CLINICAL STUDY PROTOCOL
Interventional Drug or Biologic

A Pilot Study on the Safety and Efficacy of Mavoglurant in Alcohol Drinking

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1 Synopsis

Primary Objective The purpose of this study is to evaluate interactions between a moderate dose of alcohol and a non-competitive antagonist of the metabotropic glutamate receptor subtype 5 (mGLUR5), mavoglurant, on pharmacokinetic, physiological or behavioral responses in healthy social drinkers.
Study Duration 6 years, plus 1 year for data analysis
Study Design This pilot study will examine interactions between alcohol and mavoglurant and explore the effects of mavoglurant on alcohol responses. This is a between subjects, double-blind design. We propose to recruit 40 male and female healthy volunteers (to achieve a completer sample of 28 participants) who meet criteria for social drinking (i.e., consuming 1- 6 standard alcoholic drinks per week and having engaged in at least one and no more than 12 binge drinking episodes in the past year), do not meet criteria for a DSM-V Alcohol Use Disorder, and who are willing to abstain from alcohol during the outpatient study medication treatment phase. The study will consist of five parts: 1) Eligibility: Informed consent is obtained, and eligibility is evaluated, 2) Lab Session 1: Eligible subjects will then be exposed to a fixed dose of alcohol and monitor responses; we will randomize them to study medication (mavoglurant or placebo), 3) Outpatient Medication: Subjects will come in on a daily basis (or via zoom) for 7-10 days, when they will be observed when they take the study medication, and adverse events will be monitored, 4) Lab Session 2: Subjects will again be exposed to the same fixed alcohol dose at the first lab session, the following morning they will go in for a blood/urine collection 5) Follow Up Interviews: We will follow up with participants via phone, for two days after discharge and in-person, one week after discharge to assess for any potential remaining adverse events.
Number of Study Sites This is a single site study
Study Population 40 social drinkers who are not currently seeking treatment for their drinking behavior, and who are willing to abstain from drinking alcohol during the study, and who are between 21-50 years of age.
Number of Participants 40 social drinkers will be recruited to achieve 28 completers.
Primary Outcome Variables To evaluate the effect of mavoglurant on blood chemistries, urine toxicology and physiological safety measures before and after alcohol administration.
Secondary and Exploratory Outcome Variables (if applicable) To evaluate the interactions of alcohol and mavoglurant on blood alcohol levels and mavoglurant levels.

To explore the effects of mavoglurant on alcohol responses, including stimulation, sedation, intoxication, and cognitive/motor performance.

2 Abbreviations

Abbreviation	Explanation
ADP	Alcohol Drinking Paradigm
HRU	Hospital Research Unit
CMHC	Connecticut Mental Health Center
AUD	Alcohol Use Disorder
CTNA	Center for Translational Neuroscience on Alcoholism
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BAC	blood alcohol concentration
CLIA	Clinical Laboratory Improvement Act
CIWA-AR	Clinical Institute Withdrawal Assessment for Alcohol-revised
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
DSMB	Data and Safety Monitoring Board
EKG/ECG	electrocardiogram
EtOH	ethanol
FDA	Food and Drug Administration
GGT	gamma-glutamyl transferase
HIPAA	Health Insurance Portability Accountability Act

IRB	Institutional Review Board
NIAAA	National Institutes on Alcohol Abuse and Alcoholism
PI	principal investigator
PK	pharmacokinetic
POMS	Profile of Moods State
SAE	serious adverse event
CMU	Central Medical Unit
SATU	Substance Abuse Treatment Unit
CSRU	Church Street Research Unit
BIS-11	Barrett Impulsivity Scale
BIS/BAS	The Brief- Behavioral Inhibition System/ Behavioral Activation System
MSDM	Multi-Stage Decision Making Task

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4 Introduction

4.1 Introductory Statement

This document is a protocol for a human research study. The purpose of this protocol is to ensure that this study is to be conducted according to ICH GCP guidelines, and according to CFR 21 Part 312, other applicable government regulations and Institutional research policies and procedures.

5 Background

5.1 Rationale for Project

Alcohol Use Disorders (AUD's) are leading causes of disability in the United States. At present, three medications are approved by the FDA for the treatment of alcohol dependence: disulfiram, naltrexone, and acamprosate. However, the efficacy of these agents is minimal to modest, and they are under-utilized in clinical community settings (Garbutt et al 1999, Krishnan-Sarin et al 2008).

There is a pressing need for novel medications that are more effective in reducing alcohol use. Development of new pharmaco-therapeutic approaches to treating AUDs should emerge from our understanding of the behavioral and neurochemical mechanisms mediating pathological alcohol drinking. The goal of our center (the Center for Translational Neuroscience on Alcoholism; CTNA) is to evaluate the mechanisms through which disturbances in glutamate neurotransmission within cortico-limbic circuitry contribute to vulnerability for persistent heavy drinking, and to use this information to develop new therapies for alcoholism. In previous iterations of our center we have focused on evaluating if modulation of fast synaptic transmission via altering the ionotropic NMDA receptor function alters drinking behavior; our results suggest that the NMDA receptor antagonist memantine reduced craving for alcohol but did not influence drinking. In the current study, we would like to extend this work to examine the influence of metabotropic glutamate receptors which produce slower modulation of the glutamate system through second messenger systems.

5.1.1 Preclinical – Why examine the influence of an mGluR5 modulator on alcohol responses?

Our focus is mGluR5 receptors which have been shown to reduce intravenous drug self-administration and reinstatement of drug-seeking in pre-clinical studies (Duncan and Lawrence 2012; Kenny and Markou 2004). mGluR5s are highly concentrated in nuclei associated with reward pathways such as the forebrain and limbic structures, dorsal striatum, Nacc, lateral septum, hippocampus, and cerebral cortex (Shigemoto et al., 1993, Romano et al., 1995). These receptors have also been shown to be involved in regulating motivation to self-administer alcohol (Hodge et al., 2006; Cowen et al., 2005; Besheer et al., 2008) as well as binge alcohol consumption (Tanchuck et al., 2011). mGluR5-deficient mice voluntarily consume less ethanol, are more sensitive to the hypnotic effects of ethanol (Bird et al., 2008, Downing et al., 2010), and display conditioned place preference to low doses of ethanol (1 g/kg) which suggests that they might have increased sensitivity to ethanol's centrally mediated rewarding affects. Moreover, in alcohol-preferring rats, administration of the mGluR5 antagonist MPEP Into the Nucleus accumbens reduces ethanol self-administration; an effect which is not observed when MPEP is infused into the dorsomedial caudate or medial prefrontal cortex (Besheer et al., 2010). Moreover, human genetic studies have suggested that individuals with genetic variations in mGluR5, and the NMDA NR2A receptor subunits, have higher risk of developing alcohol dependence (Schumann et al., 2008). All the above evidence suggests there might be a role of mGluR5 receptors in alcohol reward/consumption.

5.1.2 Clinical Experience with Mavoglurant

Mavoglurant (AFQ056) is an experimental drug, developed by Novartis, which is a non-competitive antagonist of the metabotropic glutamate receptor subtype 5 (mGLUR5). Mavoglurant was developed to treat the behavioral and cognitive symptoms of fragile X syndrome (FXS). Pre-clinical data looked promising (Levenga et al., 2011), but clinical trials with FXS have found mixed results (Gomez-Mancilla et al., 2014; Petrov et al., 2014; Scharf et al., 2014). Mavoglurant has also been studied in pre-clinical (Morin et al., 2010; Grégoire et al., 2011) and clinical trials (Berg et al., 2011; Stocchi et al, 2013) for L-DOPA-induced

dyskinesia (LID) in patients treated for Parkinson's Disease. Although results looked promising with antidyskinetic effects of LID, there was also inconclusive data (Kumar et al., 2013). Mavoglurant has also been studied in reducing chorea in Huntington Disease (Reilmann et al., 2015), and although the drug was well tolerated, the results did not suggest efficacy. Safety and tolerability of mavoglurant was established in a single dose trial in healthy male volunteers (Walles et al., 2013) and a clinical trial in patients with obsessive compulsive disorder (Rutrick et al., 2017), although the latter did not show efficacy. Although a clinical study was initiated in 2007 to assess mavoglurant on cigarette smoking, the results have not been published. To date, no trials have been conducted on the use of mavoglurant for alcohol use disorder (AUD).

Mavoglurant or AFQ056 is a structurally novel, subtype-selective, non-competitive antagonist at the metabotropic glutamate receptor 5 (mGluR5). We propose to use a dose of 200 mg because according to a receptor occupancy study conducted by Novartis this dose occupies about 90% of the mGluR5 receptors. The MTD of an immediate-release formulation of AFQ056 was observed to be 400 mg after single dose administration and 150 mg b.i.d. after multiple dose administration in healthy subjects. We will use a modified release formulation which has been shown to produce less fluctuation in C-max (80-90%) compared to an immediate release formulation.

6 Purpose, Risks, and Benefits

6.1 Purpose of Study/Potential Impact

The purpose of this study is to evaluate the safety and tolerability of a moderate dose of alcohol in combination with a non-competitive antagonist of the metabotropic glutamate receptor subtype 5 (mGLUR5), mavoglurant, on pharmacokinetic, physiological or behavioral responses in healthy social drinkers.

Prior to initiating a study to examine the influence of mavoglurant on drinking behaviors in heavy drinkers, we propose to conduct this study to examine the safety and pharmacokinetic interactions of administering mavoglurant and alcohol together.

6.1.1 Potential Risks

The major potential risks in this study are related to administration of alcohol, mavoglurant, and blood drawing during the physical exam and alcohol drinking period.

Risks Associated with Study Drug, Mavoglurant:

Mavoglurant of AFQ056 has been studied in a total of 2209 study subjects who have been enrolled in a total of 45 completed human studies, of which 29 were Phase I studies [single-dose: n=19; multiple-dose: n=10) and 16 were Phase II studies (eight studies in Parkinson's (PD-LID) patients, five studies in Fragile X (FXS) patients, one study in HD patients, one study in patients with GERD and one study in patients with OCD]. In these studies, a total of 1863 study subjects were exposed to AFQ056 while the remaining subjects received either placebo or an active comparator. The list of studies is included in Table 5.1 on page 47 of the investigator's brochure.

The maximum tolerated dose (MTD) of AFQ056 is 400 mg after single dose administration and 150 mg bid. after multiple dose administration (determined with immediate release-clinical service form (IR-CSF) in healthy subjects). Dose-limiting aEs were mainly hallucinations and other psychosis-like symptoms (e.g. paranoid reaction, anxiety, agitation, confusion, chaotic thoughts, disorientation in time/place, and mood changes).

Overall, the aEs observed in the various human studies were of mild to moderate severity. In patients with Parkinson's disease, dizziness (11.1%) and visual hallucination (11.1%) were the most common aEs in the AFQ056 treatment group (Table 5-10). Dyskinesia (12.0%), akinesia (8.0%), fall (8.0%) and asthenia (8.0%) were the most common aEs in the placebo group. Other AE's were headache (8.3%), anxiety, back pain, confusional state, constipation, fall, decreased hemoglobin, insomnia, muscle spasms, nasopharyngitis (common cold), nausea, edema peripheral (swelling in legs), orthostatic hypotension, parkinsonian gait, vision blurred, and asthenia, all at 5.6%.

In Fragile X Syndrome (FXS) patients, dizziness, insomnia, and headache were the most frequently reported aEs on AFQ056. Dizziness was also the most commonly reported AE in Parkinson's Disease-L-dopa induced dyskinesia (PD-LID), however primarily with the IR formulation. Other frequent aEs in PD-LID patients were mostly reflecting psychiatric disorders such as hallucination and illusion. In particular, the dose of 200 mg b.i.d. MR formulation appeared not to be well-tolerated, but this was primarily observed in patients receiving concomitant amantadine and there were no new safety concerns identified. Therefore, some flexibility in dosing is warranted to allow reduction to 150 mg b.i.d. dose, which had an acceptable tolerability profile.

The safety of AFQ056 in patients with moderate to severe OCD was assessed in a randomized, double-blind, placebo-controlled, single dose, in patients resistant to SSRI therapy (CAFQ056A2225; N=50). Patients in this study received AFQ056 200 mg BID up- and down-titration regimen (4 weeks AFQ056 BID up-titration period of 50 mg, 100 mg, 150 mg and 200 mg, followed by 12 weeks AFQ056 200 mg fixed dose and then a 3-week down

titration. This study was completed in 2015 and the results indicate that this dose of AFQ056 was safe and well tolerated. There were six SAEs in three patients during the study. Two SAEs (otitis media and 7th nerve paralysis) in one patient from AFQ056 group and four SAEs in two patients from placebo group. There were three aEs (worsening OCD, insomnia, and moderate anxiety) which led to discontinuation of the study drug. All the events were considered as unsuspected to the study drug by the investigators.

12-Oct- 2014, investigator notifications have been issued for 22 subjects in completed and ongoing studies, of whom 14 were PD-LID patients, seven were FXS patients, and one was a subject in a healthy volunteer study (Section 5.2.1.2 of Investigational Brochure). Overall the events listed suggest that the central nervous system (CNS) and psychiatric system organ class (SOCs) may be preferentially affected.

There were four cases in which a fatal outcome was reported in AFQ056 studies in patients with Parkinson's disease. The only death suspected to be related to AFQ056 by the investigator was a case of sudden death in a 77 year old male patient with a 22-yr history of PD; 18 days after starting a 50 mg b.i.d. dose, the patient complained for dizziness in the morning and died later that day; a review of the medical information did not reveal any significant changes in laboratory parameters or vital signs; the patient had an anterior hemiblock at baseline and an old inferior and/or septal myocardial infarction could not be rule out. In a second case, a 67 year old female patient with PD experienced a series of events (status epilepticus, cardiac arrest, and hypoxic ischemic encephalopathy) preceding death due to a fatal respiratory arrest; the investigator suspected a causal relationship between the seizures, cardiac arrest, the study medication and the concomitant medications (trimethoprim/sulfamethoxazole and citalopram), but did not suspect a relationship between the fatal respiratory arrest and the study medication (see Section 5.2.1.1 of Investigational Brochure).

Following the first case with a fatal outcome (sudden death, see above), an internal Data Monitoring Committee (DMC) was established. Shortly thereafter, this was replaced with an external DMC, responsible for regular monitoring of safety data for AFQ056 studies at a project level, i.e. in all indications. In addition to the regular safety monitoring, the DMC performs "real time" monitoring of suspected unexpected serious adverse reaction (SUSARs), deaths/outcomes leading to death, and serious cardiac and psychiatric events (SOC) for all ongoing studies.

Risks associated with alcohol:

Many medical conditions could potentially be worsened by acute alcohol administration (e.g., liver disease, cardiac abnormality, pancreatitis, diabetes, neurological problems, and gastrointestinal disorders). As a result, subjects with medical problems as revealed by physical exam and laboratory findings will be excluded from the study.

Alcohol may also cause nausea in high doses; however, nausea is not expected at the dose being used in this sample of healthy volunteers who will report prior experience of consuming alcohol levels similar to the quantity used in this study. Alcohol dosing will be calculated using published gender specific algorithms based on estimated body water determined from height, weight, and age and the amount of alcohol provided will raise their blood alcohol levels to 80 mg/dl which is the legal limit of intoxication to levels.

Another area of potential risk to subjects under the influence of alcohol involves their safety during the experimental procedures. Although impairment of gross motor coordination in these subjects may occur, all subjects will be under the supervision of the experimenters to prevent possible accidents such as falls. To ensure the safety of our subjects, they will be monitored until their BAC falls to below .02 or until 6pm. All participants will be provided with transportation to and from the lab sessions to ensure their saftey.

There is no data looking at the effects of alcohol with mavoglurant. However, this interaction is the purpose of this study and the amount of alcohol that will be given subjects is no more than the amount they may drink in a social environment.

Risks associated with urine collections:

Screening urine collections are performed primarily as safeguards to subjects and should add no risks other than those normally associated with these procedures. Subjects will have approximately 50cc of blood drawn at the PE appointment to determine liver and kidney functioning. We will draw approximately 70.5cc of blood during the first lab session and 85.5cc of blood at the second lab session for BALs and health profile and PK samples. The morning after lab session 2, 50cc's of blood is drawn. At the 1 week follow up 50cc will be drawn again for health profile. Therefore, the total amount of blood drawn during the study (306 ml) is well within the HIC guidelines of 450 cc within 8 research weeks, and the blood loss poses minimal risk in healthy subjects. We will advise subjects against donating blood for 6 weeks following study participation.

BLOOD DRAW	**PE**	**DS1**	**DS2**	Morning after	**1 WEEK F/U**
Chem Profile (safety labs) 50 cc/draw	X	X	X	X	X
BAL (total 11 vials/visit) 0.5 cc/draw (5.5/DS)		X	X	X	
PK Assay 15 cc/draw		X	X (2)		

Risks associated with rating scales and questionnaires:

These are all noninvasive and should add no risk. The major disadvantages are the time taken to complete them or possible discomfort in answering certain items.

Risks Associated with Blood Drawing:

Drawing blood is a safe and standard medical procedure. Sometimes a bruise will occur at the puncture site and rarely a blood clot or infection will occur in the vein. Certain individuals may feel light-headed during venipuncture.

Risks Associated with Electrocardiograms (EKG/ECGs) at the physical exam:

There is no pain or discomfort during an EKG/ECG; however, removing the pads may cause some irritation to the skin.

Risks Associated with Intravenous Access:

Insertion of an intravenous catheter involves risk for hematoma at the site of the venous puncture. Very rarely, venous puncture can also result in a blood clot or infection.

6.1.2 Potential Benefits

Subjects will not benefit from participating in this study. Subjects may benefit by receiving, at no charge, a thorough screening and diagnostic evaluation, the results of which may be shared with them, and if they wish, with their physicians. This research will also benefit scientific knowledge and may lead to the development of a potential therapy for alcoholism.

7 Study Objectives

7.1 Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of mavoglurant when used in combination with a moderate dose of alcohol in healthy social drinkers.

Specific Aim 1: To evaluate the effect of mavoglurant on blood chemistries, urine toxicology and physiological safety measures before and after alcohol administration.

7.2 Secondary Objectives (if applicable)

Specific Aim 2: To evaluate the interactions of alcohol and mavoglurant on blood alcohol levels and mavoglurant levels.

We collected and analyzed mavoglurant levels from the first 10 participants who completed this study. These results did not show any changes in mavoglurant levels after alcohol administration. We collected blood sample from the additional 14 participants who recently completed the study but at present we do not have the funding to complete these assays which are rather expensive and can only be conducted by one company in India. So we would like to not conduct these assays on the new samples but we would like to retain the deidentified samples and conduct the assays at a later date if and when funding becomes available

7.3 Exploratory Objectives (if applicable)

Exploratory Aim: To explore the effects of mavoglurant on alcohol responses, including stimulation, sedation, intoxication, and cognitive/motor performance.

8 Study Design

8.1 General Design Description

Double blind placebo-controlled trial of mavoglurant vs. placebo in light social drinkers (i.e., consuming 1- 6 standard alcoholic drinks per week and having engaged in at least one and no more than 12 binge drinking episodes in the past year). Participants will not meet criteria for a DSM-V Alcohol Use Disorder and must be willing to abstain from alcohol during the outpatient medication treatment phase. We propose to recruit 40 male and female social drinkers (to achieve a completer sample of 28 participants).

Subjects will sign informed consent and eligibility will be determined. Eligible subjects will participate in two alcohol administration lab sessions. They will be randomized to receive either 200 mg/day of mavoglurant or placebo for 7-10 days (14 in each study arm). During the outpatient medication administration phase, subjects will be observed daily as their medication is administered. Adverse events will be assessed. The first lab session will occur on Day 0 (prior to start of study medication) and the second lab session will occur following 7-10 days (as scheduling permits) of study medication. During each lab session, subjects will receive six successive doses of alcohol over a 90-min period designed to raise their blood alcohol levels to 80 mg/dl. Outcomes will include adverse events (during outpatient period and the lab session), safety labs (before and after drug and after alcohol), PK/PD of drug and alcohol, behavioral tests of cognition and body sway as well as self-reports of intoxication and other alcohol effects. Study staff will check in with subjects on the two days following the second lab session and an in-person follow up appointment will be scheduled 1 week after the second lab session.

8.1.1 Study Date Range and Duration

Subjects will participate in a screening visit and will complete lab session 1. Subjects will be seen daily, via video chat, to take their medication dose for the next 6 days (or up to 9 days, for scheduling reasons). On Day 7 (or up to day 10), they will come in for lab session 2 and take their final dose of medication. Subjects will then be followed up 1 week after the final lab session.

The enrollment period to accrue the 28 completing subjects is expected to be 6 years.

8.1.2 Number of Study Sites

One study site. Yale University will be the only site for this study

8.2 Primary Outcome Variables

The primary outcomes are clinical and laboratory measures including complete blood count and serum chemistries with calcium, magnesium, phosphate, liver function tests, B12 and TSH blood chemistries. We will also assess adverse events, heart rate, and blood pressure during the outpatient treatment period and during alcohol administration.

8.2.1 Secondary Outcome Variables (if applicable)

The secondary outcomes are blood alcohol levels on mavoglurant compared to no drug, and drug levels of mavoglurant before and after alcohol administration.

8.2.2 Exploratory Outcome Variables (if applicable)

Alcohol effects on stimulation, sedation, intoxication (Biphasic Alcohol Effects Scale), cognitive motor performance and physiological responses (blood pressure and heart rate) measured during the mavoglurant session and compared to responses measures during the baseline no-drug session.

8.3 Study Population

Participants will be social drinkers (consuming 1- 6 standard alcoholic drinks per week and having engaged in at least one and no more than 12 binge drinking episodes in the past year) who are not currently seeking treatment for their drinking behavior, and who are willing to abstain from drinking alcohol during the study, and who are between 21-50 years of age.

8.3.1 Number of Participants

We propose to recruit 40 male and female social drinkers (to achieve a completer sample of 28 participants). We anticipate having to consent approximately 90 subjects to reach these enrollment numbers.

8.3.2 Eligibility Criteria/Vulnerable Populations

All potential participants will be screened over the phone and if they appear to be eligible, will be brought in to be consented by a member of the research staff. A physical exam will be scheduled and reviewed by our Study Physician, and a psychological evaluation will be conducted by a trained clinical psychologist, or licensed social worker, to determine eligibility. In addition the participant's medical history may be verified from medical records by the study physician and study psychologist.

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

1) Screened light social drinkers who are aged 21-50.
2) Able to read English at 6th grade level or higher and to complete study evaluations,
3) Consume 1- 6 standard alcoholic drinks per week, and has engaged in at least one and no more than 12 binge drinking episodes in the past year,
4) Willing to abstain from drinking alcohol during the outpatient study medication treatment period.
5) Fully vaccinated against COVID-19 (as defined by CDC guidelines)

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

1) Seeking treatment for alcohol drinking.
2) Current DSM-V abuse or dependence criteria for alcohol, dependence criteria for other substances, other than nicotine.
3) Positive test results at any appointments after the initial intake appointment on urine drug screens conducted for opiates, cocaine, marijuana, benzodiazepines and/or barbiturates.
4) Regular use of psychoactive drugs including anxiolytics and antidepressants.
5) Psychotic or otherwise severely psychiatrically disabled.
6) Any medical conditions (including hepatic and renal impairment) that would contraindicate the consumption of alcohol or administration of mavoglurant.
7) History of neurological trauma or disease, delirium, or hallucinations, or any significant systemic illness or unstable medical condition.
8) Women who are pregnant, nursing, or refuse to use a reliable method of birth control. Urine pregnancy tests will be completed at intake and prior to administration of alcohol.
9) Subjects who report disliking spirits will be excluded because hard liquor will be provided during the alcohol administration.
10) Subjects who have taken any investigational drug and/or participated in another study which involves additive blood sampling and/or interventional measures that would be considered excessive in combination with the current protocol within 4 weeks immediately preceding admission to the treatment period.

11) Subjects who report any daily drug use during the 30 days prior to randomization for the following: anxiolytics, beta blockers, central nervous system stimulants, hypnotics, non-therapeutic doses of neuroleptics and antidepressants, drugs with psychotropic activity or drugs which cause excessive sedation.
12) Subjects who have donated blood within the past six weeks.
13) Current use (within 30 days of screening) of specific psychoactive medications (e.g., typical neuroleptics, narcotic analgesics, antiparkinsonian medications, systemic corticosteroids, or medications with significant central anticholinergic activity, etc.)
14) Current use of warfarin.
15) Use of any medications that are contraindicated with mavoglurant and alcohol.
16) AST, ALT, total bilirubin >1.5 times upper normal; serum creatinine, >2 times upper normal limit, total bilirubin>1.5 times ULN; Serum creatinine >2.0 times ULN.

9 Methods

9.1 Treatment

9.1.1 Identity of Investigational Product

The study drug being used in this study is AFQ056 (Mavoglurant). Mavoglurant has not been approved for clinical use by the FDA. Mavoglurant oral tablets and matching placebo will be provided by Novartis.

9.1.2 Dosage, Administration, Schedule

Subjects will take 200mg of Mavoglurant each day (2 x 100mg modified release tabs or matching placebo) for 7-10 days. Study drug will be prepared and packaged by the Investigational Drug Services (IDS) at Yale-New Haven Hospital (YNHH). Any dose pausing or dose discontinuation will be decided by the PI and Study Physician.

9.1.3 Method of Assignment/Randomization

This is a double-blind, placebo-controlled study. The alcohol center biostatisticians (Dr. Gueorguieva and Pittman) will create a randomization code list and forward it to the YNHH IDS pharmacy who will prepare the medication supply for each participant.

9.1.4 Blinding and Procedures for Unblinding

All staff and subjects will remain blind throughout the study. Only YNHH IDS and the study biostatisticians will have access to the blinding information. The PI will make the determination of if/when the blind needs to be broken.

9.1.5 Packaging/Labelling

Bulk supplies of the drug and placebo will be shipped from the company to the YNHH IDS in the form for 100 mg modified release tablets. The dose to be administered will be 200mg (two 100mg tablets) during the 7-10 day medication administration period. YNHH IDS will be responsible for monitoring drug supply and expiration.

Yale IDS will label all drug dispensed for this study.

9.1.6 Storage Conditions

Study drug will be received and stored under proper light/temperature conditions at YNHH IDS. Research staff will pick up the drug and dispense as appropriate to each subject. Expiration dates are observed, and drug will be dispensed accordingly. If drug needs to be returned, study staff will return to IDS and document appropriately. If called for by the study sponsor, the PI, and Novartis, IDS will destroy remaining study drug and provide documentation.

9.1.7 Concomitant therapy

Concomitant medications for each subject will be reviewed by the study physician prior to starting study medication. Warfarin use is not allowed. For all subjects, medications and illicit drugs that are forbidden during the study include opiates, cocaine, benzodiazepines and barbiturates. Regular use of psychoactive drugs, except for individuals on a stable dose of an antidepressant for at least 2 months. Also, any subjects who have taken any investigational drug within 4 weeks of the anticipated date of the first study dose.

9.1.8 Restrictions

Use of any illicit drugs is forbidden during study participation. Subjects are also asked not to come into the clinic for study appointments with a positive blood alcohol level (BAL). Since alcohol drinking is harmful to an unborn child, pregnant women may not participate in this study. As a result, the following precautions are necessary for female participants: 1) Repeated pregnancy test will be performed using a urine sample. A positive pregnancy test will result in them being excluded from the study, 2) females of childbearing potential must agree to use a reliable method of birth control during the study. Nursing mothers will also be excluded from the study.

9.2 Assessments

a) Socio-demographic/General Information: At intake, demographic data, medical history and family psychiatric history will be assessed with interviews and self-report forms that provide data on age, race, socioeconomic status, marital status, educational and occupational levels, and significant medical history. These are adapted from previous diagnostic and clinical studies at this center. As of the restart of the continuation of this study May 2022 this assessment had several sections separated out into individual assessments. These are listed below: Time to 1st Cigarette (Fagerstrom ND), NIAAA alcohol questions on Alcohol Questions, SSADDA Risk/Protective Factors.

b) SCID: The Structured Clinical Interview for DSM-V (SCID; First, et al., 1996) will be used to determine psychiatric diagnoses. This interview assesses DSM-V current and lifetime psychiatric diagnoses for anxiety, mood, psychotic, alcohol and substance use, somatoform, and eating disorders.

c) Time-Line Follow-Back Assessment Method: (Sobell & Sobell, 1992). This interview procedure will be used to obtain quantity/frequency alcohol consumption data for each day during the 30-day period prior to the study, during the outpatient stabilization period, and during the one month follow-up [33] Subjects are given a blank calendar covering the time interval to be re-constructed, and are asked to reconstruct retrospectively their drinking behavior over that interval. The process is facilitated by establishing anchor points (e.g., holidays, anniversaries, major national events, etc.). It can be scored to provide the number of days on which various levels of consumption occurred. The time-line method has good test-retest reliability and good validity for verifiable events. It has been used in numerous studies to compare pre- to post-treatment drinking.

d) SAFTEE: (Levine & Schooler, 1986) This is a standardized form for collecting side effects and adverse events. The SAFTEE includes 1) open-ended questions about any changes in physical or health problems, appearance, or activity level, and 2) yes/no responses to a specific list of symptoms (which correspond to anticipated side effects associated with NRT) for a specified time. For each symptom reported on the SAFTEE a rater also records the date of onset, severity (minimal, mild, moderate, severe), whether it was drug-related, and action taken. The SAFTEE is administered at baseline and daily during medication appointments and again before and after each alcohol challenge. We will monitor the number of patients experiencing symptoms and the severity of symptoms.

e) Biphasic Alcohol Effects Scale (Martin et al., 1993) This 14-item self-report, unipolar adjective rating scale will be used to measure the stimulant and sedative effects of alcohol during the two lab sessions. This instrument has been found to be sensitive to naltrexone's effects on alcohol intoxication.

f) Drug Effects Questionnaire -5 (Morean et al., 2013) The DEQ-5 asks the individual to report how they feel and five items: FEEL a drug effect, feel HIGH, DISLIKE the effects, LIKE the effects, and want MORE of the drug (in this case alcohol). Each item is assessed with a separate, unipolar 100mm visual analog scale rated from “not at all” to “extremely”.

g) Blood Alcohol Levels: Blood samples will be drawn to measure plasma levels of blood alcohol concentration (BAC) during the two lab sessions. Blood samples will be spun at room temperature and the serum will be stored at -4°C. Sample will be defrosted and analyzed using a clinical alcohol analyzer from Analox Instruments that uses a rapid high-performance alcohol analysis procedure using alcohol oxidase.

h) Health Profile and Urinalysis: Chemistry and CBC Panels will be drawn at baseline, prior to the lab sessions, the morning following the lab sessions, and at follow-up. Urinalysis will also be done at these times. Additionally, a pregnancy test for females will be done at intake and prior to both lab sessions.

i) Psychophysiological Measures: will include heart rate and blood pressure. The cuff of the Dinamap will be on subject's dominant arm since the IV will be placed in the non-dominant arm.

j) Multi-Stage Decision Making Task (MSDM): The MSDM is a reinforcement learning paradigm that quantifies the degree to which subjects can integrate recent trial-to-trial information about a stimulus' likelihood of reward with acquired knowledge about whether some choices generally lead to disadvantageous outcomes vs. others that more often lead to reward. Each MSDM trial requires choices to be made in two stages. In the first MSDM stage, one's choice probabilistically leads to another set of choices. Then in the second stage, subjects learn that only some stimuli are likely to give rewards. Participants will get paid based on how much "treasure" they receive on the trials. Out of the 3 trials, they will be paid their highest score. So if the win treasure 10 times, then 15, then 12; they will receive $15. Payments are expected to be $20 or less.

k) Concomitant Medications: A list of any other medications taken prior to the lab sessions, during the outpatient medication treatment period and through the follow-up will be kept for each subject indicating dosage, start date, end date, and indication. This will include all prescribed and over the counter medications.

l) Plasma Mavoglurant (AFQ056) levels: Blood samples will be stored at -70^{0}C and will be sent to Veeda Labs in India for analyses. The lab has a fully validated, FDA bioanalytical method available.

m) Body Sway: will be measured using the Wii balance board (software developed by Nelson & Lim, University of Minnesota). Objective assessments of the effects of alcohol are an important supplement to measures of subjective response of alcohol effects. Traditional methods of assessing balance have been prohibitive based on complexity or cost. However, a novel software package developed by researchers at the University of Minnesota allows for a practical assessment of balance using the Nintendo Wii Fit Balance Board. With supervision, participants will simply stand on the board, which is very sensitive to weight distribution, for 30 seconds while data on their weight distribution patterns are collected.

n) Yale Craving Scale (YCS; Rojewski et al., 2015): Labeled Magnitude Scale (gLMS), has been extended to measure hedonic ratings for foods, and we have adapted it for rating craving for tobacco and alcohol. It is not subject to the ceiling effects that often occur in craving research. We have been collecting craving data using this scale in our ongoing projects and the findings from this scale have been found to parallel those obtained using the Alcohol Urge questionnaire. A significant advantage of this scale is that following completion of baseline training to match perceived intensity of craving to the perceived brightness from the sun, each assessment timepoint only consists of a single visual analog scale of craving, making it very easy to administer.

o) Quality of Drinks Rating Scale (QDRS): This assessment first asks the participant to rate a variety of alcoholic beverages on an 11-point Likert scale. The next two questions are write in questions "What is your favorite alcohol?" and What is your favorite alcohol drinks?" For the next two questions the participant selects their preferred alcohol drink for the study's

drinking session. The liquor is selected from a list of 5 options. Lastly the participant writes in their top three fruit juice mixers.

p) Alcohol Effects Scale (AES): This 6-item questionnaire has the participant rate how they are feeling from the alcohol. There is a 10-item Likert scale ranging from 1 (Not at all) to 10 (extremely).

q) Menstrual Cycle Data: Self-reports will be obtained from all women on their menstrual/gynecological status.

r) Deary-Liewald reaction time task (Deary, et al., 2010): This computer task consists of two parts the Simple Response Time task (SRT) with just one stimulus, and when it appears, the participant needs to respond with the one response. Then there's the Choice Response Time task (CRT) that has multiple stimuli, and each stimulus requires a different response.

s) Conners' Continuous Performance Test II (CPT II; Connors, 2000): This computer task involves the participant pressing the space bar or clicking the mouse button when a letter other than X shows up onscreen. Letters appear on the screen with different time intervals between each one. Exactly 14 minutes is required for completion.

t) PROMIS Global Health: provide an assessment of a participant's individual assessment of his/her health (physical, emotional, and social), including an overall rating of pain

u) Digits Backwards: from the Digit Span subtest of the Wechsler Adult Intelligence Scale (WAIS-IV) (29): as a legacy, objective measure of working memory, a factor associated with poor decision making in those with AUD.

v) PROMIS Cognitive Function: will assess mental acuity, concentration, verbal and nonverbal memory, and verbal fluency and provide an assessment of a participant's perception of changes in cognitive abilities over the prior 4 weeks.

w) Barrett Impulsivity Scale (BIS-11): is an 8-item trait measure of impulsiveness that yields two, 4-item subscales: (lack of) Self-Regulation ($\alpha = .75$) and Impulsive Behavior ($\alpha = .72$).

x) Behavioral inhibition/activation system (BIS/BAS): is a 13-item measure that will be used to assess behavioral activation and behavioral inhibition, in response to rewards and punishment. We will use the Brief BIS/BAS, which has demonstrated scalar measurement invariance groups of interest (e.g., sex, age, race, education level, family history status, binge drinking status, and cigarette smoking status), as well as good convergent, discriminant, and predictive validity.

y) UPPS Impulsive Behavior Scale (urgency subscales): evaluates the tendency to engage in impulsive drinking in response to negative and positive affect.

z) Self-reported Habit Index (SRHI - Alcohol): provides a self-report measure (6-item) of the degree to which alcohol drinking is habitual based on features of automaticity, lack of control and identity in human subject studies.

aa) PROMIS Sleep and Impairment Measures: will measure past 7-day waking alertness, sleepiness, and impairment in function related to poor sleep because insomnia has been shown to be related to substance use and associated impairment.

ab) AUDIT-C: a 3-item well-deployed quantity/frequency measure of alcohol use.

ac) PROMIS Nicotine Dependence (ND): This 4-item scale will assess severity of nicotine dependence for cigarette smokers.

ad) Time to 1st Cigarette (Fagerstrom ND): As a legacy measure of nicotine dependence, we will retain the item assessing time to the 1st cigarette of the day from the Fagerström Test of Nicotine Dependence

ae) NIAAA alcohol questions on Alcohol Questions: Longer-term drinking will be assessed with 6 questions recommended by the NIAAA Council's Task Force on Recommended Alcohol Questions, including past 12 months patterns of alcohol use and lifetime max drinks

af) SSADDA Risk/Protective Factors: Environmental Factors experienced prior to age 13 will be assessed with a brief module from the SSADDA that was developed by Drs. Gelernter and Kranzler in 2002 to assess major environmental risk and protective factors associated with AUD, based on data presented at a NIAAA sponsored gene x environment workshop meeting.

9.2.1 Adverse Events Definition and Reporting

Adverse Events (AE) will be assessed from the time a subject starts the study through the final follow up appointment. The SAFTEE (see description above in section 6.2) will be used to assess any AE's at each visit. This procedure involves asking subject open-ended questions (e.g. How have you been feeling since your last visit) as well as reviewing a specific list of side-effects associated with the study medication and having the subject respond yes/no.

Definitions

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

An AE or suspected adverse reaction is considered "serious" (SAE) if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death,
- a life-threatening adverse event,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- a congenital anomaly/birth defect, or
- An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an 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.

Severity

Adverse events will be graded according to [name grading scale, e.g. CTCAE v5.0]. For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

*An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event (SAE). Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

Relationship to Investigational Product

All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Potentially Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- Not Related – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Expectedness

The Principal Investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Reporting

For studies conducted under an IND, there are two types of Safety Reports submitted to FDA:

- 7-Calendar-Day FDA Telephone or Fax Report: The sponsor-investigator will directly notify the FDA, within 7 calendar days after initial receipt of the information, of any adverse event that is fatal or life-threatening, unexpected, and considered at least possibly related to the investigational product.
- 15-Calendar-Day FDA Written Report: The sponsor-investigator will directly notify the FDA within 15 calendar days after initial receipt of the information, of any serious adverse event (other than those that are fatal or life-threatening) that is unexpected and considered at least possibly related to the investigational product.

Serious Adverse Events which do not meet the criteria for expedited reporting will be reported to the FDA in the IND Annual Report.

Plan for reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including Adverse Events, to the IRB.

The principal investigator will report the following types of events to the IRB:

Any incident, experience or outcome that meets ALL 3 of the following criteria:

1) Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2) Is related or possibly related to participation in the research (*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); AND
3) Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.
    1. UPIRSOs may be medical or non-medical in nature and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device effects*. ***Please note*** that adverse events are reportable to the IRB as UPIRSOs **only** if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the *prompt* reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented***.*** In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

x All Co-Investigators listed on the protocol.

x NIH/NIAAA

x Food and Drug Administration (Physician-Sponsored IND #137044)

x Study Sponsor (John Krystal, MD) and Novartis

x Center for Translational Neuroscience on Alcoholism (CTNA) DSMB

The principal investigator, Suchitra Krishnan-Sarin, will conduct a review of all adverse events upon completion of every study subject. She will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

Adverse events that meet the criteria for a Serious Adverse Event will be reported to the IRB, NIAAA, the CTNA DSMB, study investigators, and to Novartis (the company providing mavoglurant) within 24 hours by phone or fax and in writing within 1 week.

9.2.2 Pharmacokinetics (if applicable)

Pharmacokinetic testing will be done to determine levels of mavoglurant in plasma. Blood will be drawn for this purpose at the first lab session (prior to initiation of mavoglurant) and twice at the 2nd lab session (after final dose of mavoglurant and again after alcohol drinking session. Language of this testing is included in the study informed consent form. A contract with Veeda Clinical Research Labs in Gujarat, India has been set up an specimen will be shipped appropriately upon study completion.

9.2.3 Biomarkers (if applicable)

N/A

9.3 Study Procedures

Recruitment, baseline assessments, physical exam, and psychological evaluation

Potential subjects will be recruited via posted advertisements in the local newspaper and brochures and other materials distributed in the community. We will also recruit via online methods such as FaceBook, CraigsList, online newspapers, Google Ads, etc. They will be initially screened for eligibility either by phone after giving verbal consent or via an online screener, the link for which will be provided in the study advertisements. After providing consent, participants will be asked to give their contact information so that they can be contacted regarding their eligibility. They will then proceed to complete the survey, which will be housed in a different account on Qualtrics, a secure website.

Based on eligibility, participants will be scheduled for an intake appointment and complete consent via REDcap (or mail or in-person if necessary). All questionnaires, medical history, and psychological evaluation will be conducted remotely via video chat (e.g. Zoom, FaceTime, etc). If the study participant does not have internet access or a device capable of this form of communication, we will conduct the appointment over the phone or in person. Each participant will be asked comprehension questions to ensure they understand the study and will be asked to sign the consent form. Prior to all in person study appointments, COVID-19 screening questions will be asked. All participants will receive a signed copy of the consent form to retain for their records. The research assistant will schedule a physical exam, including an EKG, routine laboratory work, and hepatic, kidney and thyroid function tests. A detailed medical history will be obtained from all subjects and pregnancy tests for all females. Subject characteristics and medical history will be reviewed by the PI to ensure that the subject meets all the eligibility criteria. The study physician (Dr. Julia Shi) will review their eligibility based on their medical history and EKG.

The psychological evaluation will be completed and reviewed by a licensed psychologist after all inventories/assessments are collected. If a subject is deemed at risk, or questionable, at the time of the evaluation, the clinical psychologist will be contacted immediately and asked to reach out to the participant as soon as possible.

Lab Session 1

See appendix for detailed procedure sheet. Participants will arrive at the Hospital Research Unit (HRU), Church Street Research Unit (CSRU), or Masonicare at 8:15am. We will collect BAC, urine toxicology, and conduct paper and pencil baseline questionnaires. At 9:00am,

participants will be provided breakfast. They will then complete additional study assessments. We will put an IV catheter in the participant's arm at 11:00am and we will draw the initial set of labs. At 12:00pm, participants will be given their first drink of 80-proof vodka with a non-carbonated mixer of their choice and will be instructed to drink it in 15 minutes. They will continue to receive successive doses of alcohol in 6 equal portions (every 15 minutes) over a 90-min period designed to raise their blood alcohol levels to 80 mg/dl; we chose this dose because this the legal limit of intoxication and is close to the peak BAC we have observed in prior ADP sessions (with approx. 200 heavy drinkers) and is similar to the alcohol dose used in a previously completed similar protocol with another drug (HIC #0602001068). Alcohol dosing will be calculated using published gender specific algorithms based on estimated body water determined from height, weight (obtained at physical exam), and age and translated into ml of 80-proof vodka (Curtain & Fairchild, 2003). Regardless of the amount of vodka required, the amount of mixer will be adjusted so that the total volume of fluid will be constant. These methods of alcohol administration have been safely used by our group (Jatlow, et al., 2014), with volunteers who had similar drinking profiles. At 12:15pm, a blood pressure cuff will be placed on his/her arm to monitor vitals throughout the lab session. Safety labs will be drawn and blood samples will be collected at regular intervals (at baseline and every 15 minutes during the lab session and then hourly for the next 3 hours) to assess blood alcohol levels and to assess Mavoglurant levels. They will complete paper and pencil questionnaires about mood, medication and alcohol effects at regular time intervals, as well as the Body Sway Task.

At 2pm, subjects will be given lunch and will be monitored for any remaining alcohol effects. BAC levels will be taken every 30 minutes until the level falls to less than .02 (about 4 hours). Participants will be allowed to leave when their BAC falls to below .02 or at 6pm, whichever comes first. All participants will be provided with transportation to and from lab session.

Outpatient Treatment

At the commencement of drinking session 1, participants will be sent home with the study medication for the full period. If their second lab session is not scheduled within the designated timeframe, the participant will come in for their first medication appointment and be sent home with their medication that day. They will take their medication daily (in person or on video chat – 10min) at approximately 10am. They will be observed taking the study medication, for 7-10 days (to achieve steady state levels). This will ensure compliance with medication and allow us to monitor side effects daily. The last dose of study medication will be at 8:15 on the morning of their Lab Session 2. Participants will be asked to abstain from alcohol during the outpatient medication period; our rationale for requiring this is because this is a study to examine alcohol-drug interactions and we want to study these interactions in a controlled laboratory session.

Lab Session 2

See appendix for detailed procedure sheet. Participants will arrive at the Hospital Research Unit (HRU), Church Street Research Unit (CSRU), or Masonicare at 8:15am. They will be instructed to take their last dose of study medication. We will collect BAC, urine toxicology, and provide them with breakfast. Following breakfast, they will complete study assessments/questionnaires. We will put an IV catheter in the participant's arm at 11:00am and we will draw the initial set of labs. At 12:00pm, participants will be given their first drink of 80-proof vodka with a non-carbonated mixer of their choice and will be instructed to drink it in 15 minutes. They will continue to receive successive doses of alcohol in 6 equal portions (every 15 minutes) over a 90-min period designed to raise their blood alcohol levels to 80 mg/dl. Safety labs will be drawn and blood samples will be collected at regular intervals (at baseline and every 15 minutes during the lab session and then hourly for the next 3 hours) to assess blood alcohol levels and to assess Mavoglurant levels. They will complete paper

and pencil questionnaires about mood, medication and alcohol effects at regular time intervals, as well as the Body Sway Task.

At the end of the drinking session, the participant will be given lunch. They will be monitored for any remaining medication and alcohol effects. BAC levels will be taken every 30 minutes until the level falls to less than 0.02 (about 4 hours). Participants will be allowed to leave at approximately 6pm or when their BAC falls to below 0.02. All participants will be provided with transportation to and from lab session. The following morning participants will go to Quest for a blood draw and urine collection.

Follow Up Interviews

Subjects will receive phone calls on the two days following lab session 2 to see how they are doing and to assess any remaining side effects from the medication. Subjects will also participate in a 30-minute follow-up interview at one week after lab session 2. During this appointment, we will assess participants for any lingering side effects of the medication and obtain information about their drinking over the follow up period.

Payments for Participation (Economic Considerations)

Subjects will have the opportunity to receive up to $630 for completing all parts of the study. Payment for the intake interview will be $50. They will receive an additional $65 for the physical examination/ in-person intake and up to $20 for completing the MSDM task. Subjects will also receive $140 for participating in the 1st laboratory session and $200 for completing the 2nd laboratory session. Additionally, subjects will receive $10 to take their study medication dose (7-10 days), for up to a total of $100 and $25 for the blood draw the morning after the second drinking session. Subjects will be paid $30 for completing the one week follow-up appointment. If a subject is asked to come back in for a repeat lab appointment (blood work or EKG), he/she will be paid $25. Subjects will be reimbursed for parking.

9.3.1 Study Schedule

The study will consist of five parts: 1) Eligibility: Informed consent is obtained, and eligibility is evaluated, 2) Lab Session 1: Eligible subjects will be seen outpatient for Lab 1 where we will obtain baseline information and randomization to study medication. 3) Outpatient Medication: Subjects will be seen (virtually or in-person) on a daily basis, for 6-9 days, to take their study medication, 4) Lab Session 2: Subjects will again be seen outpatient for their second lab session. They will have their blood drawn and a urine collection the following morning. 5) Follow Up Interviews: We will follow up with participants via phone, for two days after lab session 2. They will be seen, one week after last session 2 for bloodwork, urine collection, and to assess for any potential remaining side-effects.

Phase/Day	Visits	Comments
BL	Initial Intake Screening	Informed consent obtained prior to any study procedures.
BL	Physical Exam	Includes vitals, blood, urine, EKG, and medical history.
Day 0	Lab Session #1	Randomized to drug condition, vitals, blood, and urine
Days 1-10*	Medication Administration	1x/day staff observing subject administering medication.
Day 7-10*	Lab Session #2	Last dose of study medication, vitals, blood, and urine
Day 8-11	Morning After LS 2	Blood and urine analysis
FU	1 week Follow Up	Including final blood and urine analysis.

*Medication taken for 7 to 10 days (pending schedule); Lab #2 occurs on day of last medication administration

9.3.2 Informed Consent

At the first screening visit, candidates will meet with a Research Assistant and receive an explanation of the study purpose and requirements. If still interested, the candidate will be given an opportunity to review, inquire about, and sign the study informed consent form approved by the IRB. Subjects must have a breath alcohol level (BAL) of 0.000 measured by breathalyzer when signing the informed consent document (tested shortly before or just after providing consent). Repeat measurements of BAL are permitted at the discretion of the investigator. If appointment is conducted remotely, we will be unable to collect BAL levels. Subjects will be given a copy of the signed informed consent form.

9.3.3 Screening

Screening will take place over two visits. At the initial visit, conducted remotely when possible, an interview and self-report assessments will be obtained and study schedule of visits will be reviewed. If the subject appears eligible after this visit, a second in-person screening visit will be scheduled where we will conduct a physical exam and additional assessments/questionnaires. Final eligibility will be determined by the PI and study Physician. If a subject screen fails, they may be rescreened at the discretion of the PI (and consultation with Study Physician, if applicable).

9.3.4 Enrollment

After a subject has been consented, screened, and meets eligibility criteria they will be scheduled for the first Lab Session. This will be done by consulting with the subject's schedule and room availability. Scheduling of the Medication Administration Days and the second Lab Session will also be considered at the time of enrollment due to the flow of study these following study visits being interdependent.

9.3.5 On Study Visits

Study Visit	Intake	Physcal Exam / In-Person Intake	Lab Session 1	Medication Administration (6-9 Days)	Lab Session 2	Morning After Lab Session 2	1 Week Follow-Up
Informed Consent	X						
Health History	X						
Alcohol Breathalyzer (not done for remote appointments)	X		X	X	X		
CO level			X		X		
Eligibility Checklist	X	X					
Randomization			X (before appt)				
Socio-demographic/General Info	X						
Time to 1st Cigarette (Fagerstrom ND)	X						
NIAAA alcohol questions on Alcohol Questions	X						
SSADDA Risk/Protective Factors	X						
Time to 1st Cigarette (Fagerstrom ND)	X						
NIAAA alcohol questions	X						
SSADDA Risk/Protective Factors	X						
PROMIS Nicotine Dependence (ND)	X						
EKG		X					
SCID (DSM-V) Summary and E section	X						
Time-Line Follow Back	X		X	X	X		X
SAFTEE			X	X	X		X
YCS			X		X		
Biphasic Alcohol Effects Scale (BAES)			X		X		
Psychophysiological Measures	X	X	X	X	X		X**
Blood Alcohol Levels			X		X		
Plasma Mavoglurant Levels			X		X		
Menstrual Cycle Data		X					
QDRS	X						
Body Sway Task			X		X		
CPT			X		X		
SRT			X		X		
CRT			X		X		
AES			X		X		
Drug Test and Pregnancy Test (females)	X	X	X	X*	X		
Blood Chemistry Panel and Urinalysis		X	X		X	X	X
Concomitant Medications	X		X	X	X		X
PROMIS Global Health		X					
Multi-Stage Decision Making Task (MSDM)		X					
Digits Backwards		X					
PROMIS Cognitive Function		X					
Barrett Impulsivity Scale (BIS-11)			X				
Behavioral inhibition/activation system (BIS/BAS)			X				
UPPS Impulsive Behavior Scale (urgency subscales)			X				
Self-reported Habit Index (SRHI - Alcohol)			X				
PROMIS Sleep and Impairment Measures			X				
AUDIT-C			X				
* Drug and Pregnancy tests performed once during the the week of medication administration							

9.3.6 End of Study and Follow-up

After the second lab session staff will check in with the subject via phone. A final, follow-up visit will be conducted. Adverse events will be monitored 1 week after the second lab session. The participant will come in-person for blood, along with psychophysiological safety measures (heart rate, blood pressure, etc.) only when blood pressure is signfically elevated at lab session. If a subject request a copy of results (e.g. blood analytes), I de-identified copy will be provided upon approval of the PI.

9.3.7 Removal of subjects

Each subject has the right to withdraw consent and withdraw from the study at any time. In addition, the investigator may find it necessary to discontinue a subject for any reason, including the occurrence of an AE or noncompliance with the protocol.

In the event that a subject withdraws or is discontinued from the study, the reason(s) for the discontinuation from the study will be recorded and the subject will be asked to return for their follow-up visit to obtain final safety measures.

9.4 Statistical Method

9.4.1 Statistical Design

This study is exploratory in nature and seeks to determine effect sizes to be used in subsequent years, in the larger-scale studies, and to determine if alcohol and mavoglurant can be safety used together. Therefore, no formal power calculations have been performed. The design employed here, including the chosen sample size, are relatively standard in pilot studies (Galasko et al., 1997; Sinha, et al., 1999)

9.4.2 Sample Size Considerations

As noted above, due to the exploratory nature of this pilot study, the chosen sample size is relatively standard in pilot studies.

9.5 Planned Analyses

9.5.1 Primary Objective Analysis

Adverse events will be tabulated and rated for severity (mild, moderate, and severe) and for relation to the study intervention (unlikely, possibly, probably, and likely). Area under the curve will be measured for blood alcohol levels and compared between the two sessions (mavoglurant; baseline no-drug). Changes in serum chemistries, blood cell counts, and urinalysis will be compared before and after alcohol consumption between sessions (on drug, baseline no-drug). Quantitative outcomes will be analyzed using mixed models.

9.5.2 Secondary Objectives Analyses

Drug plasma levels for mavoglurant will be compared before and after alcohol consumption.

9.5.3 Exploratory Objectives Analyses (if applicable)

Changes in subjective and cognitive motor performance measures following alcohol consumption will also be compared between sessions (on drug, baseline no-drug).

9.5.4 Safety

Not Applicable. Evaluation of safety is already a main object for this study.

9.5.5 Analysis of Subject Characteristics

Subject demographics will be collected and reported, noting any differences between active/placebo groups.

9.5.6 Interim Analysis (if applicable)

Not Applicable

9.5.7 Health economic evaluation

Not Applicable

9.5.8 Other

Not Applicable

9.5.9 Subsets and Covariates

Not Applicable

9.5.10 Handling of Missing Data

Mixed effects models will use all available data on individuals. Dropout rates will be compared between treatment groups and reasons for dropout will be evaluated in order to inform future studies.

10 Trial Administration

10.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

The study will be conducted under the ethical principles as described in 45 CFR § 46.111 and ICH GCP.

At the start of the intake session, all subjects will receive an explanation of the study including its risks, benefits, and procedures, and will be given an opportunity to withdraw from the study. Following the resolution of any questions, the subject will be asked to sign the consent form, if he/she agrees to participate. The consent form also includes language required for HIPAA Authorization.

Given that this research study is not a treatment study, there are no treatment alternatives, however subjects can decline participation.

Subjects will be paid an amount that approximates $20/hour for study visits.

10.2 Institutional Review Board (IRB) Review

The protocol will be submitted to the IRB for review and approval. Approval of the protocol must be obtained before initiating any research activity. Any change to the protocol or study team will require an approved IRB amendment before implementation. The IRB will determine whether informed consent and HIPAA authorization are required.

The IRB will conduct continuing review at intervals appropriate to the degree of risk, but not less than once per year.

A study closure report will be submitted to the IRB after all research activities have been completed.

Other study events (e.g. data breaches, protocol deviations) will be submitted per Yale's Human Investigation Committee/Human Research Protection Program policies.

10.3 Subject Confidentiality

Subject confidentiality is held in strict trust by the research team. Subject medical record review will be limited to the just the elements needed to complete the study. Only authorized HIPAA and GCP trained study team members will have access to these records.

This study has a Certificate of Confidentiality. Subjects are informed of what this means and what it covers and its limitations in the informed consent document.

Each subject will be assigned a unique study number. A master list linking the unique study number to the human subject will be maintained in a locked drawer at our offices at 34 Park St in New Haven

Data will be stored on an encrypted password protected Yale ITS managed workstation without any HIPAA identifiers. Strict confidentiality will be maintained in all records of the study by identifying subjects by code numbers. Information that is obtained in connection with this study and that can be identified with a subject will be kept confidential (subject's charts are kept in a locked room and file cabinet. Files will be kept in locked cabinets in a security system protected office. All information obtained from subjects is referred to by code number and kept in locked confidential files (subjects' paper charts are kept in an area protected with a security system, in a locked room and file cabinet). Any published results are published as group data without the use of characteristics that would identify individual subjects. We quote information only by number in conference discussions, scientific reports or publications to maintain anonymity.

10.4 Deviations/Unanticipated Problems

If the study team becomes aware of an anticipated problem (e.g. data breach, protocol deviation), the event will be reported to the Yale HIC via IRES. If deviations occur study staff will follow Yale HIC guidelines for reporting (i.e. immediately or at annual continuing review of the protocol).

10.5 Data Collection

As required by law, all reasonable efforts will be made to protect the confidentiality of subjects' protected health information, which may be shared with others to support this research, to conduct public health reporting, and to comply with the law as required (according to a HIPAA compliant research authorization form signed by the subject). Yale Staff will collect required research data through study procedures as outlined in this protocol and record it in confidential research records and protected computer files. Each subject will have a paper "research chart" created for this information, which will be kept in a locked room and file cabinet. In all study records (except for the subject's research chart which includes the subject's name and other unique identifiers and all original records received by Yale with such identifiers), subjects will be referred to by a code number (with access to codes restricted to research staff).

Data will be stored on an encrypted password protected laptop computer without any HIPAA identifiers. Strict confidentiality will be maintained in all records of the study by identifying subjects by code numbers. Information that is obtained in connection with this study and that can be identified with a subject will be kept confidential (subject's charts are kept in a locked room and file cabinet). Files will be kept in locked cabinets in a security system protected office.

All information obtained from subjects is referred to by code number and kept in locked confidential files (subjects' paper charts are kept in an area protected with a security system, in a locked room and file cabinet). Any published results are published as group data without the use of characteristics that would identify individual subjects. We quote information only by number in conference discussions, scientific reports or publications in order to maintain anonymity.

Patient health information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Compound Consent and Authorization form signed by the patient or unless permitted or required by law. Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes as permitted by an Authorization for Access/Release of Health Information form signed by the patient. Medical records that identify subjects and the consent form signed by subjects must be available for inspection upon request by representatives of the U.S. FDA and other regulatory agencies, national and local health authorities, the study investigators, the sponsor and the sponsor's representatives and collaborators, and the local IRB. Only research personnel will have daily access to the research records.

Although considered unlikely to be encountered, limits to confidentiality such as mandatory reporting requirements for abuse of children or the elderly will be complied with. Subjects will be notified of this mandatory reporting in the consent form.

10.6 Data Quality Assurance

All study staff will be trained to ensure accurate and consistent data collection. Data will be regularly checked by the study data manager to ensure validity and completeness. In addition, all study staff will keep up to date with all Good Clinical Practice and Human Research Protection trainings.

10.7 Study Records

Study records include IRB documents (protocol, consent forms, etc), IND documents (amendments, annual reviews, etc), a study subject binder consisting of de-identified source documents/case report forms, and a separate subject folder consisting research documents that may contain identifiable information (consent documents, subject contact information, study nurse/physician notes, etc) and is kept separately under lock and key.

10.8 Access to Source Documents

Source documents will be contained in study binders. This study will use Teleforms data entry software (using specific forms that are scannable into a database). As the binders/source documents are completed, research staff will provide the study data manager with the forms. They will then be scanned, validated uploaded into study specific databases.

10.9 Data or Specimen Storage/Security

Data will be stored on an encrypted password protected laptop computer without any HIPAA identifiers. Strict confidentiality will be maintained in all records of the study by identifying subjects by code numbers. Information that is obtained in connection with this study and that can be identified with a subject will be kept confidential (subject's charts are kept in a locked room and file cabinet. Files will be kept in locked cabinets in a security system protected office. All information obtained from subjects is referred to by code number and kept in locked confidential files (subjects' paper charts are kept in an area protected with a security system, in a locked room and file cabinet). Any published results are published as group data without the use of characteristics that would identify individual subjects. We quote information only by number in conference discussions, scientific reports or publications to maintain anonymity.

Study data will periodically submitted to NIH National Data Archive (NDA; https://nda.nih.gov/). Grant recipients must include language in the informed consent form, agreeing that data and supporting documentation submitted to NDA may be accessed and used broadly by approved users for research. This submitted data is de-identified. Language to be included follows:

Data from this study will be submitted to the National Institute of Mental Health Data Archive (NDA) at the National Institutes of Health (NIH). NDA is a large database where deidentified study data from many NIH studies are stored and managed. Sharing your deidentified study data helps researchers learn new and important things about brain science more quickly than before.

Deidentified study data means that all personal information about you (such as name, address, birthdate and phone number) is removed and replaced with a code number. The study researchers will have to collect your personal information from you in order to make that code number. The code number cannot be used to identify you. The study researchers will never send your personal information to NDA.

It is possible that you will participate in more than one study that sends data to NDA. NDA can connect your data from different studies by matching the code number on your deidentified data from each study. This data matching helps researchers who use NDA data to count you only one time. It also helps researchers who use NDA to better understand your health and behavior without knowing who you are.

During and after the study, the study researchers will send deidentified study data about your health and behavior to the NDA. Other researchers across the world can then request your deidentified study data for different research projects. Every researcher (and the institution to which they belong) who requests your deidentified study data must promise to keep your data safe and promise not to try to learn your identity. Experts at the NIH who know how to keep your data safe will review each request carefully to reduce risks to your privacy. Sharing your study data does have some risks, although these risks are rare. Your study data could be accidentally shared with an unauthorized person who may attempt to learn your identity. The study researchers will make every attempt to protect your identity.

You may not benefit directly from allowing your study data to be shared with NDA. The study data provided to NDA may help researchers around the world learn more about brain science and how to help others who have problems with brain science. NIMH will also report to Congress and on its website about the different studies using NDA data. You will not be contacted directly about the study data you contributed to NDA.

You may decide now or later that you do not want your study data to be added to NDA. You can still participate in this research study even if you decide that you do not want your data to be added to NDA. If you know now that you do not want your data in NDA, please tell the study researcher before leaving the clinic today. If you decide any time after today that you do not want your data to be added to NDA, call or email the study staff who conducted this study, and they will tell NDA to stop sharing your study data. Once your data is part of NDA, the study researchers cannot take back the study data that was shared before they were notified that you changed your mind. If you would like more information about NDA, it is available on-line at http://nda.nih.gov.

10.10 Retention of Records

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained. The company supplying the study medication (Novartis) will also be consulted on destruction of study materials.

10.11 Study Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, that the facilities and staffing are adequate for continued study conduct, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Council for Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s) including federal, state and local regulations and institutional policies and procedures.

Clinical site monitoring will be performed by the Yale Center for Clinical Investigation (YCCI). Monitoring visits will include a site initiation visit, regularly scheduled on-site interim monitoring visits and/ or remote interim monitoring visits while subjects are on study, and a site close-out visit at the site. Following each monitoring visit, a visit report will be generated containing information on site activities and a summary of pertinent points and action items. The report will be provided with a follow-up letter. Site-specific data status reports will be distributed to the site regularly to outline planned, missing or incomplete case report forms and any outstanding data queries.

During monitoring visits, the following may be reviewed:

- Protection of the rights, safety and welfare of subjects through review of informed consent process and documentation, adverse events (AEs) and serious adverse events (SAEs) and safety procedures
- Subject eligibility
- Source verification
- Protocol compliance
- Deviations and Non-compliance
- Investigator Site File
- ICH GCP compliance
- Investigational Drug/ Device Storage and Accountability (including quantity and disposal procedures)

- Laboratory Facilities
- Equipment maintenance and calibration
- Additional study supplies inventory and assessment
- Study progress and/or follow-up on issues with Site Principal Investigator (PI) and relevant members of the study team

The Study PI and YCCI will define the required study monitoring activities in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

10.12 Data Safety Monitoring Plan

This protocol is a moderate risk protocol and therefore requires a data safety and monitoring plan.

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator, the IRB, Novartis, or the CTNA DSMB have the authority to stop or suspend the study or require modifications.

We will be accessing the Data and Safety Monitoring Board (DSMB) developed for the Center for Translational Neuroscience on Alcoholism (John Krystal, PI) since this project is a component within this Center. The DSMB is multi-disciplinary and includes representatives with expertise in the primary components of the proposed trial. The following individuals will be on the DSMB as voting members:

Robert Swift, MD, PhD.,Prof Psych (Brown)/ASOS Res Provid. VAMC Chmn, DSMB, Robert Stout, PhD., Director, Decision Sci. Int., Statistician, DSMB, Howard Zonana, MD., Dir, Dept Psychiatry Ethics Committee, IRB Rep, DSMB, Lisa Newton, PhD., Prof. Applied Ethics, Fairfield Univ. Ethicist, DSMB

This DSMB will follow the operational guidelines outlined in the YCCI OR CNRU plan for DSMB. We hope to recruit subjects at a maximum rate of 5-10 per month, thus, the DSMB will review safety reports two times a year. More frequent meetings will be scheduled if indicated by interim findings.

10.13 Study Modification

All study modifications will be determined by the study PI. Modifications will be submitted to Yale HIC (IRB) for approval prior to being implemented. Upon approval from IRB, the Sponsor and FDA will be notified of all modifications.

10.14 Study Discontinuation

If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met

- Determination of futility

10.15 Study Completion

The study PI and Sponsor will determine the completion of the study with regards to targets for enrollment and study completers. Upon completion, IRB (Yale HIC) and FDA will be notified appropriately.

10.16 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the appropriate conflict of interest review committee has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

All investigators will follow the applicable conflict of interest policies.

10.17 Funding Source

This study is being conducted as part of the Center for the Translational Neuroscience of Alcoholism (CTNA-5) which is funded by a grant from National Institute on Alcohol Abuse and Alcoholism / NIH / DHHS (#2P50AA012870-21).

10.18 Publication Plan

Any resulting publications will be done with approval of the PI, Sponsor, and Novartis.

11 Appendices

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TIME	START OF DRINKING SESSION PROCEDURES
Prior to arrival RA	___ Confirm Dr. Shi signed off on EPIC orders ___ Confirm participant breakfast and lunch were ordered from HRU and transport was setup. ___ Confirm covid questions were filled and negative rapid covid test and send both to Lindsey.douglas@yale.edu and lynda.knaggs@ynhh.org. ___ Pick up study alcohol and meds from IDS ___ Bring to lab: alcohol, participant binder, participant folder, CTNA laptop, fruit juice mixer and frozen breakfast option (if needed). ___ Confirm participant was added to OnCore
8:15 am RA	*RA and participant to have a mask on in lab (confirm extra masks are at lab) _____ Give participant meds (if first dose is scheduled for tomorrow) Meet participant in 1st floor lobby and walk them to the CSRU on the 4th floor _____ Get study cart from OnCore/Epic Suite #404, code 9224#, Key holder (PIN 3636) Urine drug screen and pregnancy test (*RA to send urine to Quest): Neg _____ Pos _____ Record time of last drink _____ Amount of last drink _____ Instruct participant on using both (BAC and CO) step out of room. BAC Level: _____ CO Level: _____ *If BAC is positive, notify Dr. Krishnan-Sarin 860-575-9895 _____ Concurrent medications, TLFB, SAFTEE Collect subject's cigarettes (if applicable) Smoker: _____ Nonsmoker: _____ Height:_____ inches (Shoes off) Weight: _____ kgs. _____ lbs. *For data only. IDS will be using height and weight from PE for alcohol calculations. _____ Fill out Quest form for today

	Baseline PACKET #1: YCS Long, AES, BAES, BIS, BIS/BAS, UPPS, SRHI, PROMIS Sleep and Impairment Measures, AUDIT-C, W9 Baseline Assessments ____ Body Sway Task (Confirm data is recording and showing weight, if not restart task) ____ CPT ____ SRT ____ CRT
9:00 am RA	Give subject breakfast. Time: _____ (Ensure they eat, so they don't have an empty stomach) *NO FOOD AFTER 10AM, UNTIL AFTER DRINKING SESSION IS OVER
11:00 am NURSE	Place heplock in non-dominant arm (DO NOT USE A RUNNING IV) *If you experience any problems or have any concerns with the IV placement, please contact study staff PRIOR to placing IV. Record actual time of blood draw: _____ ____ DRAW "-60min" BAL (blue microtube) ____ Health Profile (CMP, CBC w/diff, TSH, Phosporous, Magnesium, Uric Acid) 2 Marble/gold 5ml top tubes (spun) and 1 lavender tube 4ml (unspun) *RA to send samples Quest ____ 1 MAV lavender 10ml pre "-60" plasma level. Put two lables on tube. Process in cold centrifuge (-80 degrees freezer or dry ice) ____ Urine (Urinalysis) *RA to send samples to Quest
11:00 am RA	____ Place labled Health Profile (2 Marble/gold 5ml top tubes (spun), 1 lavender tube 4ml (unspun), and urine sample in Quest box on 4th floor outside of room 401. ____ Call Quest for pickup or online (ensure they arrive prior to building closing) Record dose of alcohol from Pharmacist and mixer Alcohol Dose (vodka): _____ ml Mixer (Juice): _____ ml Bathroom break and ensure participant has water to drink. Premix all 6 drinks Juice (of their choice) and vodka (0.03 mg%) and cap securely. Keep drinks on ice. Setup Zoom on laptop to communicate during drinking session.

11:55 pm RA	Bring all 6 drinks into room with participant. Bring packets 2-7 into room. Set up for drinking session and READ study spiel to subject.
12:00 pm RA	Drink #1, Juice (of their choice) and vodka (0.03 mg %) Instruct participant that s/he has 15 minutes to drink cup #1 and to pace their drinking so it is consumed over the entire 15-minute period. (start timer count up)
12:15 pm NURSE	BP: _____ Pulse: _____ (BP cuff on arm opposite IV, stays on until the end of the drinking session) DRAW “+15min” BAL Record actual time of blood draw: _____
12:15 pm RA	PACKET#2: YCS, AES Drink #2, Juice (of their choice) and vodka (0.03 mg %) Instruct participant that s/he has 15 minutes to drink it (start timer)
12:30 pm NURSE	BP: _____ Pulse: _____ DRAW “+30min” BAL Record actual time of blood draw: _____
12:30 pm RA	PACKET #3: YCS, AES Drink #3, Juice (of their choice) and vodka (0.03 mg %) Instruct participant that s/he has 15 minutes to drink it (start timer)
12:45 pm NURSE	BP: _____ Pulse: _____ DRAW “+45min” BAL Record actual time of blood draw: _____
12:45 pm RA	PACKET #4: YCS, AES, BAES Drink #4, Juice (of their choice) and vodka (0.03 mg %) Instruct participant that s/he has 15 minutes to drink it (start timer)
1:00 pm NURSE	BP: _____ Pulse: _____ DRAW “+60min” BAL Record actual time of blood draw: _____
1:00 pm RA	PACKET #5: YCS, AES Drink #5, Juice (of their choice) and vodka (0.03 mg %) Instruct participant that s/he has 15 minutes to drink it (start timer)
1:15 pm NURSE	BP: _____ Pulse: _____ DRAW “+75min” BAL Record actual time of blood draw: _____
1:15pm RA	PACKET #6: YCS, AES Drink #6, Juice (of their choice) and vodka (0.03 mg %)

	Instruct participant that s/he has 15 minutes to drink it (start timer)
1:30 pm NURSE	Have subject rinse mouth out with water Breath Alcohol Level: _____ If above 0.02, repeat at 2pm DRAW “+90min” BAL Record actual time of blood draw: _____
1:30 pm RA	PACKET #7: YCS, AES, BAES Post Assessments ____ Body Sway Task (confirm data is recording and showing weight, if not restart task) ____ CPT ____ SRT ____ CRT ____ Give participant snacks for after lunch
2:00 pm NURSE	Please wait until participant has finished current task before entering room BP: _____ Pulse: _____ DRAW “+120min” BAL Record actual time of blood draw: _____ PACKET #8: YCS, AES Breath Alcohol Level: _____ Serve participant Lunch
2:30 pm NURSE	Breath Alcohol Level: _____ If above 0.02, repeat at 3:00pm PACKET #9: YCS, AES
3:00 pm NURSE	BP: _____ Pulse: _____ DRAW “+180min” BAL Record actual time of blood draw: _____ PACKET #10: YCS, AES Breath Alcohol Level: _____ If above 0.02, repeat at 3:30
3:30 pm NURSE	Breath Alcohol Level: _____ If above 0.02, repeat at 4:00pm
4:00 pm NURSE	BP: _____ Pulse: _____ DRAW “+240min” BAL Record actual time of blood draw: _____ Breath Alcohol Level: _____ If above 0.02, repeat at 4:30pm
4:30 pm	BP: _____ Pulse: _____

NURSE	Breath Alcohol Level: _____ If above 0.02, repeat at 5:00pm
5:00 pm NURSE	BP: _____ Pulse: _____ DRAW "+300min" BAL Record actual time of blood draw: _____ Remove IV catheter Breath Alcohol Level: _____ If above 0.02, repeat at 5:30pm If below .02 please contact RA to arrange participant transportation home.
5:30 pm NURSE	BP: _____ Pulse: _____ Breath Alcohol Level: _____ If above 0.02, repeat at 6:00pm If below .02 please contact RA to arrange participant transportation home.
6:00 pm NURSE	BP: _____ Pulse: _____ Breath Alcohol Level: _____ Please contact RA to arrange participant transportation home.
6:00 pm RA	Confirm Quest picked up samples from Quest box on 4th floor outside of room 401. Check on all supplies (drugs tests, pregnancy tests, breathylzer tubes, CO tubes, etc). If any thing is low resupply.

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