse Events to the BMC/BU Medical Center IRB in accordance with IRB policies:

- Unanticipated Problems occurring at BMC/BU Medical Campus will be reported to the IRB within 7 days of the investigator learning of the event.
- Adverse Events (including Serious Adverse Events) will be reported in summary at the time of continuing review, along with a statement that the pattern of adverse events, in

total, does not suggest that the research places subjects or others at a greater risk of harm than was previously known.

10.4 Stopping Rules

There are no interim analyses planned that would allow for a determination of futility or overwhelming benefit. Study enrollment will be suspended under the following circumstances:

1. Severe and Serious Adverse Events. Study enrollment will be suspended in the event of a single severe adverse event or a single serious adverse event if that is determined to be unexpected and at least "possibly related." If suspended, study recruitment will not continue until a determination has been made about whether the known risks of participation have changed and the Boston Medical Center IRB has made a finding that the risk/benefit ratio remains favorable given the possible newly identified risks.

2. Risk of intoxication. Subject recruitment will also be suspended if more than one subject of the first ten subjects enrolled is discontinued by the investigator due to intoxication during the alcohol self administration trial. Due to differences in alcohol tolerance, BAL is not a reliable measure of subjects potentially posing a safety risk. Medical staff will make a subjective determination of risk based on the subject's behavior. After 10 subjects have been enrolled, the trial will be suspended if there are more than 10% of subjects whose participation has been halted by the study team due to concerns about physical safety because of intoxication during the alcohol self-administration trial. If suspended for this reason, the study team will consider design changes to reduce the likelihood of this as a potential risk to study subjects. Recruitment would resume when the BU Medical Campus/Boston Medical Center IRB has made a determination that proposed changes to the study design have an acceptable risk/benefit ratio.

11 Data Handling and Record Keeping

11.1 Confidentiality

All staff will be fully trained in the procedures for protection confidential health information. To maintain subject confidentiality, study data will be coded on CRFs that are identified by a subject number only. Source records with identifying information and CRFs will be stored in double-locked space with access only by authorized staff. Data stored in the REDcap system have strong protections including file encryption and password access. Subject information will not be released without written permission. Upon approval of the study by an IRB, NIH will furnish a Certificate of Confidentiality.

Deidentified data from this study will be submitted to the NIAAA Data archive (https://nda.nih.gov/).

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11.2 Source Documents

Source documents in this study include:
Laboratory test results
Photocopies of the urine drug screening test result
ECG tracings
Subject locator form
Subject contact form

Data generated by the methods described in the protocol will be recorded in the subjects' source binder. Data may be transcribed legibly on CRFs for each subject or directly inputted into an electronic system or any combination thereof.

11.3 Case Report Forms

The study case report form (CRF) will be the primary data collection instrument for the study. All data requested on the CRF will be recorded. All missing data will be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, a written explanation will be included to detail why the data was not recorded. If the item is not applicable to the individual case, a notation will be made. All entries on will be printed legibly in black ink. If any entry error has been made, to correct such an error, a single straight line will be drawn through the incorrect entry and the correct data will be entered closely to the original data. All such changes will be initialed and dated. There will be no erasures or white-out on CRFs. For clarification of illegible or uncertain entries, the clarification will be printed near the item, then initialed and dated. Electronic CRFs in the REDcap system will include an audit trail.

The CRFs that will be used in this study are:
Demographics
Concomitant Medications
Adverse Events
Birth Control Assessment
Urine Drug Screening
Vital Signs
Blood Alcohol Level
Time-line Follow-back
Pregnancy test
Birth control assessment
Medical History
Physical Examination
MINI diagnoses summary
Medication Compliance log
Eligibility
ECG
C-SSRS
CIWA-AR
OCDS

AUQ
VAS
BAES

11.4 Study Records Retention

Study records will be retained for at least seven years after completion of the study.

12 Statistical Plan

12.1 Study Hypotheses and Planned Analyses

For our primary outcomes, separate analyses will be conducted on data collected during the Priming and Self-Administration periods of the test session.

Hypothesis	Proposed Analyses
1. Subjects will consume less alcohol during an alcohol self-administration trial when receiving pitolisant compared to when they are receiving placebo.	The volume of alcohol consumed during alcohol challenge trials 1 and 2 will be used to test the effect of pitolisant on alcohol consumption. We will use a mixed models repeated measures approach to test for differences between alcohol consumed between the pitolisant and placebo self-administration trials45-46. This data will be divided into first and second-hour blocks of self-administration. Within-subject factors for this analysis will include treatment and Time Block. Trial order will be used as covariate in these analyses to allow evaluation as to whether the order of treatments had a significant effect on the outcome. Appropriate covariance structures will be determined using Akaikes information criteria to evaluate the best model fit. Results analysis will be examined for both treatment effects and the Treatment x Time Block interaction results.
2. Subjects will report lower levels of craving as measured by the Visual Analog Scale (VAS) and the Alcohol Urge questionnaire (AUQ) during the pitolisant self-administration trial compared to the placebo self-administration trial.	Craving measures (AUQ and VAS) collected at 30-minute intervals during the self-administration trials will be used to test the effect of pitolisant on alcohol craving. A mixed models approach will be used to test for differences in craving between the pitolisant and placebo self-administration trials. Within-subject factors for this analysis will include Treatment and Time Block. Trial order will be used as covariate in these analyses to allow evaluation as to whether the order of treatments has a significant effect on the outcome.
3. Subjects will experience no difference in alcohol-induced stimulation, as measured on the BAES, after the consumption of the priming dose of alcohol when they are receiving pitolisant as compared to when they are receiving placebo.	BAES scores and BALs obtained during the 40-minute observation period and both of the 60-minute self-administration blocks will be used to test the effect of pitolisant on the stimulating effects of alcohol. A mixed model for repeated measures approach will be used to test for differences between pitolisant and placebo on the stimulant BAES scores at each of the 10-minute observation intervals and 30-minute self-administration intervals. This data will be analyzed with Treatment and Time used as within-subject factors.
5. Subjects will report lower levels of alcohol craving and consumption	The alcohol VAS, OCDS, and the TLFB measurements during the twelve-day period of drug exposure will be used to determine the effect of pitolisant on craving and consumption. Mixed

during pitolisant exposure period as compared to placebo exposure period.	models repeated measures approach will be used to test for differences in craving and consumption between the pitolisant and placebo trials. Treatment will be used as within-subject factor. VAS measures taken on each of the twelve days of drug exposure, repeated measures mixed models analysis will be conducted with Day and Treatment as within-subject factors.
6. Subjects will not report significant differences in the number of hours sleep per night and minutes spent awake during the pitolisant exposure period as compared to the placebo exposure period	Daily hours of sleep and number of minutes spent awake during the twelve-day period of drug exposure will be used to determine the effect of pitolisant on craving and consumption. Mixed Models repeated measures approach will be used to test for differences in sleep quality between the pitolisant and placebo trials. Treatment will be used as within-subject factor. Sleep measures taken on each of the twelve days of drug exposure, repeated measures mixed models analysis will be conducted with Day and Treatment as within-subject factors.

12.2 Sample Size Determination

A group size of 28 completers was selected for use in this study based on an assumed effect size of 0.7 suggested by similar alcohol self-administration studies with amount consumed as the primary outcome. This effect size is in the range we found for the anticonvulsant zonisamide used in a similar alcohol self-administration study. The sample size for this study is based on an estimated reduction of 1.5 standard drinks with an estimated standard deviation (2.1) of the between Challenge Trial differences in alcohol self-administration, with an effect size of this magnitude (i.e. 0.7). This requires a sample size of 28 to allow for detection of a significant within-subject difference in alcohol consumption with an alpha value of 0.01 and power value of 0.81. Based on an estimated 15-20% rate of non-completion for randomized subjects, we anticipate randomizing 36 subjects to achieve a sample of 28 completers. Given our experience with recruiting AUD populations into clinical trials, we expect a screening exclusion rate of roughly 50%. Approximately 72 subjects will be consented and screened in clinic to yield a sample of 36 eligible subjects. Given that this a laboratory based experiment we do not plan to conduct any planned interim analyses in this study.

13 Ethics/Protection of Human Subjects

This study is to be conducted according to applicable US federal regulations and institutional policies (which are based in federal regulations, guidance, and ICH Good Clinical Practice guidelines).

This protocol and any amendments will be submitted to the Boston Medical Center and Boston University Medical Campus IRB, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator. A copy of the initial IRB approval letter will be provided to the sponsor before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the IRB. The consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. Consent will be documented as required by the IRB.

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15. Appendix A: Schedule of Events

	Baseline (May be split over 2 visits)	**Randomization**	**Trial 1**	**Dispense**	**Trial 2**
Clinic Visit #	**0**	**1**	**2**	**3**	**4**
Informed Consent	**X**				
Urine Drug Screen[A, B]	**XX**	**X**	**X**	**X**	**X**
Locator Form	**X**				
Demographics	**X**				
Medical History	**X**				
Physical Exam	**X**				
MINI V 6.0	**X**				
SCISD-R	**X**				
Metabolic panel (Alb, Tbil, Ca, CO2, Cl, CRG, G, ALP, K, TP, Na, ALT, AST, BUN) 14.1.1 PT/INR	**X**				
Urinalysis	**X**				
Vital Signs, weight, Blood Alcohol Level[B]	**XX**	**X**	**X**	**X**	**X**
ECG	**X**				
Prior and Concomitant Meds	**X**	**X**	**X**	**X**	**X**
CIWA-AR	**X**	**X**	**X**	**X**	**X**
Eligibility Checklist		**X**			

	Baseline (May be split over 2 visits)	**Randomization**	**Trial 1**	**Dispense**	**Trial 2**
Clinic Visit #	**0**	**1**	**2**	**3**	**4**
Drug compliance/accountability			**X**		**X**
Urine Pregnancy Test	**X**	**X**	**X**	**X**	**X**
Birth control assessment	**X**	**X**	**X**	**X**	
AEs	**X**	**X**	**X**	**X**	**X**
C-SSRS	**X**	**X**	**X**	**X**	**X**
Dispense medication/placebo		**X**		**X**	
Brief Telephone Interview		**Mid-week call 3-4 days, 6-7 days, and 9-10 days after starting medication**		**Mid-week call 3-4 days, 6-7 days and 9-10 days after starting medication**	
Treatment Referral					**X**
TLFB (28 day at baseline)	**X**	**X**	**X**	**X**	**X**
VAS		**X Daily during 12-day medication exposure period**	**X**	**X Daily during 12-day medication exposure period**	**X**
OCDS		**X Days 7 and 11 of medication exposure period**	**X**	**X Days 7 and 11 of medication exposure period**	**X**
AUQ		**X**	**X**	**X**	**X**
BAES			**X**		**X**
National Sleep Foundation Sleep Diary		**Daily during 12-day medication exposure period**		**Daily during 12-day medication exposure period**	

A) Test for opioids, cocaine, amphetamines, methamphetamine, tetrahydrocannabinol (THC), barbiturates, oxycodone, buprenorphine, methadone and benzodiazepines.
B) If the baseline visit is split between two days, UDS, vitals, breathalyzer, and weight are to be taken at each visit.

16. Appendix B: Schedule of assessments during the alcohol challenge

	Observation	Self-admin Block1	Self-admin Block2
Assessment			
BAC	**Every 10 minutes**	**Every 30 minutes**	**Every 30 minutes**
VAS[a)]	**Every 10 minutes**	**Every 30 minutes**	**Every 30 minutes**
AUQ		**Every 30 minutes**	**Every 30 minutes**
BAES	**Every 10 minutes**	**Every 30 minutes**	**Every 30 minutes**