Brown University
Application for Full Board / Expedited IRB Review

Protocol Title: **Probenecid as a pharmacotherapy for alcohol use disorder**

Principal Investigator: **Carolina Haass-Koffler**

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Is this a graduate student project?* ☐ **Yes** ☒ **No**

If student PI, please provide the following:

Advisor: **Phone number:**

Department: **Email address:**

Is this an undergraduate student project?* ☐ **Yes** ☒ **No**

If yes, name of undergraduate student:

Human Subjects CITI training is complete (PI, advisor (if student PI)): ☒ **Yes** ☐ **No** G1 CITI OK

Good Clinical Practice (GCP) training is complete (clinical trials only): ☒ **Yes** ☐ **No** ☐ **N/A** GCP CITI OK

HIPAA training is complete (if using PHI): ☐ **Yes** ☐ **No** ☒ **N/A** \

Are there multiple sites involved with this study? ☐ **Yes** ☒ **No**

- If "yes," review the Application for IRB Authorization Agreement

Funding Source(s):

- If externally funded, provide the following:

  Project title: **Probenecid as pharmacotherapy for alcohol use disorder**

  Grant/Contract #: **NIH R21 AA027614 – This protocol is in response to requested JIT**
- If there is no external funding for the project, write "University;" if funded by a specific internal funding mechanism (e.g., Mellon Mays Fellowship, Royce Fellowship, UTRA, OVPR Seed funds, etc.) please specify**:**

PART I. HUMAN SUBJECTS RESEARCH SCREENING

Full Board/Expedited studies must meet the federal definition of "Human Subjects Research." Answer the following questions to determine if your proposed study meets the federal definitions of both "Research" and "Human subjects."	
☒ Yes ☐ No	Is this study a systematic investigation?
☒ Yes ☐ No	Is the *primary design intent* of this study to contribute to generalizable knowledge?
☒ Yes ☐ No	Is the information being obtained *about* living individuals?
☒ Yes ☐ No	Will you collect information through some type of intervention or interaction? **OR** Will you have access to individually identifiable information? **OR** Will you have access to private information?
STOP	If you answered "no" to any of the above questions, your study does not meet the definition of "Human Subjects Research." You are not required to submit an Application for IRB review to the Brown HRPP.
Before proceeding, be sure to review the revised Common Rule categories for Exemption to determine if your study meets criteria for Exempt review and the Application for Exemption.	

PART II. RISK ASSESSMENT & EXPEDITED ELIGIBILITY SCREENER

1. Minimal Risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests.

Using this definition, do you believe this research presents:

☐ No greater than minimal risk (**Expedited**)	Briefly justify this selection (and proceed to Question 2):
☒ Greater than minimal risk (**Full Board**)	Briefly justify this selection (and proceed to Part III): Potential risks of the study include discomfort from answering questionnaire items, breach of confidentiality, issues associated with coercion, discomfort from alcohol craving, side effects or drug interactions with probenecid.

2. Below are Research Categories *eligible* for Expedited Review. Select one or more of the categories that are applicable to your proposed research, if any.	
☐ Category 1	Clinical studies of drugs and medical devices only when condition (a) or (b) is met (please select one): ☐ (a) research on drugs for which an IND application is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review); OR ☐ (b) research on medical devices for which (i) an IDE exemption application is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
☐ Category 2	Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

	☐ (a) from healthy, non-pregnant adults who weigh at least 110 pounds. For these participants, the amounts drawn must not exceed 550 ml in an 8-week period and collection may not occur more frequently than 2 times per week; OR ☐ (b) from other adults and children, considering the age, weight, and health of the participants, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these participants, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period and collection may not occur more frequently than 2 times per week.
☐ Category 3	Prospective collection of biological specimens for research purposes by noninvasive means. Examples may include: (a) hair and nail clippings in a non-disfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicated a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue; (f) placenta removal at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routing prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.
☐ Category 4	Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples may include: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.
☐ Category 5	Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). NOTE: Some research in this category may be Exempt. Review the categories for Exemption before selecting this option.
☐ Category 6	Collection of data from voice, video, digital, or image recordings made for research purposes.
☐ Category 7	Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. NOTE: Some research in this category may be Exempt. Review the categories for Exemption before selecting this option.

PART III. RESEARCH DESIGN & METHODS

1. Introduction and Background.

The proposed clinical trial advances a novel hypothesis of the potential relationship between pannexin 1 channels and alcohol-related effects with the goal of elucidating novel pathophysiological mechanisms that could pave the way for new therapeutic targets for the treatment of alcohol use disorder (AUD). The premise prompting this investigation on testing probenecid as a novel medication for treating AUD is based on the direct evidence from our preliminary work with probenecid in a preclinical model of AUD. This work demonstrated that probenecid is able to reduce alcohol consumption in alcohol-dependent rats. The scientific rational for testing probenecid in AUD was derived by the well-known mechanism of action of probenecid as a pannexin 1 channel inhibitor, its role in alcohol-induced extracellular adenosine release, and that this process is promoted by a history of exposure to excessive alcohol. This application holds the potential to evaluate the role of pannexin 1 channels and provide the possibility to discover new AUD therapeutic opportunities, and will be the first to assess the efficacy of probenecid for AUD in an integrated behavioral and clinical setting. The data obtained from this exploratory, proof-of-concept clinical trial will demonstrate the safety and tolerability of probenecid while consuming alcohol and can pave the way for further testing probenecid in an appropriately-powered larger R01 application.

2. Specific Aims and Study Objectives.

This proposed clinical trial is a proof-of-concept, within-subject, crossover, double-blind, placebo-controlled human alcohol laboratory study in non-treatment-seeking individuals with AUD (***N* = 34**) randomized to probenecid or matched placebo. In a controlled alcohol laboratory session, randomized participants will receive one oral dose of 2 g probenecid or matched placebo, with a drink designed to raise the breath alcohol content (BrAC) to 0.08 g/dL.

Particularly relevant for this application, pannexin 1 channels are expressed throughout the central nervous system (CNS), in neurons, astrocytes, and oligodendrocytes. They mediate the release of adenosine 5`-triphosphate (ATP) and the excitatory neurotransmitter glutamate. They function primarily as a single-membrane, large-conductance channel. Dephosphorylation of ATP outside of cells contributes to the majority of extracellular adenosine, which is a potent neuromodulator involved in physiological and pathological processes. Adenosine levels, in the brain extracellular space, increase dramatically during metabolically stressful conditions (e.g. ischemia, seizures, or trauma) and alcohol use.

Although some progress has been made in the advancement of our understanding of different neurobiological component of AUD, there are still many avenues which have not been explored. The contribution of pannexin 1 channels and adenosine in alcohol and opioid use disorders has only been recently described and unlocking this relationship could hold the key to the development of new treatments.

In cultured neurons, acute alcohol exposure increases extracellular adenosine. This spike in adenosine concentration contributes to the intoxicating and/or rewarding effect of alcohol. Furthermore, both high and low concentrations of alcohol could convert isolated neuronal bursts of activity into continuous activity. The loss of activity-dependent adenosine release removes the negative feedback provided by adenosine (A1) receptor activation. The promoted continuous activity, may contribute to the alcohol's tolerance with chronic alcohol use. Taken together, these observations prompt the hypothesis that probenecid (which is used in the clinic to treat hyperuricemia), may represent a valuable pharmacophore to evaluate the role of pannexin 1 channels in AUD.

The goal of this research is to elucidate novel pathophysiological mechanisms that could pave the way for new therapeutic targets for the treatment of alcohol use disorder (AUD).

The specific aims of this study will test the effects of probenecid, compared to placebo to:

Aim 1: assess the safety and tolerability of probenecid, compared to placebo after alcohol administration using a battery of physiological/psychological assessments that measures potential adverse events.

Aim 2: test the hypothesis that probenecid will reduce stimulant effect of alcohol by using the stimulation sub-score of Biphasic Alcohol Effects Scale (BAES). This hypothesis is based on the premise that probenecid, as pannexin 1 channel inhibitor, will reduce adenosine concentration, a contributor of the intoxicating and/or rewarding effect of alcohol.

Aim 3: test the hypothesis that probenecid will reduce alcohol tolerance using the cued go/no-go reaction time. This hypothesis is based on the premise that probenecid, as a pannexin 1 channel inhibitor, may re-establish the activity-dependent adenosine release and facilitate the negative feedback provided by adenosine (A1) receptor activation, a mechanism that may contribute to the alcohol's tolerance with chronic alcohol use.

Exploratory Aim: test for medication effects on: alcohol craving by the alcohol urge questionnaire (AUQ), intoxication by the subjective intoxication rate and session preference (session they felt *less/more drunk*, and which they *liked more).* These objectives are exploratory and therefore we do not predict direction of these effects.

Significance

Probenecid as a candidate therapeutic for Alcohol Use Disorder (AUD) preclinical data

The direct evidence that supports the possible role of pannexin 1 channels in alcohol use disorder (AUD) is provided by our published preclinical data (*Probenecid Reduces Alcohol Drinking in Rodents. Is Pannexin1 a Novel Therapeutic Target for Alcohol Use Disorder? Alcohol and Alcoholism, 2019 on press*).

Probenecid pharmacological characteristics and relationship with pannexin 1 channels

Probenecid was approved for therapy and prevention of gout and hyperuricemia in the United States in 1951. It is well-known that probenecid blocks organic anion transport and treats gout by its inhibition of renal reuptake of uric acid, by an anion transporter. Probenecid also inhibits pannexin 1 channels that have no known relationship with transporters. They exert their physiological role as non-junctional membrane channels, providing a pathway for exchange of molecules between the cytoplasm and extracellular space.

Adenosine and Alcohol Use Disorder (AUD)

Alcohol produces some of its multiple effects by interacting with adenosine signaling mechanisms. In particular, there is strong evidence that ethanol can increase the extracellular concentration of adenosine in the brain, and some of the effects of ethanol can be reduced by adenosine receptor antagonists. After repeated alcohol administrations, a fall in the increase of adenosine was observed, suggesting depletion of the intracellular adenosine stores in rats' hippocampus. Adenosine is responsible for balancing neurotransmitter release, reducing neuronal excitability and regulating ion channel function through activation of four classes of adenosine receptor: A1, 2A, A2B and A3. Alcohol can also reduce the basal activity of A1 receptor, resulting in an enhancement of synaptic transmission. The mechanism could be a reduction in activity-dependent adenosine release. The decrease in A1 receptor activation may result from ethanol inhibiting ectonucleotidases (NTPDases, reducing conversion of ATP to adenosine.

Acute alcohol exposure in cultured neurons is known to increase extracellular adenosine. This spike in adenosine contributes to the intoxicating and/or rewarding effect of alcohol. Both high and low concentrations of alcohol could convert isolated bursts of activity into continuous activity. The loss of activity-dependent adenosine release removes the negative feedback provided by A1 receptor activation. This effect promotes continuous activity, which may contribute to the alcohol's tolerance associated with chronic alcohol use.

Mounting evidence supports a role for pannexin 1 in alcohol-induced adenosine release and this process is promoted by a history of exposure to excessive alcohol. Also interestingly, it was recently shown that pannexin 1-mediated ATP releases from microglia during morphine withdrawal and that degrading endogenous spinal ATP contributes to withdrawal manifestation. Consistently, a pannexin 1-blocking peptide or probenecid suppressed ATP release during morphine withdrawal, and reduced the severity of withdrawal manifestations. Probenecid, as a pannexin 1 channel inhibitor, and an FDA-approved medication, could be an ideal candidate for the treatment for AUD. Also, the use a medication familiar to the practitioner community (not a psychoactive drug) may facilitate the incorporation of probenecid into clinical practice for the treatment of AUD. Taken together with the aforementioned observation that excessive alcohol promotes pannexin 1 opening and that probenecid

reduces alcohol drinking during acute withdrawal, these observations support the present hypothesis that inhibition of pannexin 1 channels may be beneficial for the treatment of AUD.

Scientific Rigor and Reproducibility
For this exploratory study, we will apply the utmost scientific rigor to ensure robust and unbiased experimental design, methodology, analysis, interpretation and reporting of results of the study. The PI and co-investigators will meet regularly to discuss methods for ensuring double blinded, unbiased, transparent, rigorous, and reproducible results and analyses. The proposal was designed based on the extensive clinical experience of the investigators. We will perform the data analyses in consideration of sex as a critical variable, because of the evidence that sex differences may be associated with significant differences in biological underpinnings related to women's greater physiological sensitivity to the effects of alcohol.

STOP **If your study ONLY involves the use of identifiable secondary data / biospecimens, including coded data from which you may be able to ascertain identity, skip to PART VI. Otherwise, please continue.**

3. Materials, Methods and Analysis. *The study design, methods and procedures must be adequately described in order for the IRB to understand all activities in which human subjects will participate. The IRB must also be able to differentiate those procedures that are performed for research purposes from those that are performed for routine care or evaluation.*

NOTE: The focus of this section is on methods and procedures. Risks will be described later.

This proposal meets the criteria for an NIH phase I clinical trial. The design is a randomized, within-subject, crossover, double-blind, placebo-controlled human alcohol laboratory study with one oral dose of 2g probenecid or placebo administered in two laboratory sessions. The pharmacological intervention is shown in **Figure 1** below, and the list of the assessments are in **Table 2 (Appendix D, DSMP)**.

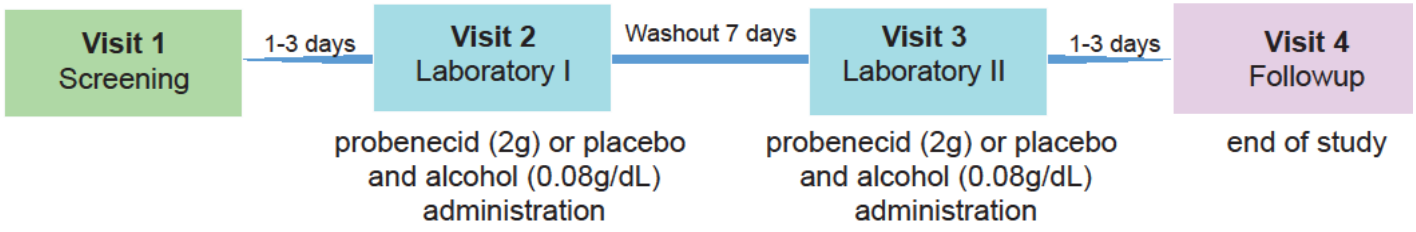

Figure 1: Project design and pharmacological intervention. There will be a total of four study visits. Visit 1 is the screening for eligibility (medical and physical examination). On Visits 2 and 3, participants will undergo an alcohol laboratory session with a one week washout period before administering the alternate therapy. The study will conclude at Visit 4.

Visit 1 (Screening) Following a breath analyzer (BrAC=0.00), the informed consent process is conducted. Participants are assessed on demographics, medical history, a physical examination, vital signs and ECG. Blood and urine clinical assessments are performed to screen individuals for inclusion/exclusion criteria. A Licensed Clinician will conduct eligibility screening. The psychological/behavioral assessments are administered by a trained personnel. After the initial visit, a study medical provider reviews the medical history and lab results. When confirmed eligible for treatment by the medical provider, the participant is called with the results by the RA, and scheduled for Visit 2. Randomization is performed at Visit 2.

(Remind PI, if not already done, to contact the Institutional Biosafety Committee to review and approve the collection of blood in the study.)

Visits 2 and 3 (Probenecid/Alcohol Laboratory Session) Participants are instructed to not consume alcohol for 24-hrs (BrAC=0.00) prior to any assessment. We administer the CIWA-Ar to monitor alcohol withdrawal symptoms (Score>10) and vital signs (within normal limits) before confirming enrollment. The RA administering the CIWA will have thorough training on how to administer the assessments, and will be trained on how to alert the study clinician if the participant scores $\geq$ an 8. The participants will then be randomized to receive either probenecid or placebo. After 1 hour, participants will begin the baseline assessments, and the cued go/no-go reaction time (RT) task powered by Inquisit 5 Lab. After 2 hours, according to probenecid pharmacokinetics, participants will receive two drinks designed to raise the BrAC to 0.08g/dL. Subjects will have 1 minute to finish each drink, and the drinks will be served 4 minutes apart. The next battery of physiological and psychological assessments will be administered to measure potential adverse events (*Aim 1*), stimulant effects of alcohol will be assessed using the Biphasic Alcohol Effects Scale (BAES) (*Aim 2*) and alcohol's tolerance by the RT task (*Aim 3*). The BrAC will be collected at 10, 20, 30, 40, 50, 60, 70, 80, 90, 105, 140 and 180 min after alcohol administration. After a one week washout period, participants will be asked to return for the second lab session (administration of the other condition).

Visits 4 (Follow-up) After one week, participants are asked to return to complete the final assessments and are given a Substance Use Resource List (**Appendix F3**).

Assessments A list of assessments that will be administered during the study period are described in **Table 1**.
Alcohol measures:

- Alcohol consumption 90-days before the screening is assessed by the Timeline Follow-Back (TLFB).
- Alcohol Withdrawal Assessment (CIWA-Ar) is a 10-item scale that determines the stage or severity of alcohol withdrawal.
- Alcohol Urge Questionnaire (AUQ) consists of eight statements about the respondent's feelings and thoughts about drinking as they are completing the questionnaire.
- Alcohol Dependence Scale (ADS) is a 25 question assessments addresses participants' reliance on alcohol.
- Stimulant/sedative effects of alcohol are assessed using the Biphasic Alcohol Effects Scale (BAES).
- The Drinker Inventory of Consequences (DrinC-2R) is a 23 question assessment asking participants personal consequences related to his/her/their alcohol intake.
- The Family History of Alcoholism asks participants his/her/their family history of alcoholism- first and second degree relatives.
- The Age of Onset of Alcoholism asks participants when drinking first had a negative effect on their life.
- Alcohol tolerance will be measured by the cued go/no-go reaction time and subjective intoxication rate/session preference (session they felt *less/more drunk*, and which they *liked more* etc.).

Mood, Anxiety, and Trauma:

- The SCID 5 will be administered at the first session to measure any potential disorder/potentially traumatic event.
- The NP will use the Suicide SAFETE as a way to access suicidal risk factors in participants.
- Hamilton Anxiety & Depression Rating Scales (HAM-A and HAM-D) are 14-item scales that measure anxiety and depression symptoms (i.e., psychic anxiety, somatic anxiety and depression).
- State-Trait Anxiety Inventory (STAI) is a 40-item measure that is split into state anxiety (20 items) and trait anxiety (20 items) symptoms, the scale measures worry, tension, apprehension and nervousness.
- Life Events Checklist for DSM-5 (LEC-5) will be given as an identification of traumatic events index.
- The PCL-5 is a 20 question self-report aimed at addressing potential PTSD symptoms.
- The Brief Trauma Questionnaire asks about participants' history of traumatic events.
- The Perceived Stress Scale (PSS) asks about participants' thoughts and feelings to assess stressful events within the past week.

Additional Assessments

- Sections 6-14 of the Menopause Health Questionnaire will be given to eligible female participants asking symptoms/concerns relating to menopause.
- An Adverse Events Evaluation form will be given to each participant at each session to check for potential side effects or adverse events that could have occurred since the previous visit.

- Additional assessments include the Medical History Questionnaire and Probenecid Eligibility Checklist conducted by the NP to assess eligibility to enroll in the study.

TABLE 1

Assessments	Visit 1 Screening	Visit 2 - 3 Alcohol Lab I-II	Visit 4 Follow-up	Done By	Recorded On
Informed Consent	X			RA/Participant	Paper
Vitals	X	X	X	NP/Physician/PI/RA	Paper
Urine toxicology	X			RA	Paper
Pregnancy test	X	X	X	RA	Paper
Blood collection	X			PI/NP	Paper
ECG	X			RA/PI/NP/Physician	Paper
Concomitant Medications	X	X	X	PI	Paper
Medical History Questionnaire*	X			NP/Physician	Paper
Physical Assessment	X			NP/Physician	Paper
Menopause Health Questionnaire*	X			NP/Physician	Paper
Probenecid Eligibility Checklist	X			PI/NP/Physician	Paper
Alcohol Timeline Followback (**TLFB**)*	X	X	X	RA	Paper
Adverse Events Evaluation (**AEE**)*	X	X	X	RA/NP/PI	Paper
Structured Clin Interview DSM-5 (**SCID-5**)	X			RA/PI/NP	Paper
Alcohol Withdrawal Ass. (**CIWA-Ar**)*	X	X	X	RA/NP/Physician	Paper
Biphasic Alcohol Effects Scale (**BAES**)		X		Participant	Paper
Brief Trauma Questionnaire (**BTQ**)	X			NP/Physician	Paper
Suicide SAFE-T	X			NP/Physician	Paper
Age of Onset of Alcoholism*	X			Participant	Qualtrics
Alcohol Depend. Scale (**ADS**)*	X			Participant	Qualtrics
Alcohol Urge Questionnaire (**AUQ**)		X		Participant	Qualtrics
Drinker Inv. Consequences (**DrinC-2R**)*		X		Participant	Qualtrics
Self-Eval. (**STAI-y1**)	X			Participant	Qualtrics
Self-Eval. (**STAI-y2**)	X	X	X	Participant	Qualtrics
Life Events (**LEC-5**)	X			Participant	Qualtrics
Perceived Stress Scale (**PSS**)	X	X	X	Participant	Qualtrics
PTSD Checklist (**PCL-5**)	X			Participant	Qualtrics
Family History Alcohol (**FH**)*	X			Participant	Qualtrics
Hamilton Anxiety & Depression (**HAM-A/D**)	X	X	X	Participant	Qualtrics
Subject Intoxication Report		X		Participant	Qualtrics
Go/no go task		X		Participant	Inquisit

Key: Assessments in blue and in green- performed on paper and secured in locked file cabinets in the laboratory; assessments in red- performed on Qualtrics and secured in the CAAS VPN Secured Sever; assessment in black performed with toolbox and secured in CAAS VPN Secured Sever;
**matching assessments with treatment seeking clinical trials*

Due to the brevity of individual questionnaires, the surveys assessed via Qualtrics will accessed under one link. All data completed by the participant via the Qualtrics link and by Inquisit will be completed by the participant in real time. Data completed via paper assessment (either by the participant, RA, NP or PI) will be manually entered into Qualtrics (CAAS VPN Secured Sever) by the RA after that session has ended. Study coded participant assessments on paper will be kept in the participant binder in a locked filing cabinet at the RA desk during the duration of the sessions until the data is manually entered into Qualtrics. Once the participant has completed the study, the participant binder will then be moved to the PI's locked office. For each data secured file location see the DSMP (**Appendix D**).

THE BLUE TEXT IN THE FOLLOWING SECTIONS IS A GUIDE TO ENSURE ALL RELEVANT INFORMATION IS INCLUDED IN YOUR APPLICATION. YOU MAY DELETE THE BLUE TEXT BEFORE SUBMISSION

4. **Participant Population.**

Participants and Recruitment

One hundred non-treatment-seeking individuals with AUD will be screened, 34 will be randomized (50% women). Drs. Haass-Koffler and Swift have extensive experience in successfully recruiting these participants in the Providence, RI area. Advertisements, such as paper flyers and ads, will be posted to recruit participants by the RA in the Providence, RI area (**Appendix B**). Participants will respond to the recruitment materials by telephone/email and will be pre-screened for initial eligibility and exclusion criteria (**Appendix G**). Eligible participants will be invited for an in-person screening, where they will provide written informed consent (**Appendix H**) and undergo a full physical examination. Participants will be enrolled in the study after confirmation of eligibility by the study's medical provider (**Table 2**).

Table 2
Inclusionary Criteria
• Male or female, 21-70 (inclusive) years; women >7 drinks/week; men >14 drinks/week; • meet any DSM-5 criteria score for AUD; • Breath alcohol Content (BrAC)=0.00 at each visit; • In good health as confirmed by medical history, physical examination and lab tests; • Willing to adhere to the study procedures; • Understand informed consent and questionnaires in English at an 8th grade level
Exclusionary Criteria
• Women who are breastfeeding or have a positive urine screen for pregnancy • CrCl < 60mL/min • Taking aspirin (salicylates may reduce effect of probenecid) • Taking penicillin • Taking methotrexate (may increase concentration) • Taking other medications that may interact with probenecid • History of suicide attempts in the last three years • Current diagnosis of another substance disorder(s) other than nicotine, as assessed by self-reports and urine toxicology screen at baseline • History of hypersensitivity to sulfa drugs
NOTE: The exclusion criteria is based in enhancing participants' safety. Participants need to speak English and be able to understand informed consent and questionnaires in English which will be written exclusively at an 8th grade level.

Probenecid and alcohol: dose selection and administration protocol

The medications will be prescribed by Dr. Swift. Eligible participants will receive a single oral dose of probenecid or matching placebo in two laboratory sessions.

Sample Size Estimates

This study is a randomized within group, crossover, double-blind, placebo-controlled Phase I Clinical Trial in non-treatment-seeking alcohol-dependent individuals in an alcohol laboratory setting. *Primary Aim 1* focuses on the safety of administering probenecid with alcohol, as determined by descriptive effect estimates and a maintained level of non-significant difference (p>0.05) scores on the AEE throughout the trial. The AEE difference to be detected is based on a judgement concerning the minimal effect which has clinical relevance in

the management of patients. In aims of this nature, the exact sample size cannot be fixed in advance because it depends upon the chosen stopping guideline, see our Data and Safety Monitoring Plan (DSMP) in the Human Subject Form. Therefore, the study is powered primarily on secondary aims.

For *Aim 2*, the sample size was calculated using power analysis to detect differences in mean changes in the individual alcohol-related stimulation from the BAES of one of our pharmacological human laboratory studies. In this pilot study of 10 participants, randomized to either idazoxan or placebo in a double-blind, crossover design, it was observed that the study medication significantly reduced the stimulant score ($p<0.05$) compared to placebo with a medium-to-large effect (d =0.75). To power the current trial, we selected the more conservative, lower bound of the anticipated effect size to power Aims 2 and 3 (i.e., medium). Therefore, assuming α (two-tailed) = 0.05, N = 34 will provide β = 0.8 to detect a medium effect size for measuring the probenecid decreased alcohol-related stimulation.

For *Aim 3*, power analysis was conducted to detect differences in mean changes in the individual reaction time (RT) on the cued go/no go paradigm from a human laboratory study that measured the RT (ms) on the effect of alcohol compared to placebo. This pilot study of 20 participants, randomized in a double-blind, crossover design, showed that, on the go task, alcohol (dose 0.08g/dL) slowed RT compared with placebo ($p<0.01$) with a medium-to-large effect (d =0.626). Based on this pilot study, and assuming α (two-tailed) = 0.05, N = 34 will provide β = 0.8 to detect at least a medium effect size for measuring if the probenecid significantly antagonizes the reduced alcohol RT compared to placebo. With 20% attriters, we predict that we need to enroll 41 participants to maintain an N of 34 completers.

The outcomes of previous studies used to power the secondary Aims of this proposal speaks to the novelty of this proposal and the need for a Phase I Clinical trial using probenecid in non-treatment-seeking alcohol-dependent individuals. In each statistical analyses conducted for the Aims, effect size estimates to determine power for a future clinical trial will be of primary interest in this Phase I study.

5. Recruitment Methods

Drs. Haass-Koffler and Swift have extensive experience in successfully recruiting these participants in the Providence, RI area. Participants will respond to the recruitment materials by telephone/email and will be pre-screened for initial eligibility and exclusion criteria (**Appendix G**). Eligible participants will be invited for an in-person screening, where they will provide written informed consent and undergo a full physical examination. Participants will be enrolled in the study after confirmation of eligibility by the study's medical provider (**Table 1**).

Potentially eligible participants will be invited for an in-person screening by the RA and the nurse practitioner, where they will provide written informed consent and undergo a physical examination, blood work and electrocardiogram (ECG). Various assessments will also be administered either by the RA or NP to check for eligibility criteria. After confirmation of eligibility by the study physician (Dr. Swift), participants will be enrolled in the study by the PI (Dr. Haass-Koffler), with the support of the RA.

The biomedical assessments (urine test and ECG) will be performed by a trained RA under the supervision of the nurse practitioner and the blood will be collected by a phlebotomist or nurse practitioner.

The RA will receive training to administer the screening assessments by trained research personnel (either by the PI or the nurse practitioner). Screening tests and procedures ensure that potential participants are eligible to participate. The nurse practitioner will administer the CIWA at the screening, and the RA administering the CIWA during the other visits will have thorough training on how to administer the assessments, and will be trained on how to alert the study clinician if the participant scores ≥ an 8.

NOTE: The de-identified screening data (study code) will be kept after eligibility is determined for research purpose. The document that links the study code with identifiable information will be destroyed after conclusion of the trial. The screening consent process is fully described in Part V. All screening material will be in English.

Participant Selection

In this exploratory proposal, we selected to enroll non-treatment-seeking individuals with AUD because our primary goal is to assess health-related (alcohol/probenecid interaction) outcomes. The specific aims will assess the safety, tolerability and biobehavioral response of probenecid when co-administered with alcohol. As recommended by the FDA, these outcomes are critical for developing AUD pharmacotherapies, but ethically, can be accomplished only in a population that has not expressed intent to be treated. We recognize the importance of translating our outcomes to treatment seeking populations and we will consider demographic factors and clinical variables as recently recommended. To further control for discrepancies between treatment seekers vs non-treatment seekers in medication response, for this proposal, we have included matching assessments (**Table 1**) between ours and other larger clinical trials that have enrolled treatment-seeking participants. This strategy will help inform future AUD medication development.

Standard care: none
Intervention: 2 g of Probenecid or placebo

6. Compensation / Reimbursement

Visit #	1	2	3	4
Type of Visit	Screening	Alcohol Lab I	Alcohol Lab II	Follow-Up
Time Involved	2-3 hours	5 hours	5 hours	1 hour
Amount Compensated	$25	$120	$120	$25 + bonus of $10

Participants will receive $25 dollars at visit 2 (screening), $120 dollars at both lab sessions (Alcohol Lab I and Alcohol Lab II), and $25 dollars at visit 4 (follow-up). An additional $10 will be awarded at the follow-up visit for completion of the study. Therefore, maximum compensation for study completion is $300 cash.

Participants will be compensated in cash and for the sessions that they complete. Participants who do not complete the study will be compensated for the sessions that they complete. The amount of compensation is based on the time spent in each session and based on other similar studies conducted by the PI or Dr. Swift at Brown University. Participants will receive parking validation or RIPTA tickets (both ways) as reimbursement for travel cost. Study procedures, such as a physical, ECG, urine tests, blood analysis, etc., will be provided for the participants.

7. Potential Research Risks / Discomforts to Participants

Risks of the study include:

1) discomfort from answering questionnaire items
2) breach of confidentiality
3) issues associated with coercion
4) discomfort from alcohol withdrawal
5) side effects or drug interactions with probenecid
6) craving for alcohol

Participants will be protected against any potential risks and will be closely monitored throughout the study.

1) Participants may experience some discomfort when answering questionnaires, however, we expect that the risks will be low. Based on past and current research by Drs. Haass-Koffler, Swift and Cioe, participants have not had any discomfort or issues that have arisen from questionnaires.
2) The risk of breach of confidentiality is low and strict precautions will be taken to minimize the risk of breach of confidentiality. A Data Safety Monitoring Plan (DSMP) (**Appendix D**) is in place that follows Brown's IRB guidelines.
3) The risk of coercion is low. Monetary compensation for this study is commensurate with the amount of time and effort that is required for the study.
4) Participants may experience some discomfort from alcohol withdrawal, but these should be minimal since this is a non-treatment seekers (non-abstinent) individuals with AUD and the withdrawal phase is in the

controlled setting of the laboratory. As outlined below, several precautions will be taken to help minimize any alcohol withdrawal symptoms that participants may experience.

5) A detailed procedure to minimize risk associated with probenecid is defined below.
6) Participants may experience craving for alcohol after being exposed to alcohol cues. Past research by Drs. Swift and Haass-Koffler, have shown that participants do not have significant craving or subsequent drug use after cue exposure. Also, it was shown that cue reactivity elicits urge to drink in the first 6 minutes of alcohol exposure, followed by a gradual and significant decrease. Importantly, there were no differences in alcohol-related behavior in AUD individuals in their first or fourth week (after cue reactivity exposure). As such, running the laboratory phase before the naturalistic phase will not affect the results of the naturalistic phase.

As detailed in the Description of Potential Risks, the following will be set forth to protect against risks of the study:

1) To protect against or minimize discomfort from answering questionnaire items, participants may refuse to answer questions that they do not feel comfortable answering. Participants with discomfort may withdraw from the study with no penalty and will be referred to Dr. Swift for a clinical assessment if distress continues.
2) To protect against a breach of confidentiality, all data acquired during the study will only be accessible to the research staff and used for research purposes only. All research data will be kept in a locked filing cabinet or on a password-protected computer database behind locked doors in the study office. Only participant code numbers will be used to identify participants. Consent forms and logs with participant's names and codes will be locked in a separate cabinet in the PI's office as an extra layer of security. All biological samples will be guarded in a similar manner. Only participant code numbers will be labeled on biological samples and will be locked in a laboratory suite. All interviews and assessments will be conducted in an interview room with a closed door to ensure participant privacy and confidentiality. We are also covered by the Certificate of Confidentiality at the NIH to protect against disclosing any identifying information/characteristics of participants in legal demands such as court orders or subpoenas. The Certificate will ensure further protection of participants' confidentiality.
3) To protect against issues associated with coercion, participants will be compensated appropriately for their time and effort. The study involves about a week of participation and given the considerable time commitment and involvement, compensating participants for their time and travel costs is appropriate and comparable to other study protocols. Those who drop out of the study early will be compensated for sessions that they completed.
4) To protect against or minimize any discomfort from alcohol withdrawal, participants will be closely monitored throughout the study. Alcohol withdrawal will be assessed before each visit and since individuals with a CIWA-Ar $\geq$ 8 will be excluded from the study at screening, we do not expect withdrawal from alcohol to be severe. Dr. Swift will be accessible 24/7 during the study and participants will be instructed to call if they experience any withdrawal symptoms. Emergency medical services will be immediately called if a serious adverse event arises during the study.
5) To protect against or minimize any risk of side effects associated with probenecid or any drug-drug or drug-alcohol interactions, potential risks will be judiciously outlined to participants and thorough screening procedures will be in place to minimize recruitment of those that might be at a higher risk of adverse events. The study physician (Dr. Swift) will carefully review all participant screens and the PI (neuropharmacologist) will evaluate the individual medication profile to minimize any risk association with the medication. The participants will be instructed on the proper administration of the medication and they will return the medication bottle at the last visit.
6) The safety of probenecid is supported by clinical practice since the medication was FDA-approved in 1951, and is still being used to treat gout and hyperuricemia in the United States today. Dr. Swift's contact information will be provided to participants so that participants can contact him between visits if necessary.
7) The protocol involves an intervention with a medication that has been prescribed since 1951. There are minimal risk for participants in their daily lives, however, they may feel discomfort during the laboratory procedures (alcohol administration). See below additional consideration to prevent the additional risks:

Dr. Swift will prescribe medication for eligible participants. The dose of probenecid was decided based on clinical work. We will administer probenecid (2 mg single dose) in the laboratory sessions (visits 2 and 3).

Medications (probenecid and matching placebo)

Dose selection
The 2g probenecid dose for this proposal was selected based on clinical practice (FDA-approved since 1951) and current research studies. In clinical practice, probenecid is administered up to 2g/day to treat chronic gout; to prolong penicillin serum level 500 mg/four times daily. In clinical research, probenecid was administered for: systolic heart failure, 2g/twice daily for seven days (NCT:01814319) and for calcium pyrophosphate deposition disease, 2g/day for five days (NCT02243631). As such, the 2g administered in one dose is within in the safety range of the administration of probenecid in clinical practice. One single dose administration of probenecid should be sufficient to measure the outcome in this application since it has been shown in a rat model for opioid use disorder that one dose of probenecid was sufficient to alleviate morphine withdrawal in rats. This approach is consistent with the preliminary and proof-of-concept nature of other early phase studies that have already taken place with other medications such as naltrexone, baclofen and gabapentin. A follow-up R01 study will be needed to look at chronic administration.

The 0.08gr/dL alcohol dose was chosen based on prior research showing that it impairs the ability to quickly activate and inhibit responses, as measured by the cued go/no-go task. Doses will be calculated based on body weight and gender, and will be administered as absolute alcohol divided equally into two drinks, each containing one part alcohol and three parts mix. Subjects will have 1 min to finish each drink, and the drinks will be served 4 min apart. This dosing procedure produces BrAC peak at ~60 min from the onset of drinking.

Administration protocol As depicted in **Fig. 2**, the study drug-alcohol administration protocol for this application was derived by the pharmacokinetics profile of the administration of a single oral 2g probenecid (**Fig. 2A**) and of an alcohol dose to reach BrAC = 0.08g/dL (**Fig. 2B**). Probenecid is well absorbed after oral administration, with a half-life of 4-12 h and peak plasma levels reached within 2 h. Before probenecid reaches peak (C_{max}), we will start the baseline assessments without the presence of alcohol (60 min). Probenecid remains at a steady-state for ~2 h, which will allows for the administration of alcohol and the battery of physiological and psychological assessments that measure potential adverse events (*Aim 1*), the stimulant effects of alcohol (*Aim 2*) and alcohol's tolerance (*Aim 3*) during alcohol's ascending and descending limb (**Fig. 3B**). The assessments post-experiment will be used to measure safety before discharge. We will also measure BrAC at this time to determine if it is safe for the participant to leave.

Probenecid and matching placebo will be prepared as opaque capsules by JB Pharmacy, which has prepared medications for all of our other double-blind studies. Risks of medications will be minimized through careful and detailed screening of participants by the PI (Dr. Haass-Koffler) who is a pharmacologist and the Co-Is: the study physician, Dr. Swift, who is a practicing physician and psychiatrist and, Dr. Cioe, the nurse practitioner. Each investigator has extensive experience in addiction research. The medical team will act to minimize recruitment of those who might be at higher risk for adverse events or drug-drug interaction, as well as careful and detailed monitoring of adverse events and participant well-being during the study.

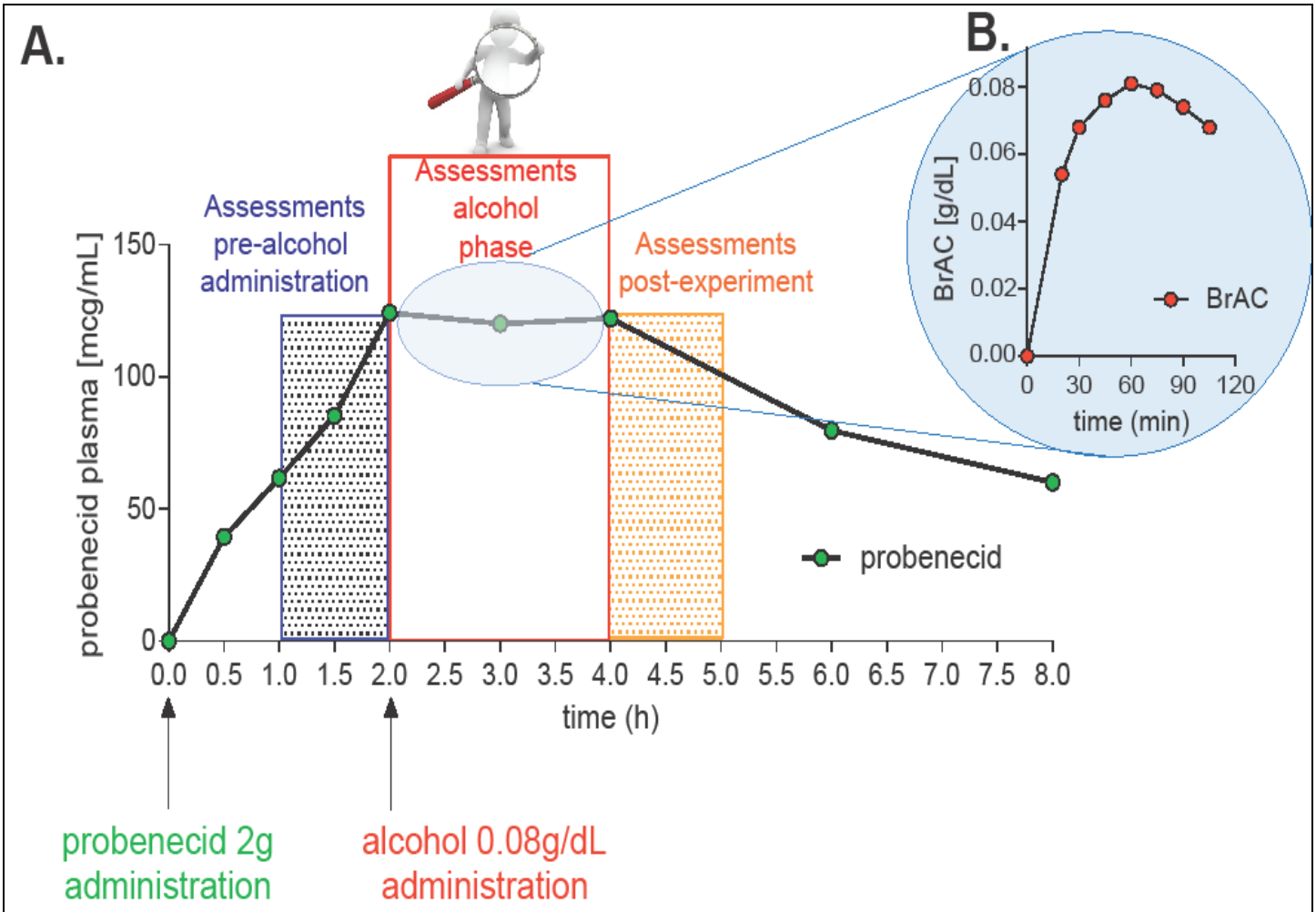

Fig. 2 – **Schematic representation of the administation of probenecid and alcohol in the laboratory**. (**A**) *Probenencid pharmacokinetic profile*: Time 0 h corresponds to the time of probenencid administration and time 2 h corresponds to the C_{max}. Probenecid remains at steady-state (constant concentration) for ~2 h after administration which will allow running the experiments during the alcohol phase. At Time 2 h, the alcohol administration starts (0.08g/dL, two drinks in 6 min). (**B**) *Alcohol pharmacokinetic profile*: Time 0 min corresponds to the time of alcohol administration and the peak concentration will be achieved after 60 min. Ascending limb (30-60 min) and descending limb (after 60 min). The graphs were adapted from (Selen, Amidon, & Welling, 1982) (oral 2g probenecid) and from (Fillmore, Marczinski, Bowman, 2005) (alcohol administration to reach BrAC = 0.08g/dL).

Side Effects

Common side effects of probenecid include headache, anorexia, nausea, and vomiting, joint pain, redness or swelling. *Uncommon side effects* include dizziness, flushing or redness of the face, frequent urge to urinate, alopecia, and sore gums. *Rare side effects* of probenecid include cloudy urine, cough or hoarseness, fast or irregular breathing, fever, pain in back and/or ribs, sores, ulcers, or white spots on lips or in mouth, sore throat, sudden decrease in the amount of urine, swollen and/or painful glands, unusual bleeding or bruising, unusual tiredness, yellow eyes or skin, and weight gain.

Drug-drug interactions

To protect against any risk of additional drug-drug interactions, participants will be thoroughly screened for any prescriptions or over-the-counter medications that may interact with Probenecid. Dr. Haass-Koffler will oversee the possible drug-drug interactions that may arise from the co-administration of existing medications taken by participants with the study medication. She will evaluate the medication profile for each screening visit and she

will prepare a full pharmacokinetics/ pharmacodynamics (PK/PD) report for the final review by Dr. Swift using the Clinical Pharmacology database provided by Brown. Participants will be instructed to immediately call the PI if they start taking new medications. The PI will then contact Dr. Swift who will recommend next steps. Participants will be asked to avoid any medications that could interact with Probenecid.

The following medications should be avoided when taking Probenecid: Avibactam, Cefotaxime, Doripenem, Ketorolac (nasal and systemic), Meropenem, Pegloticase, Methotrexate, aspirins, and those taking penicillin
This list is not complete. Other drugs may interact with Probenecid, including prescription and over-the-counter medicines, vitamins, and herbal products. Not all possible interactions are listed. The PI will review specific drug-drug interactions before enrolling participants in the study.

Storage of Medication
Probenecid tablets should be stored in well closed containers at temperatures between 15-30 deg C. Commercially available preparations containing probenecid and colchicine should be protected from light. Following the date of manufacture, commercially available probenecid tablets have an expiration date of 3-5 years depending on the packaging.

Adverse Events
Adverse events (AEs) will be recorded and tracked for this protocol. Adverse events will be reported to Brown University IRB. An annual report will be submitted by the PI to the Project Officer summarizing all adverse events.

An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the study, whether or not the event is considered related to the investigational product. A new illness, symptom, sign or clinically significant clinical laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs.

Female participants in the study must not be pregnant or nursing; those who do not meet this criteria will be excluded. To verify the possibility of pregnancy, we will perform a pregnancy test at the start of each visit during the study. Should a female participant become pregnant during the study, she will be terminated from the study immediately and referred for obstetrical follow-up. If a woman has a positive or borderline pregnancy test after enrollment, the pregnancy will be recorded as an AE. The investigators will contact the subject at least monthly and document the subject's status until the pregnancy has been terminated or completed, also in order to verify if the definition of serious adverse event will apply (described below).

All AEs regardless of severity, will be followed until satisfactory resolution. At the follow-up visit, AEs will be recorded and followed to resolution only if they are serious or unexpected, or if the study physician assesses them to be clinically significant.

In accordance with FDA reporting requirements, all AEs occurring during the course of the study will be collected, documented, and reported by the investigators. The occurrence of AEs will be assessed starting on the day of randomization, after first dose of doxazosin.

Unexpected Adverse Events.

An unexpected AE is one that is not described with respect to nature, severity, or frequency in the current product package insert.

***Serious Adverse Events (SAEs*)**

Each adverse event or reaction will be classified by a study physician as being serious or non-serious. Based on the seriousness of the adverse event or reaction, appropriate reporting procedures will be followed. The Code of Federal Regulations Title 21 part 312.32 and International Conference on Harmonization (ICH) Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH-E2A March 1995, as implemented by the U.S. Food and Drug Administration, defines an SAE or serious adverse drug experience as any untoward medical occurrence at any dose that:

- results in death;

- is life-threatening; (NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect.

In addition, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug reaction, when based on appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. If a study subject withdraws from the study or if an investigator decides to discontinue the subject from the study because of an SAE, the subject must have appropriate follow-up medical monitoring including, if necessary, hospitalization. Monitoring will continue until the problem prompting hospitalization has resolved or stabilized with no further change expected or is discovered to be clearly unrelated to study medication or progresses to death.

Unexpected and Serious Adverse Events Reporting

Any Unexpected AE or SAE, including death due to any cause, which occurs to any subject from the time of admission through discharge whether or not related to the investigational product, will be reported **within 24 hours** of knowledge of the event to our local IRB and to the Project Officer of this project via fax or phone call.

A detailed written documentation for all unexpected AEs/SAEs will be submitted to the Project Officer of this project **within three (3) days** of reporting the event and **within seven (7) days** to our local IRB. Required documents that must be submitted include the following information:

- title of protocol;
- description of the unanticipated adverse event;
- a determination of whether the event was related to the research study;
- name of the drug;
- where and when the event occurred; and
- to whom else has the event been reported.

Upon receipt of a notification of an unanticipated adverse event or death, the IRB will determine whether further investigation of the event is required. Depending on the circumstances the investigator may be required to suspend the study pending the outcome of an IRB review. Also, the IRB may require modification of the risks section of the consent form. These documents may be submitted by facsimile, as email attachments, or via overnight courier.

Follow-Up of All AEs/SAEs

All adverse events must be followed until they are resolved, or until all attempts to determine the resolution of the AE/SAE are exhausted. This may require an extended hospitalization period or a change in status from outpatient to inpatient. All treatments, outcomes and information regarding whether or not the subject was referred to their Primary Care Provider for additional follow-up must be recorded in the source document. Any unexpected AEs and/or SAEs occurring to study participants during the follow up period will be reported within 24 hours of knowledge of the event to our local IRB and to the Project Officer of this project via fax or phone call. All follow-up AEs will be recorded and followed to resolution only if they are serious, or if the study physician assesses them to be clinically significant.

Periodical Review of the Safety Data

Dr. Haass-Koffler (PI), Dr. Swift (Co-I and Study Physician) and Dr. Cioe (Co-I and nurse practitioner), will meet prior to the enrollment of the first subject to review the research protocol, informed consent documents and plans for safety and data monitoring of the study. This review will determine the risks and benefits to research subjects,

protection and safety of the subjects and to offer suggestions for improving the study design. Moreover, Drs Haass-Koffler, Swift and Cioe will meet on regular basis during the duration of the study. 'Ad hoc' and/or emergency meetings will take place if needed for specific and/or safety reasons. Minutes of these meetings will be taken and filed in the regulatory binder of this project.

The goals of these meetings will be to:

1. determine adherence to treatment plan;
2. determine specific data to be analyzed;
3. evaluate end point/stop point rules;
4. review protocol violations and deviations to assess adequacy of study;
5. ensure documentation of informed consent;
6. Enrollment (followed eligibility criteria, enrollment numbers, visit compliance, screening failure information);
7. discuss investigator or key personnel changes;
8. review completeness and quality of data collection forms;
9. evaluate the aggregate analysis of AEs/SAEs;
10. review vital signs, clinical tests, etc.;
11. review confidentiality.

The major outcomes following data review include: (1) continuing the trial unchanged; (2) modifying the protocol and/or consent form; or (3) terminating the study. If the protocol and/or consent form should be changed, or the study should be terminated, Dr. Haass-Koffler will be responsible for all the necessary communications with the Project Officer and the IRB.

Data and Safety Monitoring Plan (DSMP) is attached to this protocol **(Appendix D).**

8. **Potential Benefits of the Research. NOTE: Compensation for participation is not a benefit and should not be included in this section.**

- Potential benefits to human subjects and to others: There are no direct benefits to participants in this study. However, considering the potential benefits and the knowledge to be gained, we believe that the benefits outweigh the risks. The risk-benefit ratio provides a justification for conducting this study, which could ultimately lead to more effective treatment options for alcohol use disorder.

- Importance of the knowledge to be gained: With the serious health and economic consequences associated with alcohol use disorder, this study provides a much needed understanding of the behavioral and biological factors involved with alcohol craving and use. This study aims to examine the potential efficacy of a novel pharmacological treatment for individuals with alcohol use disorder during stress conditions. If effective, the findings of this study could lay the groundwork for an effective treatment strategy for alcohol use disorder and individuals with other addictive disorders.

PART IV. APPENDICES SCREENER

Please complete & attach the following Appendices to this Application, as applicable.

Incl.	N/A	
☐	☒	Appendix A. Children as Subjects *To be attached when minors are included as participants [please be aware of the age of majority for your specific research site(s)]*

☐	☒	Appendix B. Prisoners as Subjects *To be attached when prisoners are included as participants.*
☒	☐	Appendix C. Use of Drugs *To be attached when the research includes the use of FDA-regulated or unregulated drugs.*
☐	☒	Appendix D. Use of Devices *To be attached when the research includes the use of FDA-regulated or unregulated devices.*
☒	☐	Appendix E. Prescription Drug / Medication Management *To be attached when study procedures include administering prescription medications to study participants.*
☒	☐	Appendix F. Mental Health Safety Plan *To be attached when participants may experience significant emotional distress, or be at risk of themselves or others.*
☐	☒	Appendix G. Use of protected health information (PHI) for Research *To be attached when study procedures include a plan to access, use or disclose Protected Health Information (PHI) of participants.*

LIST OF ATTACHMENTS
A. Probenecid Drug Manual
B. Recruitment Material
C. Use of Drugs
D. Data and Safety Monitoring Plan
E. Prescription Drug/Medication Management
F. Mental Health Safety Plan
    F2. Mental Health Safety Plan Checklist
    F3. Substance Use Resources
G. Pre-Study Telephone Screen
H. Informed Consent Document
I. Assessments & Measures

PART V. INFORMED CONSENT

Informed consent is a *process*, not just a form. The IRB must ensure the informed consent process clearly discloses and facilitates the understanding of all information needed to make an informed decision to participate while promoting the voluntariness of participation.

Please review the Consent/assent templates and related guidance on the HRPP Forms & Templates page before developing your consent forms.

1. **Describe the informed consent process, including:**

In a private room in Dr. Haass-Koffler's laboratory, following a breath alcohol content (BrAC) = 0.00, participants will provide written informed consent to participate. Participants will be asked to read the document thoroughly and indicate that they have done so in order to proceed to the study. Potential participants have the option of refusing to participate in the study, withdrawing their participation at any time, and/or refusing to answer any questions that they feel uncomfortable responding to (**Appendix H**).

2. **Facilitate Understanding**

To ensure that participants understand the informed consent, participants will read and signature each page. All participants will be informed of the study procedures, study rationale and any potential risks and benefits. The PI or Research Assistant will answer any questions about the informed consent and study that participants may have.

Fluency in English is part of the study inclusion criteria and thus participants will not be permitted to enroll in the study unless they meet this criterion

We will ensure ongoing consent by adding language to remind participants that they have the option to refuse to participate in the study, may withdraw their participation at any time, and/or refuse to answer any questions that they feel uncomfortable responding to.

3. **Documentation**

Participants will be asked to sign a copy of the consent form that the researcher will keep on file in a locked storage cabinet. A second copy of the consent form will be provided for study participants to keep.

4. **Additional Considerations**

All study participants will be consented. This study does not involve minors, any deception, and all data including biospeciments will be fully de-identified.

Proceed to PART VII. DATA SECURITY ASSESSMENT

PART VI. USE OF SECONDARY DATA / BIOSPECIMENS

1. From what source(s) will you acquire or access the data / biospecimens?

Research data collected from participants will include interviews, questionnaires, task responses, physiological responses (heart rate, blood pressure), and biological samples (breath, blood and urine). Breath samples will be taken at the start of each visit for BrAC. Urine samples will be taken to test for pregnancy (at each visit) and drug screening (the first visit and additional visits if deemed necessary). Blood samples will be obtained during the physical at the in-person screening. All data collected will be for research purposes only. Only authorized, trained research personnel certified by the Collaborative Institutional Training Initiative (CITI), will have access to the data. All data will be identified with numbers (labeled sequentially) with no personal identifiers

2. Describe the type(s) of data and date range(s) of the data you will use and the characteristics of the study research population (e.g., age range, sex, and any other pertinent demographic information.)

Research data collected from participants will include interviews, questionnaires, task responses, physiological responses (heart rate, blood pressure), and biological samples (breath, blood and urine). Breath samples will be taken at the start of each visit for BrAC (which must read 0.00) a urine sample will be collected at each visit to test for pregnancy, and at the first visit to conduct a toxicology screen, and at additional visits if necessary. Blood samples will be obtained during the physical at the in-person screening. All data collected will be for research purposes only. Only authorized, trained research personnel certified by the Collaborative Institutional Training Initiative (CITI), will have access to the data. A total of 100 individuals will be pre-screened by telephone, 50 will be screened in person in the CAAS laboratory, 41 will be randomized by urn randomization, and a total of 34 are expected to complete the study. The participants will be males or females ages 21-70 who fit the DSM-5 criteria for AUD **(table 2)**. Participants must be in good health as deemed by his/her medical history, physical examination and lab tests conducted by research personnel, and must be willing to adhere to the study

procedures with knowledge that he/she has the option to excuse his/herself from the study at any time **(Appendix H)**. Participants will understand informed consent and questionnaires in English at an 8th grade reading level **(table 2)**.

4. HIPAA and Protected Health Information (PHI): NA

5. Do any of the source(s) require a Data Use Agreement (DUA) or other Agreement that requires institutional signature to obtain, access or use the data / biospecimens? ☐ Yes ☒ No

If "yes," please include a copy of the Agreement(s) with this submission and also follow the Data Use Agreement review and signature processes.

Proceed to PART VII. DATA SECURITY ASSESSMENT

PART VII. DATA SECURITY ASSESSMENT

1. Do the study data / biospecimens include identifiers? Video and audio recordings are considered identifiable.

☒ Yes ☐ No*	*If "no," I affirm that I have read and will abide by the Level 1 Risk Minimum Security Standards: ☐ Yes ☐ No Proceed to Question #2. If "yes," answer the following questions. A. Describe the identifiers associated with the data / biospecimens. Biospeciments will be coded by de-identified study numbers immediately after collection. The file connecting the participant ID to their study code will be kept in a secured password protected department folder, which will be destroyed after conclusion of the trial. B. Justify why identifiers are required to conduct the research. This is a biomedical study that requires breath, urine, and blood collection for screening eligibility, safety measure and to answer research questions. C. Described the proposed research use of the identifiable data / biospecimens. The de-identified data will be used for the purpose of this study. D. Self-classify the Risk Level of these data / biospecimens (select the *highest level of risk* for all data / biospecimens being collected). ☒ Level 2 Risk ☐ Level 3 Risk

2. How will study data / biospecimens be collected?

☐ Brown desktop
☐ Laptop
☒ Departmental server
☐ CIS managed server
☒ Brown Qualtrics
☐ REDCap; Please describe what instance of REDCap is being used (Brown does not have an instance of REDCap):
☐ MTurk (AMT)
☐ Text messaging → You must complete the Text messaging section after completing Qs 3 – 5.
☐ Mobile App (on tablet, iPad, Phone) → You must complete the Mobile App section after completing Qs 3-5.
☐ Zoom
☐ Other audio / videoconferencing tool; please describe the tool:
☒ Paper records, including photographs. Please describe, including how you will securely store the paper records:

Subject's identifiable information (i.e. screening questionnaires) will be stored separately from individual data. Paper records will be maintained in locked file cabinets in locked offices. The file connecting the participant ID to their study code will be kept in a secured password protected department folder, then destroyed after conclusion of the trial.

☐ Web-based site / survey / other tool not listed above → You must complete the Web-based Other section after completing Qs 3 – 5.

☐ Other; please describe:

3. Who will have access to the study data / biospecimens?

☐ A. Brown PI only. How will unauthorized access by others be prevented?

☒ B. Brown PI and other Brown research team members. How will unauthorized access by others be prevented?

Data will be stored on a Brown University protected drive. Unauthorized access by others will be prevented by password protecting the folder that the file is located in, as well as the file itself. All computer and biospeciment information will be de-identified and referred to by a subject identification number following collection. All electronic records will be maintained on password protected fileservers in a locked office, further protected by firewalls and other security procedures.

☐ C. Data will be shared with research collaborators external to Brown. This data sharing intent **must** be described as part of your consent process / form. Please describe how you will securely share / transfer the data outside of Brown:

*Note that an Outgoing Data Use Agreement **is required when sharing identifiable data external to Brown**. Please follow the procedures outlined here. You do not need to submit a copy of a DUA to the HRPP. This will be linked by the ORI administratively.*

4. Where will the study data / biospecimens be stored?

☒ Departmental server
☐ CIS managed server
☐ Stronghold
☐ Campus file storage
☐ REDCap
☒ Other. Please describe:

Data collected via Qualtrics will be kept within Brown University Qualtrics.

5. If traveling with your data, describe how your data will be secured.

NA

6. For how long will you retain identifiable data / biospecimens? How will you destroy identifiers when no longer required?

We will be deleting the file connecting the participant ID to their study code at the completion of the study.

Text Messaging (only complete if instructed above.)

1. Are you using the current text messaging service available on the device?

☐ Yes ☒ No	If "no," you must also complete the Mobile App section.

2. Whose device will be used? ☐ Participant's personal phone ☐ Brown-issued phone NA

3. Content of messaging: (If brief, insert here; otherwise, please provide as an attachment) NA

4. Is the communication one-way or two-way? ☐ One-way ☐ Two-way NA

Mobile App (only complete if instructed above.)

1. Name of the mobile app: NA

2. Has this site / tool been reviewed by CIS IT Security? NA

☐ Yes ☐ No	If "no," answer the following: a. Who created the site / tool (vendor name or off the-shelf app creator name)? b. Where is it hosted? c. Is the site / tool scanned for security vulnerabilities? ☐ Yes ☐ No d. What version of software is being used, if applicable: ☐ N/A or e. How are the data encrypted?

3. Whose device will be used? ☐ Participant's personal phone ☐ Brown-issued phone NA

If Participant's person phone:

a. How is the app downloaded to the device?

b. Is a password or PIN required for the app? ☐ Yes ☐ No

4. Will data be stored on the device for any period of time? NA

☐ Yes ☐ No	a. If "yes," please describe (i.e., queue on phone and then transmitted to server): b. Is the app data encrypted on the device? ☐ Yes ☐ No

5. Device features mobile app can access ☒ N/A

- ☐ Device ID and call information
- ☐ Identity
- ☐ Contacts
- ☐ Camera
- ☐ SMS or chat
- ☐ Storage
- ☐ Device and application history
- ☐ Phone
- ☐ Photo / media / files
- ☐ Microphone
- ☐ Location
- ☐ Other; please describe:

6. Will a third-party have access to research data through this app? ☐ Yes ☐ No NA

7. Is data transmitted by the device? NA

☐ Yes ☐ No	If "yes," how is it encrypted in transit?

8. Are phone numbers or mobile identification numbers stored with the data? ☐ Yes ☐ No NA

Web-based Other (only complete if instructed above.)

1. Name of the site / tool: NA	
2. Has this site / tool been reviewed by CIS IT Security? NA	
☐ Yes ☐ No	If "no," answer the following: a. Who created the site / tool (vendor name or off the-shelf app creator name)? b. Where is it hosted? c. Is the site / tool scanned for security vulnerabilities? ☐ Yes ☐ No d. What version of software is being used, if applicable: ☐ N/A or e. How are the data encrypted?
☐ Yes ☐ No	If "no," answer the following: a. Who created the site / tool (vendor name)? b. Where is it hosted? c. Is the site / tool scanned for security vulnerabilities? ☐ Yes ☐ No d. What version of software is being used, if applicable: ☐ N/A or e. How are the data encrypted?
3. Is informed consent being obtained via this site / tool? NA	
☐ Yes ☐ No	If "yes," how is re-identification prevented?
4. Does the technology allow for the explicit exclusion of the collection of IP address of the participant's connection? NA	
☐ Yes ☐ No	If "yes," will you use this option to exclude the collection of IP address? ☐ Yes ☐ No

Brown Qualtrics: CIS has pre-vetted Brown Qualtrics for collection/storage of up to Risk Level III data. Qualtrics is the preferred survey tool for all Brown research data collection.

REDCap: Brown does not currently have its own instance of REDCap. Access to REDCap through a Lifespan collaborator must be explicitly identified.

Data collection: The expectation is that data collection *devices* will only store data during active data collection. Data must then be transitioned to more secure long-term storage solutions.

Departmental/CIS managed servers: If data are collected/entered directly onto a Departmental or CIS managed server, **you must ensure** that the server meets the security standards described in the Minimum Security Standards for Servers based on the Risk Level of the data identified in 1D.

PART VIII. INTERNATIONAL RESEARCH

1. Does the research involve human subjects activities outside of the United States?

☐ Yes ☒ No

If "yes," please list the countries:

If "no," you are not required to complete this Part of the application. Proceed to PART IX. ATTACHMENTS.

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b. What is the status of permissions / approvals from local ethics boards or committees?

☐ Received; please append to this Application.

☐ Pending

☐ N/A. Please explain:

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c. Will this research take place in a non-public setting (including a school, hospital or clinic) for which local permission is required? ☐ Yes ☐ No

If "yes," please append a letter(s) of support or permission(s) to this Application.

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d. Describe how you have taken into account any social, political, or cultural issues that may impact participants.

☐ I have reviewed the current version of the *International Compilation of Human Research Standards* and agree to abide by relevant local laws, regulations and guidelines.

☐ I have reviewed the *General Data Protection Regulations guidance* and will abide by any requirements.

☐ I have reviewed ORI's export control guidance on international travel, international collaborations, and international shipping (*if applicable*)

Proceed to PART IX. ATTACHMENTS

PART IX. ATTACHMENTS

Please attach the following materials to this Application for Full Board / Expedited IRB Review, as applicable.

Incl.	N/A	
☒	☐	Informed consent documents / scripts
☒	☐	Data collection materials (questionnaires, surveys, interview scripts, etc.)
☐	☒	Permissions, approval documents, and/or support letters identified in PART VII.
☒	☐	Recruitment materials (emails, flyers, letters, scripts, posters, brochures, etc.)
☐	☒	Application for IRB Authorization Agreement
☐	☒	Data Use Agreement from data provider(s)
☐	☒	HIPAA Authorization
☒	☐	Data Safety Monitoring Plan
☒	☐	Other: See complete list below

PART X. CONFLICT OF INTEREST

The *Brown University Conflict of Interest Policy for Officers of Instruction and Research* *("COI Policy")* defines the term "Investigator" as "the project director or principal investigator and any other person, regardless of title or position (e.g., full or part-time faculty member, staff member, student, trainee, collaborator, or consultant), who is **responsible** for the **design, conduct, or reporting** of sponsored research."

Using this definition of "Investigator," please ensure that all Investigators on this protocol answer questions (1) and (2) below. Attach additional sheets for any Investigators who are not the PI; additional sheets are available on the HRPP website.

1. Have you completed a conflict of interest disclosure (i.e. *COI Reporting Form*) within the past 12 months and is it accurate and up-to-date as of the time of this submission, as required by Brown's COI Policy? (You may access the InfoEd system here to confirm.)

☒ Yes ☐ No	If "no," please do so before submitting this Application

2. Do you have a significant financial interest (SFI) that is related to this research protocol?
"Related" could mean the research involves products, technology, intellectual property, or services made, owned, or provided by the entity/ies in which you have an SFI. It could also mean that the SFI could be affected by the proposed research or its results.

☐ Yes ☒ No	If "yes," please identify the SFI and explain the relatedness:
☐	Additional COI sheets for Investigators are attached to this Application. ***(Required for Advisors)***

PART XI. INVESTIGATOR & FACULTY ADVISOR AGREEMENTS / PRINCIPAL INVESTIGATOR RESPONSIBILITIES

A. Conduct of the Research

1. I accept responsibility for the ethical conduct of this research and protection of participants as set forth in the Belmont Report, Common Rule, and Brown University policies.
2. I accept responsibility for ensuring this research is conducted in accordance with:
   a) Sound research design and methods;
   b) The parameters of the research plan and activities described in this Application;
   c) The applicable terms of the grant, contract, or other signed funding agreements;
   d) Applicable laws and regulations, including those protecting the rights, safety and welfare of human subjects.
3. I certify that I am, or my faculty advisor is, sufficiently qualified by education, training and experience to assume responsibility for the proper conduct of this research. I accept responsibility for ensuring that all member of the research team have or will complete human
4. subjects CITI training before any work with participants or identifiable data / biospecimens begins.
5. I accept responsibility to personally conduct and/or directly supervise this research. I certify that I have sufficient time and resources to properly conduct and/or supervise this research.

B. Ensuring and Maintaining Compliance

1. I will comply with relevant regulatory and institutional reporting requirements, including Brown University's *Reportable Events Policy*.
2. I understand that it is my responsibility to ensure that any research personnel, including myself, responsible for the design, conduct or reporting of the research declares any conflicts of interest related to this research. I will ensure that any changes that impact my or other research personnel's answers to the questions in PART IX. Conflict of Interest, are reported promptly to Brown's HRPP.
3. I will ensure that prospective agreement and/or informed consent is obtained and a copy is provided to participants, when appropriate.
4. If there are changes to the research described in this Application for Full Board / Expedited IRB Review that may impact the study's classification as Full Board or Exepdited research, I will promptly notify the Brown HRPP of such changes.
5. I will notify the Brown HRPP when I have completed all activities involving human subjects or identifiable participant data or identifiable biospecimens.
6. I will maintain approval, as applicable, with collaborative parties, including approvals from other countries or jurisdictions.
7. I will cooperate with any post-approval monitoring or auditing of study activities and/or study records as requested and/or required by the Brown ORI, the Brown IRB, funding entities, sponsors, and/or any federal or state regulatory agencies.

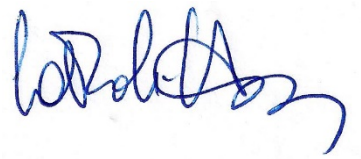
C. Study records, Reports and Documentation

1. I will maintain all research protocol materials and consent materials for the duration of this study.
2. I will maintain research records for at least three years following the end of this research, or for a longer length of time if specified in applicable regulations or sponsor requirements. I will take measures to prevent accidental or premature destruction of these records.
3. I will abide by all terms of any Data Use Agreement (or equivalent agreement) related to this study, including those agreed to electronically (through an online attestation).
4. I will ensure that the data security measures for acquisition, collection, transfer and use of study data described in PART VI. of this Application are adhered to by all members of the research

team.

By my signature below, I certify that I have read and agree to uphold all of you and/or Advisor Responsibilities in PART XI.

Principal Investigator signature: **Date:** 8/30/2019



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An Advisor's signature is required for all graduate/medical student projects

Advisor certifies the following: Advisor has read the complete protocol, approves this project, and will remain available to advise the student throughout the course of the proposed human subjects research, or will transfer responsibilities to another Advisor if unable to advise for the entirety of the project.

Advisor's name (please print):

Advisor's signature: **Date:** Click here to enter a date.

For IRB Use Only

Signature of the IRB:

Date of IRB approval: Click here to enter a date.