1. Principal Investigator: Albert Arias, MD

2. Title of the project:

Rapid Determination of The Clinical Utility Of Perampanel For The Treatment Of Alcohol Dependence

3. Purpose, hypothesis and key questions

3.A. PURPOSE: There is a great need to develop more effective medications to treat alcohol dependence. Pre-clinical studies show that activation of glutamatergic AMPA receptors (AMPA-Rs) promotes the return to drug and alcohol seeking behavior in mammals. AMPA receptor (AMPA-R) antagonist (i.e., blocking) medications such as perampanel, a recently FDA approved anticonvulsant, may be useful in treating alcohol dependence. A good way to test the potential usefulness of a medication in the treatment of alcohol dependence (in humans) is to examine its effects on the response to alcohol in the laboratory setting. The main goal of the proposed study is to determine whether the AMPA-R antagonist *perampanel* alters the response to ethanol (i.e., the rewarding and reinforcing effects) using a validated laboratory paradigm of intravenous (IV) ethanol infusion. Fifty non-treatment seeking heavy drinkers (NTSHDs, N=50), and twenty-five social drinkers (N=25) will undergo three test days each: once after receiving a placebo medication, once after receiving moderate dose perampanel, and once after receiving a higher dose of perampanel. ***This experiment is the first step in a series of expedient studies that will rapidly determine perampanel's potential as a treatment for alcohol dependence.*** If findings show perampanel reduces the rewarding and reinforcing properties of alcohol in the laboratory setting (in humans), it would provide a strong rationale for clinical treatment trials with this medication. This approach is innovative because it tests a highly novel AMPA-R antagonist for the treatment of alcoholism, and uses a state-of-the-art computer assisted IV alcohol pump infusion system (called CAIS) to reduce variability in blood alcohol concentrations, thus improving the data quality.

3.B. SPECIFIC AIMS/DESIGN/HYPOTHESES*:* This is a within subject, randomized, double-blind, counterbalanced, crossover study, in which subjects receive perampanel (or a placebo) titrated over 1 week, and then participate in a three-stage, clamped, IV alcohol administration procedure. Each subject will have three IV alcohol administration sessions; two preceded by perampanel (moderate and higher dose), the other preceded by pretreatment with placebo, in double-blind fashion, separated by a 21 day "wash-out" period.

3.B.1. Primary Aim/Hypothesis: To evaluate perampanel's effects on the subjective response to (i.e., the perceived positive and negative reinforcing, as well as aversive effects of) IV alcohol administration such as stimulation, sedation, and euphoria (or "high"), using the **Biphasic Alcohol Effects Scale (BAES) and the Drug Effects Questionnaire (DEQ) for the co-primary outcome measures** (perampanel will be given orally, alcohol will be given IV), in **N=50** NTSHDs and N=25 Social Drinkers. *We hypothesize that NTSHDs will have less self-reported stimulation, increased sedating/unpleasant effects, and attenuated euphoric effects during an IV alcohol administration session after pretreatment with perampanel, dose-dependently, compared to placebo.*

3.B.2. Secondary Aim/Hypothesis: To examine the effects of perampanel on ratings of craving for alcohol, alcohol-induced changes in mood, anxiety, and impulsivity (inhibition) in NTSHDs during IV administration of alcohol. *We hypothesize that subjects will endorse a*

significant attenuation of cravings and mood changes during an IV alcohol administration after pretreatment with perampanel as compared with pretreatment with placebo. Further we hypothesize that alcohol-induced impulsivity will be attenuated by perampanel. Secondary aims will be measured using the Subjective Effects of Alcohol Scale (SEAS) the Alcohol Urge Questionnaire (AUQ), the Go-No-Go task, the balloon-analogue risk task (BART), and the Profile of Mood States (POMS, short version).

3.B.3. Exploratory Aims/Hypothesis: We will also obtain DNA for genotyping. The subjects' family history of alcoholism (FHA) will also be explored as a moderating factor in the response to alcohol and the investigational medication. *We hypothesize that subjects on perampanel, compared to placebo, will experience less change in mood, and greater reduction in anxiety levels,. We hypothesize that perampanel effects on alcohol response are moderated by variation in genes related to glutamatergic neurotransmission, and that the effect of genotype is greater than that of FHA status.*

4. BACKGROUND:

4.A. Glutamate and Addiction: Glutamate, the major excitatory neurotransmitter in the brain, participates in neuroprolific, neurotoxic, and neuromodulatory processes (1). Altered glutamatergic neurotransmission plays a significant role in the pathophysiology of alcoholism (2, 3). Glutamatergic neurotransmission within and on dopaminergic pathways is thought to be a key and likely necessary component for the development and maintenance of addiction (4). Glutamatergic efferents from the prefrontal cortex (PFC), amygdala, and hippocampus, innervate the cell bodies of neurons in the ventral tegmental area (VTA) and the nucleus accumbens shell (NAS), facilitating dopaminergic transmission in these key areas of the "reward pathway" (4).

4.B. AMPA Receptors and Alcoholism Pathophysiology: Glutamate acts on N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxyl-5-methyl-isoxazole-4-proprionic acid (AMPA), and kainite receptors. AMPA receptors may have a more significant role than other glutamatergic receptors in glutamate-facilitated dopamine release in the NAS and subsequent reward. AMPA receptors play a significant role in addiction related neuroplasticity and learned behaviors. Glutamatergic activation of VTA dopaminergic neurons and subsequent dopamine release in the (NAS) is important in addiction, but activation of AMPA receptors pre-synaptically in the NAS, and also activation of AMPA receptors in the PFC further potentiates dopaminergic neurotransmission (and thus reward and reinforcement) in the NAS. Infusion of an NMDA antagonist into the NAS of rats does not block cocaine-induced relapse to cocaine self-administration, but infusion into the NAS of an AMPA antagonist does (4, 5). This may be related to the physiology of medium spiny neurons of the NAS in which AMPA but not NMDA receptors are active due to the relative state of hyperpolarization. AMPA-R antagonists may reduce the reward and reinforcement of alcohol and other drugs and may reduce craving and relapse. More recent animal studies have confirmed these previous findings and suggest that AMPA-Rs are involved in the return to drug seeking behaviors (6-11).

AMPA-R antagonists injected into the Nucleus Accumbens Core (NAC) attenuate cue-induced relapse to cocaine (12). Sanchis-Segura et al., (13) showed the AMPA antagonist GYKI 52466 reduced cue-elicited reinstatement of alcohol seeking behavior and the alcohol deprivation effect in two animal models. An AMPAR antagonist injected into the NA reduced conditioned place aversion from naloxone in rats (14). A very recent study in rats confirmed the theory that enhanced AMPA-R mediated glutamatergic transmission due to neuroadaptation from chronic alcohol exposure is a main component of the drive to drink excessively and to crave alcohol after being exposed to cues (15). In that study, an AMPA-R **agonist** increased ethanol

consumption and cue-elicited relapse in alcohol preferring rats; an effect that was blocked by an AMPA-R **antagonist** (like perampanel). These studies strongly support perampanel as a good candidate for alcoholism treatment.

Additional support for the critical role of the AMPA receptor in AUD pathophysiology comes from genetic studies of AUD, which emphasize the network of genes related to trafficking of the AMPA-R as a component of addiction-related neuroplasticity. Karpyak et al., (29) examined variants in the genes encoding proteins in this so-called "NMDA dependent AMPA receptor trafficking cascade" in association to alcoholism in humans. They studied a set of ~1000 single nucleotide polymorphisms (SNPs) in 13 genes related to the pathway, finding via gene set analysis that the set was significantly associated with AUD. Further, some of the most significantly associated SNPs were located in genes responsible for encoding subunits of AMPA receptors, specifically *GRIA2A*, *GRIA3*, and *GRIA4*. Meyers et al., (30) studied genetic variants in the mGluR–eEF2–AMPAR pathway in association to alcohol drinking behaviors in humans. They found that 206 genetic variants across the same pathway (including ones in the *GRIA1* and *GRIA4* genes) were found to predict number of drinking days per month (corrected *P*-value <0.01) when considered as a set. They were able to replicate the finding to some degree in another sample, where variants in two of the genes seemed to be predictive of amount of alcohol consumed. This genetic work strengthens the evidence base linking AMPA-R related glutamatergic neurotransmission to AUD pathophysiology, and also gives us good genetic targets to examine when devising a pharmacogenetically-guided intervention.

The next step in translating this research would be to use a three-stage, fixed-dose alcohol administration paradigm (such as the one described in this application) to study perampanel's effects on the reinforcing and rewarding properties of alcohol in humans. Fixed-dose alcohol administration paradigms' have been used successfully in the development of other medications for alcohol use disorders such as naltrexone and topiramate, as both have been shown to reduce the positively reinforcing effects of alcohol (16, 17). *Use of the IV paradigm is innovative, delivers alcohol without the variability of oral alcohol administration, and is the most efficient and accurate way to test new medications for their clinical utility ahead of clinical treatment trials*. Alternative approaches include a cue-elicited craving paradigm or self-administration paradigm. Craving is a complicated concept and not reliable for medication development. For example topiramate which is clearly efficacious for alcoholism*, does not consistently reduce cue-elicited craving* in the laboratory (16). Further, some medications such as memantine decrease craving but do not reduce drinking (18-20). Floor effects limit self-administration paradigms because the artificial setting of a laboratory can deter subjects from drinking.

4.C. Perampanel: Perampanel is a noncompetitive (allosteric) antagonist of the AMPA-R that is well-absorbed (100% bioavailability), has good blood-brain-barrier penetration, and rapidly reaches peak plasma concentrations (1 hour) (21). Perampanel is now FDA approved for the adjunctive treatment of refractory partial-onset seizures. Phase III trials in epilepsy have demonstrated that perampanel is very well tolerated, and safe (22-24). In vitro studies of rat hippocampal slices have demonstrated the selective action of perampanel on the AMPA receptor (25). Perampanel does not appear to block the ion channel, but binds the AMPA-R at an allosteric site referred to as the GYKI receptor (25, 26). In human subjects, perampanel is well tolerated at doses of 8mg or 12mg daily, although some titration is needed to reach those doses for ongoing therapy (23, 24). Medication related adverse events/side effects with chronic dosing in epilepsy trials have included; dizziness, somnolence, irritability, headache, fall, and ataxia (23, 24). For the proposed study, subjects will receive perampanel for a week, followed by a brief taper/washout period. Because of that, we will use a 2mg daily dosing for 1 week, and

then subjects will take a one-time larger dose (moderate 6 mg or high 10mg) the morning of the lab test session. This brief titration with a one-time higher dose for the test session should be safe and well tolerated, and will allow us to estimate the effects of a larger dose of the drug without taking several additional weeks to titrate the drug. Pharmacokinetically, perampanel has an elimination half-life $T_{1/2}$ of over 52 hours (estimated at 70 hours, but with a wide range from 52-129 hours) and reaches peak plasma concentration (T_{max}) approximately 1 hours post-ingestion (21). Perampanel is primarily metabolized by CYP3A4 and exhibits linear pharmacokinetics. **To date, there have been no clinical trials of AMPA-R antagonists (e.g., perampanel) for the treatment of alcoholism.**

5. Significance: This study will gather critical information about perampanel's potential as a treatment for alcohol dependence. It will provide information on perampanel's effects on craving and impulsivity with alcohol, and help describe the mechanism of action of the medication relative to alcohol dependence treatment. New treatments are needed, and perampanel has pharmacodynamic and safety profiles that suggest it could be a beneficial addition to the treatment options for alcohol dependence.

6. RESEARCH PLAN/EXPERIMENTAL METHODS:

6.A. Subjects/Recruitment: Standard NIAAA alcohol administration study recruitment and safety guidelines will be followed to determine patients' eligibility for participation (27). Participants will consist of fifty NTSHD (N=50) and twenty-five (N=25) Social Drinkers,. To meet criteria for NTSHD, subjects will have to drink more than 4 standard drinks (SD) per day on at least one day per week on average for men, and >3 SD/day at least once weekly for women, and must have become intoxicated to the point of being "drunk" on at least one occasion (meaning at least 5 SD) within the last year without untoward effects. Criteria for Social Drinkers is defined as drinking at least twice per month (two occasions), and have tolerated 5 standard drinks (in one drinking occasion) over the past year without untoward effects. The NTSHD population has been used in prior alcohol administration studies (28, 29). Baseline drinking, and drinking in between the lab administration sessions will be evaluated using the Timeline Follow Back Method (TLFB). The study plan will be to enter 75 subjects in the sessions, 50 NTSHD approximately 35 male and 15 female and 25 social drinkers approximately 15 males and 10 females, with the sample inclusive of minorities and representative of the greater Richmond Metro Area. Participants will be recruited through advertisement in the community and we may access our CARI registry (HM20014185) of previously screened participants who have indicated that they may be contacted for future studies. We will recruit and screen up to 150 subjects, with the goal to enter 75 subjects and to complete 50 subjects. Subjects will earn $315 for the first session, $315 for the second, and $315 for the third laboratory session. Subjects can earn up to an additional $90 from the study based on their scoring on one of the tasks in the study, the Balloon Analogue Risk Task. Subjects will also receive $50 for completing the screening process and $15 for the initial outpatient visit and $25 at the outpatient visits prior to Phase II and Phase III (3 separate visits to pick up the take home supply of study medication). If there is a need to repeat a laboratory test to confirm any values obtained at screening, we will offer them an additional $10 . We will ask the first 5-10 participants to return to the clinic for an additional visit between days 7-10 post-lab sessions in order to evaluate a PK level. We may choose to extend this to all participants if it becomes clear that it is necessary for monitoring, and they will receive $20 for this visit. Thus, participants can potentially earn up to $1200 for their participation.

The ***inclusion criteria*** will be: 1) males and females; 2) between the ages of 21 and 70 years (inclusive); 3) NTSHDs as defined above, and must have had at least 5 SD in one day on at

least one occasion in the past and been able to tolerate it without an adverse reaction, or Social Drinkers who drink at least twice per month and on at least one occasion in the past been able to tolerate 5 drinks without an adverse reaction, 4) generally medically and neurologically healthy on the basis of history, physical examination, EKG, screening laboratory results (CBC w/ differential, TSH, Free-T4, AST, ALT, GGT, BUN, creatinine, electrolytes, urinalysis, beta-HCG, infectious hepatitis serology). Individuals with LFTs that are no more than 2-3 times above the normal levels will be included; we will use the AST, ALT, and Total Bilirubin to determine this (AST or ALT must be no more than 2-3 times above normal, with a Child-Pugh score of no greater than 5, and total bilirubin no more than 2 times above normal based on the normal cutoff levels for assays at the laboratory); 5) women of child-bearing potential (i.e. no hysterectomy, bilateral oophorectomy, or tubal ligation or <2 years postmenopausal), must be non-lactating, practicing two reliable methods of birth control and one must be a non-hormonal based method (like condoms or a diaphragm and spermicide), and have a negative serum pregnancy test prior to initiation of treatment 6) negative breath alcohol at screening and on each test day; 7) In past 30 days: are not taking opioids, are not taking any CNS depressants (e.g. benzodiazepines, barbiturates, sedating anthistamines), are not taking any anti-epileptic drugs; and 8) are non-treatment seeking.

Exclusion criteria: 1) Need for detoxification determined by a CIWA (Clinical Institute Withdrawal Assessment for Alcohol Scale) (30) score >8 or history of alcohol detoxification in the past; 2) have been in treatment for an alcohol problem within the last 6 months, or if the severity of their alcohol problem based on the research physician's assessment warrants definitive treatment; 3) may not have a history of bipolar or primary psychotic disorder (e.g., Schizophrenia) (assessed by Structured Clinical Interview for DSM-V Disorders: SCID 5)(31); other psychiatric diagnoses that are not currently active (e.g. major depression) and are under control (e.g. with medication or other treatment), or in remission, are not exclusions; 4) May not have a currently active psychiatric or substance use disorder diagnosis (i.e., one that is not under control or in remission), other than alcohol abuse/dependence, cannabis abuse/dependence, and nicotine dependence; those diagnoses will be allowed; participants can be either smokers up to 1 pack per day or non-smokers, based on history and psychiatric evaluation that includes a structured diagnostic interview 5) unwillingness to remain alcohol-free 12 hours prior to test days; 6) have a significant ongoing serious medical condition such as Diabetes Mellitus, liver disease (see above LFT guideline), renal disease (as evidenced by serum creatinine above our laboratory's reference limit of 1.7 mg/dL, or have a history of adverse reaction to IV placement/blood draw; 7) are currently taking any medication that is a moderate to strong CYP3A4 inhibitor or inducer if participants are required to initiate these medications by an outside provider during the course of this study, they will be tapered off the study regimen and we will have them terminate early).

6.B. Laboratory Session Overview: Participants will complete 3 test days each, at least 21 days apart, in a randomized counter-balanced order, under double-blind conditions, following either pretreatment with daily perampanel 2mg or placebo 7 days prior to each test day, and then observed dosing (of placebo, moderate 6mg dose perampanel, or high dose 10mg) in the lab 1.5 hours before alcohol infusion (a one time dose). Adherence will be assessed by addition of riboflavin 25mg to medication, and detection of riboflavin in urine on test days. Each lab session occurs exactly a week after starting the medication for that phase, which means participants will have taken it for 7 days prior to the lab session, and the lab session will be the eighth day in a row on the study medication. The wash out period between lab test session phases will be 21 days. Subjects will receive 2 days of 2mg perampanel after each lab to taper

down (included in the washout period). Subjects will receive the observed 6mg and 10mg perampanel doses on lab session days only after the week of pretreatment with perampanel 2mg daily. Those sessions will be followed by the tapering dose of actual perampanel. The observed placebo dose on placebo lab session days will occur following a week of placebo pre-treatment, and will be followed by a tapering period using placebo pills.

The next appointment after a lab session will be a brief one at the start of the next phase (see day 1 of the phases in figure 1 below), at which point the next week of low dose perampanel or placebo will be started. We will allow the dose dispensation to occur up to 2 days prior to the first day of dosing. With the washout period (21 days) and the 7 day medication administration of the next phase, the actual lab sessions will occur approximately 28 days apart. All test days will involve administration of alcohol with the same 3 target doses (target BrAc=20mg%, BrAc=60mg%, and BrAc=100mg%) in a step-wise fashion. We will maintain phone contact with subjects during the week that they are on medication and will talk to them once by phone in days 2-4 on the medication, and once between days 5-7, inquiring about side effects, especially neuropsychiatric side effects. If there is a concern we will ask them to come to the research center for evaluation by study staff and/or a study physician as needed. They will be able to contact the Principal Investigator or study staff personnel at any time. After the screening visits, which will take place most likely on 2 separate days (1-2 visits), subjects will begin the medication and laboratory administration phases (see below schematic). We will ask the first 5-10 participants to return to the clinic for an additional visit between days 7-10 post-lab sessions in order to evaluate a PK level. We may choose to extend this to all participants if it becomes clear that it is necessary for monitoring.

FIGURE 1: OVERVIEW SCHEMATIC

Phase I			*Phase II*			*Phase III*		
Day 1 Outpatient Visit: Start PRM 2mg daily or PLC (up to - 2 days prior to starting medication)	*Day 8 Lab Session:* PRM 6mg or 10mg, or PLC	*Washout for* 14 days: Includes 2 days of 2mg PRM or PLC taper	*Day 1 Outpatient Visit:* Start PRM 2mg daily or PLC Repeat labs (up to - 2 days prior to starting medication)	*Day 8 Lab Session:* PRM 6mg or 10mg, or PLC	*Washout for* 14 days: Includes 2 days of 2mg PRM or PLC taper	*Day 1 Outpatient Visit:* Start PRM 2mg daily or PLC Repeat labs (up to - 2 days prior to starting medication)	*Day 8 Lab Session:* PRM 6mg or 10mg, or PLC	*Finish* Includes 2 days of 2mg PRM or PLC taper

PRM= Perampanel, PLC= Placebo

6.C. Screening and Initial Assessments*:* After providing written informed consent, subjects will be interviewed using the SCID. We may opt to use an online version of the SCID for ease and clarity. The timeline follow-back (TLFB) (33) will be used to document heavy drinking status and the degree of daily alcohol consumption prior to entry. The CIWA will be used to assess for current symptoms of alcohol withdrawal. EKG, urine toxicology, and other screening labs (CBC w/ differential, TSH, Free-T4, AST, ALT, GGT, BUN, creatinine, electrolytes, urinalysis, beta-HCG, infectious hepatitis serology) will be collected at this appointment. Subjects will have a psychiatric/medical examination by a study psychiatrist or Nurse Practitioner. Family history of alcohol problems will be evaluated using the family history assessment module (FHAM) (34). Trait impulsivity will be measured with the Barrett Impulsivity Scale (BIS) (35). The screening and initial assessments will likely be completed in 1-2 visits. During the initial lab session bloodwork, a DNA sample will also be collected to be evaluated for potential genetic variants which may contribute to alcoholism.

6.D. Experimental procedure: After initial screening, eligible participants will be randomized to receive double-blind perampanel (moderate and high dose) or placebo in a counterbalanced order (i.e., each subject will receive all three conditions; perampanel moderate dose, high dose, and placebo, but in a random and counterbalanced order). Perampanel and placebo will be packaged in identical looking capsules. The research pharmacist will perform randomization. Study staff will be blinded during the study to medication/order assignment. All subjects will be informed of receiving alcohol and how much (peak BrAC) on both occasions but will be kept blind to the real-time BrAC levels during the lab sessions. Participants will be asked to refrain from using caffeine and alcohol for 12 hours before their scheduled test session (example: refrain from 8:00 PM if test day starts at 0800) and to fast starting at midnight the night before the scheduled test session. Participants will be asked to come to the laboratory at approximately 8:00 A.M on test days. Upon arriving for each test session, subjects will have a urine drug screen, urine pregnancy test (females), and Breathalyzer to measure breath alcohol levels. Symptoms of alcohol withdrawal will be assessed using the CIWA. If the CIWA score is > 8, or if the urine drug screen, pregnancy test, or Breathalyzer is positive, then a decision will be made by study staff and the PI about whether to end the subject's participation or to allow them to reschedule for some point over the next 7 days. The 2mg daily perampanel would be extended for up to 7 days in the case of rescheduling. Otherwise, before eating a standardized breakfast, an IV line will be inserted and we will take a blood sample for a CBC, the DNA sample, and perampanel trough levels. Participants will then take their 6mg,10mg perampanel, or placebo dose in the lab. In order to maximize perampanel absorption breakfast will be given 60 minutes after the medication is taken. One and a half hours (1.5) after ingesting perampanel, the infusion of alcohol will begin.

The infusion will begin with a placebo alcohol infusion (i.e. y-tubing using normal saline at 50mL, infused over 10-15 minutes to gauge participant baseline and placebo effect) prior to the alcohol infusion. Alcohol will be administered by IV for 7 minutes to achieve the first target BrAc level of 20mg%. Once the first BrAc is achieved, it will be maintained using a clamp procedure for 35 minutes for measurements (outcomes) to be obtained. This will be followed by additional administration of alcohol to achieve BrAc level of 60mg% for 14 minutes. This alcohol level will be maintained for 35 minutes. The last phase of the alcohol administration will consist of alcohol infusion to reach BrAc level of 100mg%, over 14 minutes, and this level will be maintained for 35 minutes. The subjects will remain on the Clinical Research Services Unit for several hours until the effects of alcohol have worn off. A healthcare provider will clear subjects at the end of each test day. For safety monitoring, during the initial few (potentially between 3-5) participants' laboratory sessions, we plan to observe them overnight in our hospital-based Clinical Research Services Unit which is where the infusions and labs will occur. If we determine that there is additional benefit that outweighs participant burden, we may adjust to have additional participants stay overnight. Subjects must have a BrAC of ≤ 20mg% before leaving the unit. The 3 step increasing IV ethanol dose paradigm is a reliable and valid method (17, 36, 37). ***See Table 1 below.*** Prior to testing, subjects will be asked to make arrangements for transportation home from the test session, or the study staff will arrange for a car service to drive the subject home, in order to avoid difficulties driving with any residual sedation.

IV Alcohol Solution: The IV alcohol solution is a 6% alcohol solution in 0.9% saline, with approximately 2 oz. of ethanol in each bag. We will use two IV solution bags with a dual pump controlled by a computerized assisted infusion system that adjusts for optimal alcohol administration based on personalized parameters.

6.E. Behavioral Assessments: On experimental session days (after the pretreatment with perampanel or placebo), participants will complete self-report measures of recent substance/alcohol use. Smokers will complete the Fagerstrom Test for Nicotine Dependence [FTND] (38) at baseline, and will complete the Minnesota Nicotine Withdrawal Scale (39) along other measures during lab sessions, in order to measure and control for nicotine withdrawal effects. Subjects will be asked to have their last cigarette prior to starting pre-lab medication administration and activities, at each session.

6.E.a. During the ethanol infusion sessions: measures of subjective responses to alcohol activation, stimulation, and craving ("**the alcohol effects battery**"), will be administered at baseline and at each of the BrAC levels 0.00, 0.02, 0.06, and 0.10 g/dL (see Table 1). Participants will also be assessed by research staff using the H Impairment Index (HII), and the SEAS (Subjective Effects of Alcohol Scale) and direct observations by the PI will be made before proceeding further.

Co-Primary Outcomes:

Biphasic Alcohol Affects Scale (BAES): A 14-item scale with 7 items designed to assess stimulant effects from alcohol intoxication and 7 items developed to measure the sedative effects of alcohol. This scale was selected as a primary outcome measure because it is sensitive to the effect of alcohol (40).

Drug Effects Questionnaire (DEQ) (41): consists of four items that measure current alcohol effects: 'feel alcohol', 'feel high', 'like alcohol', and 'want more alcohol'.

Secondary Outcomes:

Visual Analog Scales of Mood States (VAS): A 5-item scale designed to assess subjective alcohol effects: high, anxious, drowsy, irritable, and nauseous. It has been used in previous studies by our group and has good sensitivity to drug effect.

Alcohol Urge Questionnaire (AUQ): A valid eight-item Likert-type scale designed to assess acute alcohol craving (42).

Subjective Effects of Alcohol Scale (SEAS): a psychometric self-rating scale of 22 variables which measures self-reported alcohol effects immediately after the "final drink" and again at 90 minutes after the "final drink".

Side Effect Questionnaire (SEQ): This consists of a list of side effects associated with perampanel (e.g., fatigue, dizziness), rated from 0="none" to 4="severe".

POMS 2 Short Versions: The POMS 2 short version contains a subset of 35 items from the full-length versions. This subset comprises those five items on full version POMS scale that exhibited good item-total correlations and best predicted their respective scale scores (44, 45).

Stop Signal Test (SST, also know as Go/No-Go): SST is a commonly used test of response inhibition. This test consists of two parts. In the first part, the subject is introduced to the press pad, and told to press the left hand button when they see a left-pointing arrow or press the right hand button when they see a right-pointing arrow. There is one block of 16 trials for the subject to practice this. In the second part, the subject is told to continue pressing the buttons on the

press pad when they see the arrows, as before, but, if they hear an auditory signal (a beep), they should withhold their response and not press the button.

The Balloon Analogue Risk Task (BART): This is a valid and commonly used test of risk-taking, an aspect of impulsivity. This task is computerized, and subjects press a button to analogously pump air into a balloon on the screen. Subjects are told they can earn 1 cent for each pump of the balloon banked to a reward account before they cash out and stop pumping. The balloons break at various random intervals and if the balloon breaks, the subjects lose money out of the reward account. We will use a 10-balloon paradigm, a briefer but valid version of this task. They can earn a maximum of 7.5 dollars per administration, with 4 administrations per lab, for a total of up to $90 additional pay over the course of the study, though actual payouts will likely be substantially less.

Number of Drinks Scale (NDS): used to assess how many drinks the subject feels he/she has consumed at a specific timepoint.

Safety Questionnaires:

H-Impairment Index (HII): A 5-question scale scale which uses a group of common bedside tests to determine the severity of alcohol impairment.

Clinical Institute Withdrawal Assessment Scale (CIWA): A clinician administered assessment used to rate the severity of alcohol withdrawal symptoms. The CIWA will be administered at each appointment.

Columbia-Suicide Severity Rating Scale (C-SSRS) (46): The C-SSRS has both lifetime/recent and since last visit versions. The “Lifetime/Recent” version gathers information on lifetime history of suicidality and recent suicidal ideation/self-injurious behavior. The “Since Last Visit” version of the C-SSRS asks about any suicidal thoughts or behaviors the subject has exhibited since the last time administered the C-SSRS.

SAFTEE: (47) A technique that is used for the systematic assessment of side effects in clinical trials. The SAFTEE will be reviewed by the study nurse and specific symptoms, as well as severity, will be recorded. The SAFTEE will be administered during each outpatient visit and test session.

Table 1. Experimental Session Day

Time (minutes)	Assessments
T-100	Urine drug screen, urine pregnancy test (females), breathalyzer, CIWA, TLFB, SAFTEE, Vital Signs, IV line inserted, perampanel blood level drawn, blood sample for CBC collected, DNA
T-90	Take oral study medication (either perampanel or placebo), Vital Signs,
T-45	Alcohol-effects assessment battery (NDS, BAES, DEQ, VAS, AUQ, MNWS, SEQ , POMS, SST, BART, HII, SEAS)
T-30	Standardized breakfast
0	Infusion begins, Vital Signs During PLC infusion: Alcohol-effects battery (NDS, BAES, DEQ, VAS, AUQ, MNWS, SEQ, POMS, SST, HII, SEAS) and BrAC 0.00 g/dL
T+07	Infusion clamped (approximately 35min) alcohol BrAC 0.02 g/dL, Vital Signs
T+12	Alcohol-effects assessment battery (NDS, BAES, DEQ, VAS, AUQ, MNWS, SEQ , POMS, SST, BART, HII, SEAS)
T+42	Infusion increased to target next alcohol level, Vital Signs

T+56	Infusion clamped (approximately 35 min) alcohol BrAC 0.06 g/dL, Vital Signs
T+61	Alcohol-effects assessment battery (NDS, BAES, DEQ, VAS, AUQ, MNWS, SEQ, POMS, SST, BART, HII, SEAS)
T+91	Infusion increased to target next alcohol level, Vital Signs
T+105	Infusion clamped (approximately 35 min) alcohol BrAC 0.10 g/dL, Vital Signs
T+110	Alcohol-effects assessment battery (NDS, BAES, DEQ, VAS, AUQ, MNWS, SEQ, POMS, SST, BART, HII, SEAS),
T+140	Infusion ends
T+ 170	Lunch
T+ 200	Alcohol-effects assessment battery (NDS, BAES, DEQ, VAS, AUQ, MNWS, SEQ, POMS, SST, HII, SEAS), Vital Signs
T+260	Test day debriefing, C-SSRS, Vital Signs, and discharge when BrAC ≤ 0.02 g/dL

6.F. Data Analysis: We have well developed statistical methods to analyze alcohol challenge studies. All statistical testing will be at a two-tailed alpha level of 0.05 and will be performed in SAS. For the primary, and secondary hypotheses we will use mixed-effects models to assess change in stimulation, sedation, and craving for alcohol during intravenous infusion of alcohol. Pretreatment medication (perampanel moderate versus high dose versus placebo) and gender will be used as between-subject factors, and alcohol concentration doses (target BrACs of 0.00, 0.02, 0.06, and 0.10 g/dL) as a four-level within-subject factor. The primary goal of these analyses will be to test for differences in measures of stimulation, enjoyment, craving, and sensitivity to alcohol as a function of perampanel pretreatment. The primary outcome dependent variable will be stimulation as measured by BAES. We will explore the measure of trait impulsivity (BIS) as a covariate, but will also explore the effect of genotype in a mixed model analysis as in independent variable in a pharmacogenetic model. We will explore the effects of perampanel, alcohol, and genotype on measures of state impulsivity and risk taking.

Power Analysis: No human studies have examined perampanel in psychiatric/substance-using populations. We calculated an effect size for naltrexone based on Ray et al. (17), for the effect of naltrexone on stimulation (BAES) and will extrapolate this effect to perampanel. Based on this calculated effect size (d) of 0.45 (e.g. a moderate effect size), we should be able to show a significant difference between perampanel and placebo groups using a two-sided, paired sample t-test, with alpha = 0.05 and power (1-Beta) of at least 0.80 with n = 25 subjects in each experimental group (total **N = 50**). We will recruit and enter N = 150 subjects, in order to complete at least 50.

7. Limitations and/or potential pitfalls: Perampanel is a new medication, and we may need to adjust the dosing slightly in the beginning of the study, but this should not be a major pitfall. We will assess the tolerability and safety during of the proposed dosing regimen in the first 3-5 subjects and make a determination of whether or not changes need to be made. We would only decrease the dosing, not increase it in response to the experience and review of data from the first few subjects. Essentially, if there are too great a degree of adverse effects from the 6mg and 10mg dosages, we will decrease the dosages to ensure safety and adequate tolerability.

8. HUMAN SUBJECTS PROTECTION:

8.A. Data and Safety Monitoring Plan (DSMP): Albert Arias, M.D., a board certified psychiatrist and the principal investigator of the study, will be charged with the duty of determining the

severity rating of adverse events. The study staff (P.I., co-investigators, clinical research coordinator) is responsible for collecting and recording all clinical data. As these results are collected, all toxicities and adverse events will be identified, graded for severity and assigned causality, reported to the required entities, and compiled for periodic review. After assigning causality, the P.I. will decide the course of action for the study participant. The P.I. will evaluate every adverse event and determine whether it affects the risk/benefit ratio of the study and whether modifications to the protocol or informed consent form are required. Serious adverse events will be reported to the VCU IRB, as well as the NIAAA, within 48 hours. An annual report summarizing all adverse events will be prepared and reported to both IRB and the NIAAA. In addition, other co-investigators will be notified. Reports of adverse events, protocol deviations, and any other relevant safety information (drop outs, etc.) will be reviewed by the research team on an ongoing weekly basis at regular meetings, and the research team will discuss whether the study should continue as planned, or if changes are needed, or if the study should be stopped.

As noted above, precautions for pregnant or reproductive age women are in accordance with NIAAA requirements and this will be monitored on an ongoing basis by the PI and co-investigators. All adverse events in the taper/follow-up time-period will be reported to the VCU IRB, as well as the NIAAA, with serious adverse events being reported within 48 hours.

In addition to monitoring by Dr. Arias, this protocol will be reviewed weekly in study meetings. We will use a Data and Safety Monitoring Plan (DSMP) which will be referred to in order to determine safety and feasibility of continuing the study.

All data will be stored without direct identifiable information, but will be identifiable via a linking code. Any hard copy records associated with the study will be kept in locked offices in our research facility. The secured research records are labeled with code numbers only (names and other identifying information are kept separate from research records). Access to hard copy data is only given to staff members working on the study. Only staff members designated to handle or analyze study samples will have access to the samples and their storage. We may use REDCap for data tracking and storage. As per routine in the IDAS, all electronic files (e.g., database, spreadsheet) will be password protected. Any computer hosting such files will have a password-protected drive to prevent access by un-authorized users.

Data used for safety monitoring will include serious adverse events, dropout rates and reasons for dropout, enrollment numbers, subject interviews, medication compliance, review of symptoms or performance status, review of clinical/diagnostic test results, review of physical examination, review of vital signs, review of evaluation performed, protocol deviations, and blinded data. If it has been determined, for any reason, that there will be a suspension of this study, the PI will suspend enrollment of new subjects but continue intervention/monitoring of previously enrolled subjects if it is in the best interest of those subjects. We have determined that this study involves only a greater than minimal risk to subjects, and that potential benefits outweigh potential risks of participation.

The administration of alcohol to human subjects proposed in this study is in compliance with NIAAA guidelines for alcohol administration. (27)

8.B. RISK/BENEFIT RATIO. Risk/Benefit Ratio. The risk associated with ethanol is minimal. Although the pharmacological intervention carries some risks, perampanel is generally well tolerated. The potential risks of these agents are minor, and research has shown that non-treatment seeking subjects who participate in self-administration studies significantly reduced their drinking after participation (48). Thus, the risk/benefit ratio appears most favorable toward the proposed treatments. Subjects will receive the benefit of free medical, laboratory, and

psychiatric examinations. The benefit to society that would result from improved effectiveness in treating alcoholism is also significant, given the high societal cost of alcoholism.
This study is expected to contribute to knowledge regarding whether perampanel influences the response to alcohol and how that may affect treatment response for alcoholism. Subjects participating in the alcohol challenge sessions will receive a free medical evaluation, including physical examination and laboratory testing and will be paid $50 for the screening appointment. If there is a need to repeat a laboratory test to confirm any values obtained at screening, we will offer them an additional $10, They will also be compensated $15 for the initial outpatient visit they attend and $25 for the outpatient visits prior to Phase II and Phase III (3 visits for a maximum amount of $65). Subjects will be paid $315 for each lab session (3 sessions total so they can earn a maximum of $945 for lab sessions). Subjects can also earn additional money in each lab session with the Balloon Analogue Risk Task (BART). They can earn a maximum of $7.50 dollars per administration of the BART, with 4 administrations per lab ($30 maximum each lab session), subjects can earn a total of up to $90 additional pay over the course of the study, though actual payouts will likely be substantially less from this task (likely under $50 per subject). We will ask the first 5-10 participants to return to the clinic for an additional visit between days 7-10 post-lab sessions in order to evaluate a PK level. We may choose to extend this to all participants if it becomes clear that it is necessary for monitoring. Altogether, subjects will be able to earn up to $1200 for their participation in the study.

Subjects will also receive feedback and education about their “risky” drinking, and the option of referral for treatment if they so decide. There is no other direct benefit for subjects. The benefit to society concerns the effects of perampanel on behavioral effects of alcohol, which may be important to understanding the neuropsychopharmacologic basis of alcohol’s effects and the etiology of alcohol dependence and for the improvement upon existing treatments, as well as development of novel pharmacological treatments for alcoholism. Although the risk is greater than minimal risk, we believe that risk-benefit ratio for this study is favorable. Furthermore:

- The administration of ethanol to human subjects described in this protocol is in compliance with NIAAA guidelines for ethanol administration.
- We will carefully screen NTSHD subjects to **exclude alcohol naïve subjects. (please see below for special consideration for heavy drinkers).** All subjects must meet the minimum recent drinking requirements; *To meet criteria, subjects will have to drink more than 4 standard drinks (SD) per day on at least one day per week on average for men, and >3 SD/day at least once weekly for women, and must have become intoxicated to the point of being “drunk” on at least one occasion (meaning at least 5 SD) within the last year without untoward effects.*
- Subjects with a history of alcohol use disorder that are abstinent currently will be excluded. They will be informed exactly what level of BrAC they will reach in the study, and the approximate drink equivalent.
- The investigators in this protocol have extensive experience with the administration of ethanol to healthy individuals and to alcohol abusing or dependent individuals using a number of different laboratory paradigms.
    - a) Since 1992, we have administered ethanol at doses comparable to those described in this protocol to well over 300 subjects, both healthy subjects and heavy drinkers. Of these subjects over 150 have participated in an IV ethanol “clamp” procedure and over 150 have participated in an alcohol drinking paradigm.
    - b) We have had no reportable medical adverse events associated with the IV clamp procedure.
- The clamping procedure has several safety measures in place:
    - a) The concentration of ethanol in the infusate is 6% by volume.

  - b) The limit on the amount of ethanol that can be infused is determined by hanging two one liter bag of the infusate (6% by vol ethanol ~ 2 oz ethanol at most) at a time.
  - c) Frequent BrAC measurements, using a rotation of 5 instruments, assure that the BrAC will not exceed 105 mg%
  - d) The research nurse will be monitoring breath alcohol levels at proscribed times (never less frequent than every 10 minutes) with a breathalyzer.
- Experienced medical personnel will be present during the entire laboratory session. In case of a significant adverse event, a physician will be called immediately. Subjects will not be released from the Laboratory until the BrAC is less than or equal to 20mg% (20mg% = 0.02%), confirmed with at least two tests, which is below the threshold of BrAC associated with any impairment in motor coordination or judgment in humans.
- If the subject reports disturbing experiences, these will be reviewed in detail and support will be offered. *If adverse experiences occurred, a decision will be made at that time whether to discontinue further testing.* If the subject reported significant distress or if clinicians observed significant distress associated with testing, but no residual effects are reported at the end of the test day, the PI will still review the incident and the potential advisability of overnight hospitalization for observation.
- The PI will be available on-call while subjects are on the Clinical Research Services Unit, and subjects can contact research staff and physicians after hours with any problems they might have.

8.C. Special Considerations for Individuals who are Heavy Drinkers: Ethanol is a drug of abuse. The entire protocol is in accordance with the NIAAA Guidelines on Ethyl Alcohol Administration. These guidelines have stated that heavy drinkers need not be excluded from this type of research, but should receive special consideration in assessing risk/benefit ratio. In this study, we have instituted several safeguards to ensure the safety of participants. Subjects are warned about the potential abuse liability of ethanol, and treatment-seeking subjects will be excluded. Further, we will carefully screen subjects to ensure that they are not physiologically dependent on alcohol and will standardize the approach by excluding individuals with a CIWA rating >8. Finally, we will conduct a brief safety and wellbeing check in follow-up contact with research subjects and propose to contact each research subject by telephone 1 week following their last test day to monitor the impact of participating in this research study.

All subjects will be advised of their “risky” drinking status and will be informed if they meet criteria for alcohol abuse or dependence. They will also be advised about health risks of their continued heavy drinking and will be offered referral to treatment. Subjects choosing treatment will be assisted by study staff and physicians in obtaining treatment, and we will help them investigate treatment options, including setting appointments for subjects, not just giving them a list of options. They may also qualify for a clinical treatment trial. At the end of the third laboratory session, participants will be presented with normative drinking information, as well as guidelines for non-hazardous alcohol consumption, and they will also receive a brief motivational interviewing session about their drinking along with the offer for a referral for further treatment. Subjects may decline the brief intervention at the end of the study if they continue to have no interest in any level of treatment engagement. The motivational brief session will be tailored to each individual’s level of drinking and related consequences and other assessments.

8.D. MEDICATION RISKS AND SIDE EFFECTS:
(PERAMPANEL): The most common side effects seen with perampanel have been, dizziness, somnolence, irritability, headache, fall, and ataxia(23, 24, 44). Dizziness and

somnolence were common in epilepsy trials (>10% of subjects). Side effects occurring in 1-10% of subjects in epilepsy clinical trials were; appetite changes, aggression, anger, anxiety, confusion, irritability, difficulty with coordination, double vision, blurred vision, nausea, back pain, room-spinning dizziness, difficulty walking and falls. Subjects will be monitored closely for rare potential neuropsychiatric side effects such as violent or homicidal ideation, as these symptoms have been reported in epilepsy trials with the medication. All subjects will be monitored regularly for suicidal ideation as this can be a risk with all anticonvulsants. Because perampanel is newly FDA approved, all the side effects may not yet be known. However, we will work to anticipate possibilities for additional side effects known to occur with anticonvulsants, such as agranulocytosis. The US Drug Enforcement Agency (DEA) has determined that there is some potential for people to abuse perampanel. Because some anticonvulsants can be harmful to a fetus, women will be screened for pregnancy before and during participation in the study. Pregnant and breastfeeding women will be excluded. Perampanel is a category C medication. Women will be required to be using two forms of birth control for the study duration, and one must be non-hormonal based. Perampanel may lower the effectiveness of oral contraception containing levonorgestrel. The doses of perampanel used in this study were NOT found (in epilepsy trials) to decrease blood levels of oral contraceptive hormones, but a 12mg daily dose was. We choose to err on the side of caution with regard to birth control in this study. We will obtain a CBC at each lab session to monitor for blood dyscrasia, a side effect of many anticonvulsants. We will maintain frequent phone contact with subjects while taking medication, and will also contact them the day after lab sessions by phone to assess any changes in mood or neuropsychiatric side effects.

The black box warning states that serious or life threatening psychiatric and behavioral adverse reactions, including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking perampanel. Monitor patients for these reactions as well as for changes in mood, behavior, or personality that are not typical for the patient, particularly during the titration period and at higher doses. Perampanel should be reduced if these symptoms occur and should be discontinued immediately if symptoms are severe or are worsening

Alcohol Effects: Possible effects of consuming alcohol are blurred vision, nausea, vomiting, flushing, headache, and lightheadedness. These effects should reach their peak during the infusion and decline thereafter. There is a potential for people to abuse alcohol. It is unclear whether exposure to alcohol in the laboratory can result in problems with alcohol abuse or alcoholism.. It should be noted drinking more than 2 drinks per day in healthy men and 1 drink per day in healthy women can be hazardous to a person's health. Also, if at any point after completing this study a subject becomes concerned about abusing alcohol, they are encouraged to contact us. We will refer subjects to the VCUHS Motivate clinic or an appropriate treatment facility if necessary. To minimize possible injury as a result of alcohol consumption, participants will be kept on the Clinical Research Services Unit until their blood alcohol level is at a very low level (Breathalyzer ≤ 0.02). If a participant does not feel comfortable and does not want to continue or the research staff feels that they are at risk, the test day will be discontinued.

Risks of combining alcohol and perampanel:
This was studied a little bit by the drug company marketing the drug, and they found that combining the two can impair psychomotor activity greater than with just alcohol alone, and impaired complex psychomotor tasks such as driving a car (tested in a simulator). If new risks

become known we will notify the IRB and subjects. Subjects will be advised to notify us of any side effects during pre-treatment in a timely manner. We will advise them that there is the possibility that alcohol and perampanel, when combined, could make them oversedated, or have difficulty with their balance or coordination, including with driving a car. We will advise them to avoid driving if drinking alcohol while on the perampanel. Additionally, we will advise them to see how they react to the initial perampanel 2mg dose on day 1 before driving or operating heavy machinery.

Additional safety measures:
Subjects will be asked to arrange for a ride home after each laboratory session. Transportation will be arranged for those who cannot arrange it on their own. We will provide a taxi (20mile radius). Subjects will be asked to follow general seizure precautions for 48 hours after each lab session such as showering instead of taking baths, no swimming, and no driving. Given the long half-life of the medication and two-day 2mg taper dose after each lab session, “rebound” or withdrawal seizures are unlikely after the lab sessions but we will err on the side of caution.

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