YALE UNIVERSITY
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Biomedical Research
100 FR1 (2015-2)

SECTION I: ADMINISTRATIVE INFORMATION

Title of Research Project: Fyn Kinase Inhibitors and Alcohol Drinking			
Principal Investigator: Suchitra Krishnan-Sarin, PhD		**Yale Academic Appointment:** **Professor**	
Department: Psychiatry			
Campus Address: 34 Park Street, Suite S-208, New Haven, CT 06519			
Campus Phone: 974-7595	**Fax:** 974-7606	**Pager:**	**E-mail:** suchitra.krishnansarin@yale.edu
Protocol Correspondent Name & Address (*if different than PI*): Tricia Dahl, 34 Park Street, Suite S-215, New Haven, CT 06519			
Campus Phone: 974-7599	**Fax:** 974-7606	**E-mail:** tricia.dahl@yale.edu	
Yale Cancer Center CTO Protocol Correspondent Name & Address (*if applicable*):			
Campus Phone:	**Fax:**	**E-mail:**	
Business Manager:			
Campus Phone :	**Fax :**	**E-mail**	
Faculty Advisor:(required if PI is a student, resident, fellow or other trainee) ☐ **NA**		**Yale Academic Appointment:**	
Campus Address:			
Campus Phone:	**Fax:**	**Pager:**	**E-mail:**

Investigator Interests:

Does the principal investigator, or do any research personnel who are responsible for the design, conduct or reporting of this project or any of their family members (spouse or dependent child) have an incentive or interest, financial or otherwise, that may affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? Note: The Principal Investigator (Project Director), upon consideration of the individual's role and degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

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See Disclosures and Management of Personal Interests in Human Research
http://www.yale.edu/hrpp/policies/index.html#COI

☐ Yes ☐ No

Do you or does anyone on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an invention) or copyright (exclusive rights to an original work) interests related to this research protocol?

☐ Yes ☐ No

If yes to either question above, list names of the investigator or responsible person:

The Yale University Principal Investigator, all Yale University co-investigators, and all Yale University individuals who are responsible for the design, conduct or reporting of research must have a current financial disclosure form on file with the University's Conflict of Interest Office. Yale New Haven Hospital personnel who are listed as co-investigators on a protocol with a Yale University Principal Investigator must also have a current financial disclosure form on file with the University's Conflict of Interest Office. If this has not been done, the individual(s) should follow this link to the COI Office Website to complete the form: http://www.yale.edu/coi/

NOTE: The requirement for maintaining a current disclosure form on file with the University's Conflict of Interest Office extends primarily to Yale University and Yale-New Haven Hospital personnel. **Whether or not they are required to maintain a disclosure form with the University's Conflict of Interest Office, all investigators and individuals deemed otherwise responsible by the PI who are listed on the protocol are required to disclose to the PI any interests that are specific to this protocol.**

SECTION II: GENERAL INFORMATION

1. **Performing Organizations:** Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:

a. Internal Location[s] of the Study:

☐ Magnetic Resonance Research Center (MR-TAC)
☐ YCCI/Church Street
☐ Yale Cancer Center/Clinical Trials Office
☐ Yale Cancer Center/Smilow YCCI/Keck
☐ Yale-New Haven Hospital Yale-New Cancer Data Repository/Tumor Registry
☐ Yale University PET Center
☐ Research Unit (CSRU)
☒ (CTO) YCCI/Hospital Research Unit (HRU)
☐ Laboratories
☐ Haven Hospital—Saint Raphael Campus

Specify Other Yale Location:

b. External Location[s]:

☒ APT Foundation, Inc.
☒ Connecticut Mental Health Center
☒ Haskins Laboratories
☒ John B. Pierce Laboratory, Inc.

☐ Clinical Neuroscience Research Unit (CNRU) ☐ Veterans Affairs Hospital, West Haven ☐ Other Locations, Specify: SATU International Research Site

(Specify location(s)):

c. Additional Required Documents *(check all that apply)*: ☐ N/A

☒ *YCCI-Scientific and Safety Committee (YCCI-SSC) Approval Date:
☐ *Pediatric Protocol Review Committee (PPRC) Approval Date: *YCC
☐ Protocol Review Committee (YRC-PRC) Approval Date:
☐ *Dept. of Veterans Affairs, West Haven VA HSS Approval Date: *Radioactive
☐ Drug Research Committee (RDRC) Approval Date:
☐ YNHH-Radiation Safety Committee (YNHH-RSC) Approval Date:
☒ Yale University RSC (YU-RSC) Approval Date: Magnetic Resonance Research
☐ Center PRC (MRRC-PRC) Approval Date: *Nursing Research Committee
☐ Approval Date:
☐ YSM/YNHH Cancer Data Repository (CaDR) Approval Date:
☐ Dept. of Lab Medicine request for services or specimens form
Imaging on YNHH Diagnostic Radiology equipment request form (YDRCTO request) found at http://radiology.yale.edu/research/ClinTrials.aspx)

Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.

2. **Probable Duration of Project:** State the expected duration of the project, including all followup and data analysis activities. 3 years

3. **Research Type/Phase: (Check all that apply)**

a. **Study Type**

☒ Single Center Study
☐ Multi-Center Study

Does the Yale PI serve as the PI of the multi-site study? Yes ☐ No ☒

☐ Coordinating Center/Data Management ☐ Other:

b. **Study Phase** ☐ **N/A**

☐ Pilot ☐ Phase I ☒ Phase II ☐ Phase III ☐ Phase IV

☐ Other (*Specify)*

4. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:

☒ Clinical Research: Patient-Oriented ☐ Clinical Research: Outcomes and
☒ Clinical Research: Epidemiologic and Behavioral Health Services
☐ Translational Research #1 (“Bench-to- ☐ Bedside”) ☐ Interdisciplinary
☐ Research

Translational Research #2 ("Bedside-to-Community") Community-Based Research 5. Is this study a clinical trial? Yes ☒ No ☐

NOTE the current ICMJE (International Committee of Medical Journal Editors) definition of a clinical trial: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and processof-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events" If yes, where is it registered?

Clinical Trials.gov registry ☒
Other (*Specify*)

*Registration of clinical trials **at their initiation** is required by the FDA, NIH and by the ICMJE.*

For more information on registering clinical trials, including whether your trial must be registered, see the YCCI webpage, http://ycci.yale.edu/researchers/ors/registerstudy.aspx or contact YCCI at 203.785.3482)

1. Does the Clinical Trials Agreement (CTA) require compliance with ICH GCP (E6)? Yes ☒ No ☐

7. Will this study have a billable service? *A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either YaleNew Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects*.

Yes ☐ No ☒

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

8. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes X No ___ If *Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.*

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? Yes

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b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? No

c. Will a novel approach using existing equipment be applied? No

If you answered “no” to question 8a, or "yes" to question 8b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. ***By signing this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH****.*

SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

1. **Funding Source:** Indicate all of the funding source(s) for this study. Check all boxes that apply. Provide information regarding the external funding source. This information should include identification of the agency/sponsor, the funding mechanism (grant or contract), and whether the award is pending or has been awarded. Provide the M/C# and Agency name (if grantfunded). If the funding source associated with a protocol is “pending” at the time of the protocol submission to the HIC (as is the case for most NIH submissions), the PI should note “Pending” in the appropriate section of the protocol application, provide the M/C# and Agency name (if grant-funded) and further note that University (departmental) funds support the research (until such time that an award is made).

PI	Title of Grant	Name of Funding Source	Funding	Funding Mechanism
John Krystal (Center PI); Suchitra Krishnan-Sarin (Project PI)	Center for Translational Neuroscience on Alcoholism	NIAAA	☒ Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For Profit ☐ Other	☐ Grant-M# P50AA12870 ☐ Contract# ☐ Contract Pending ☐ Investigator/Department Initiated ☐ Sponsor Initiated ☐ Other, Specify:

IRB Review fees are charged for projects funded by Industry or Other For-Profit Sponsors. Provide the Name and Address of the Sponsor Representative to whom the invoice should be sent. ***Note: the PI’s home department will be billed if this information is not provided.***

Send IRB Review Fee Invoice To:

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Name:
Company:
Address:

Research Team: List all members of the research team. Indicate under the affiliation column whether the investigators or study personnel are part of the Yale faculty or staff, or part of the faculty or staff from a collaborating institution, or are not formally affiliated with any institution. **ALL members of the research team MUST complete Human Subject Protection Training (HSPT) and Health Insurance Portability and Accountability Act (HIPAA) Training before they may be listed on the protocol. See NOTE below.** *****See IRES for the list

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NOTE: The HIC will remove from the protocol any personnel who have not completed required training. A personnel protocol amendment will need to be submitted when training is completed.

SECTION IV: PRINCIPAL INVESTIGATOR/FACULTY ADVISOR/ DEPARTMENT CHAIR AGREEMENT

As the **principal investigator** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- I assume full responsibility for the protection of human subjects and the proper conduct of the research.
- Subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- All members of the research team will be kept apprised of research goals.
- I will obtain approval for this research study and any subsequent revisions prior to my initiating the study or any change and I will obtain continuing approval of this study prior to the expiration date of any approval period.
- I will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set by the University and qualify to serve as the principal investigator of this project or have acquired the appropriate approval from the Dean's Office or Office of the Provost, or the Human Subject Protection Administrator at Yale-New Haven Hospital, or have a faculty advisor.
- I will identify a qualified successor should I cease my role as principal investigator and facilitate a smooth transfer of investigator responsibilities.

PI Name (PRINT) and Signature _____ Date _____

As the **faculty advisor** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- This project has scientific value and merit and that the student or trainee investigator has the necessary resources to complete the project and achieve the aims.
- I will train the student investigator in matters of appropriate research compliance, protection of human subjects and proper conduct of research.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- The student investigator will obtain approval for this research study and any subsequent revisions prior to initiating the study or revision and will obtain continuing approval prior to the expiration of any approval period.
- The student investigator will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set forth by the University and qualify to serve as the faculty advisor of this project.
- I assume all of the roles and responsibilities of a Principal Investigator even though the student may be called a PI.

_____ _____

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Advisor Name (PRINT) and Signature Date

Department Chair's Assurance Statement

Do you know of any real or apparent institutional conflict of interest (e.g., Yale ownership of a sponsoring company, patents, licensure) associated with this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC.)
☐ No

As Chair, do you have any real or apparent protocol-specific conflict of interest between yourself and the sponsor of the research project, or its competitor or any interest in any intervention and/or method tested in the project that might compromise this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC)
☐ No

I assure the HIC that the principal investigator and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research trial. I also assure that the principal investigator has departmental support and sufficient resources to conduct this trial appropriately.

_____ _____ _____

Chair Name (PRINT) and Signature Date

_____

Department

YNHH Human Subjects Protection Administrator Assurance Statement

Required when the study is conducted solely at YNHH by YNHH health care providers.

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As Human Subject Protection Administrator (HSPA) for YNHH, I certify that:

- I have read a copy of the protocol and approve it being conducted at YNHH.
- I agree to notify the IRB if I am aware of any real or apparent institutional conflict of interest.
- The principal investigator of this study is qualified to serve as P.I. and has the support of the hospital for this research project.

_____ _____ _____

YNHH HSPA Name (PRINT) and Signature Date

SECTION V: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.
Alcoholism is a disorder that is mediated by multiple genes and environmental factors. Existing medications like naltrexone and acamprosate are not efficacious in all drinkers. Therefore, we need to develop new and effective strategies to treat alcoholism. Development of medications for this disorder should be based on our understanding of the behavioral and neurochemical mechanisms mediating alcohol reward and drinking. There is extensive preclinical evidence suggesting that glutamatergic circuits are involved in the acute behavioral effects of alcohol as well as in alcohol tolerance and withdrawal. This project will evaluate the effect of an agent that indirectly modulates NMDA-R signaling without directly antagonizing NMDA-Rs on alcohol drinking. Specifically, we will test the influence of Saracatinib, a Src/Fyn protein tyrosine kinase inhibitor that modulates NMDA-R signaling via Fyn inhibition.

Primary Aim 1: To evaluate the effects of Saracatinib (125 mg/day) versus placebo on alcohol craving.
Primary hypothesis 1a: Saracatinib (125 mg/day) will reduce craving for alcohol after exposure to the priming drink of alcohol, and during the free-choice drinking period, when compared with placebo.

Primary Aim 2*:* To evaluate the effects Saracatinib (125 mg/day) versus placebo on alcohol drinking
Primary hypothesis 1b: Saracatinib (125 mg/day) will reduce number of drinks consumed during the free-choice drinking period, when compared with placebo.

Secondary Aim 1: To evaluate the effects of Saracatinib (125 mg/day), versus placebo, on alcohol-induced stimulation and sedation during the ADP.

Secondary Aim 2: To examine the tolerability of Saracatinib (125 mg/day) in heavy drinkers.

Exploratory Aims: To explore predictors of Saracatinib response. The predictors have been selected based on findings from our earlier work and include behavioral outcomes like impulsivity, habit and deficiency in loss-avoidance learning, genetic markers related to alcohol drinking or glutamate and Src/Fyn systems, and neural networks/markers identified using multimodal neuroimaging.

2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.
This novel project will conduct the first test of whether human alcohol consumption may be altered by targeting an intracellular signaling protein implicated in alcohol dependence, Fyn kinase.

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Alcohol-seeking behaviors involve complex interactions between neurotransmitters like dopamine and opioids that underlie reward in the nucleus accumbens and engage habits in the dorsal striatum, and glutamatergic pathways from the prefrontal cortex and basolateral amygdala to the nucleus accumbens that are involved in the reinstatement of alcohol drinking (e.g. Koob and Volkow, 2010).

Using the alcohol drinking paradigm (ADP) that is being used in the current study, we showed in our earlier studies that naltrexone reduced drinking in FHP heavy drinkers (Krishnan-Sarin et al., 2007) but did not reduce alcohol craving. In subsequent studies we observed that a low dose (20 mg) of the NMDA receptor (NMDA-R) antagonist, memantine, reduced alcohol craving, but not drinking (Krishnan-Sarin et al., in press). Further, the higher dose of memantine (40 mg) reduced alcohol craving, but increased drinking and alcohol-induced stimulation among those who were more behaviorally impulsive. Therefore, we hypothesized that a more nuanced approach of altering NMDA-R signaling, that reduces alcohol drinking and craving without increasing positive alcohol effects, might be needed. In an ongoing project, we are studying the potential synergy of low dose memantine (which reduced craving) with 50 mg naltrexone (which reduced drinking; HIC protocol 1005006779). In this project, we propose to examine the effects of an agent that indirectly modulates NMDA-R signaling without directly antagonizing NMDA-Rs. Specifically, we will test the influence of Saracatinib on drinking behaviors.

Saracatinib is a Src/Fyn protein tyrosine kinase inhibitor that modulates NMDA-R signaling via Fyn inhibition. Importantly, this agent could target pathways in the corticostriatal circuitry where NMDA-upregulation may emerge as a consequence of heritable or alcohol-induced (Martinez et al 2005) reductions in dopamine D2 receptor signaling and subsequent upregulation of Fyn (Hattori et al 2006). Saracatnib or AZD0530 is an inhibitor of Src Family kinases, blocking Src, Fyn, Yes and Lyn, with 2- 10 nM potency. At 10-100 fold higher concentrations the compound also inhibits Abl family kinases, but there is no detectable activity in this concentration range against other kinase families, including c-kit, Csk and PDGFR. An in vitro screen of AZD0530 against 307 different pharmacological targets, showed ≥50% inhibition of binding or function of only 9 targets at 10 μM and one additional enzyme at 100 μM (unpublished data from Astra Zeneca). It is estimated that the IC50 values for all 10 non-SFK targets are likely to be in the region of at least 3-100 μM (compared to a Fyn IC50 of 0.005 μM), and so any inhibition is unlikely to be clinically significant.

AZD0530's specific inhibition of Fyn and SFKs have led to its development as therapy for solid tumors, because Src family kinases regulate tumor cell adhesion, migration and invasion, and also regulate proliferation. Clinical tolerability and oral bioavailablity have been demonstrated, but Phase II studies have demonstrated limited benefit as a single agent in specific oncological indications. For tumor cell migration and for oncological applications, it is estimated that >98% kinase inhibition is required so clinical doses have targeted concentrations >20-fold above the kinase IC50, in the 200-1000 nM concentration. Saracatinib has been studied in healthy individuals and patients with solid tumors (Dalton et al., 2010; Baselga et al., 2010; Fujisaka et al., 2013; Hannon et al., 2012) and in older patients with mild-moderate Alzheimers disease. Steve Strittmatter and colleagues from Yale recently conducted a 4-week Phase Ib multiple ascending dose, randomized, double-blind, placebo-controlled trial of AZD0530 in AD patients with Mini-Mental State Examination (MMSE) scores ranging from 16 to 26 (Nygaard et al., 2015). They observed that the 100 and 125 m doses of AZD were generally safe and well tolerated that these doses achieved CSF drug levels corresponding to brain levels that rescued memory deficits in transgenic mouse models. Moreover, one-month treatment with AZD0530 had no significant effect on clinical efficacy measures or regional cerebral glucose metabolism.

We recently completed a pilot study to evaluate the preliminary safety, tolerability and effects of the combined administration of AZD0530 (125 mg/day) and alcohol (HIC# 0602001068). Five heavy

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social drinkers (mean age = 26 ± 2.2) completed a baseline inpatient alcohol administration session and a second alcohol administration session after taking AZD0530 for 8 days (to reach steady state levels). During each alcohol administration session, subjects received successive doses of alcohol designed to raise their blood alcohol levels to 80 mg/dl. We observed the drug was safe and tolerable over the 8-day outpatient administration period. Only mild adverse events were reported by two subjects and no other adverse events were reported. Complete blood counts and serum chemistries were similar across all pre- and post- drug and alcohol time points, with all values within the appropriate reference range, with only glucose and calcium slightly elevated. As expected, given the acute effects of alcohol, changes in heart rate and systolic blood pressure were seen within each drinking session, as were changes in blood alcohol levels and urine alcohol levels. No session related differences were observed indicating no effect of AZD0530 on these parameters. Furthermore, the results of the cognitive measures suggest that AZD0530 does not have an independent effect on cognitive performance or in combination with alcohol, but that alcohol affects these measures as expected. We also observed a promising signal on the alcohol intoxication assessment (reduced stimulation, intoxication, feel good drug effects) following exposure to alcohol. Thus, this study of 125 mg of AZD0530 given to healthy social drinking controls over 8 days in an alcohol administration session, raising blood alcohol to 80 mg/dl, did not result in any concerning changes in physiological or behavioral outcome measures and showed some promise for reducing alcohol related positive effects after exposure to alcohol.

The current proof-of-concept trial will test the effects of 125 mg dose of Saracatinib versus placebo on alcohol drinking behaviors using the ADP. We have determined that there is a need to focus on the 125 mg dose and that there is no advantage to testing a lower dose (50 mg) of the drug as proposed in the grant. The 50 mg dose is known to be inferior to the 125 mg in terms of Src family target coverage both peripherally and centrally and therefore the pharmacologic effect of the 50 mg dose should not be superior to the 125 mg dose. In addition, this will also allow Astra Zeneca to provide us with the 125 mg and matching placebo over a 3-year period without having to conduct additional stability testing over an extended period of time. Therefore, with the goal of getting this proof of principle trial done in an efficient manner, we will now focus on an adequately powered examination of the 125 mg dose, the dose we believe will be effective based on our preliminary data and knowledge of target engagement. Specifically, in the first three years of the grant, we will recruit 60 subjects and randomize 40 subjects to the 125 mg Saracatinib dose and 20 subjects to placebo. We anticipate a 10% drop out, leaving a final sample of 50 completers.

Thus, 60 non-treatment seeking, heavy drinkers will receive Saracatinib (0 or 125 mg/day), stratified by gender(to achieve 50 completers). Subjects will participate in a baseline ADP, followed by seven days of treatment with the study medication, and then a second ADP when they will take their last dose of study medication. Drinking behavior, alcohol craving and alcohol-induced stimulation/sedation will be measured in each ADP. Adverse events and drinking will be monitored during the treatment period, and at follow up. Potential behavioral predictors of Saracatinib response will obtained at baseline and post-treatment ADP, and the CTNA core assessment battery will be obtained at baseline.

2. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths**. Describe the setting in which the research will take place.

A between subjects design will be used to examine the effects of Saracatinib on alcohol craving, drinking and subjective responses in heavy drinkers. Non-treatment seeking heavy drinkers will

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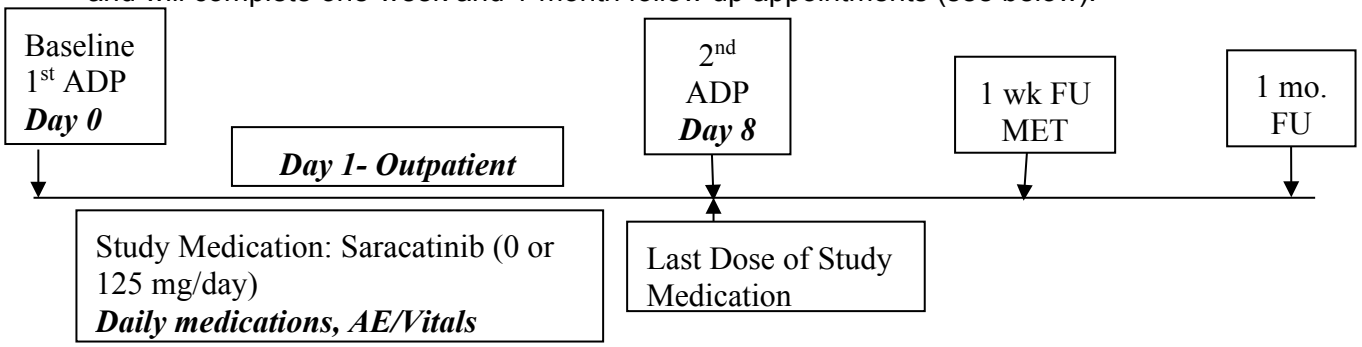
participate in two ADP sessions, occurring prior to and after eight days of medication treatment, and will complete one-week and 1-month follow up appointments (see below).



60 heavy drinkers, drinking on at least 4 days per week (20-65 weekly standard drinks for women and 30-70 for men) will complete this study. All subjects will be 21-50 years of age, physically healthy non-treatment-seeking heavy drinkers. Volunteers will be recruited through advertisements in local newspapers, postings in community locations (bars, coffee shops, grocery stores) and advertisements on free community TV channels. Subjects who do not meet the inclusion/exclusion criteria described below will be excluded.

The study will consist of six phases: 1) recruit subjects, obtain informed consent and evaluate eligibility for the study, 2) potentially eligible subjects will then receive a full physical examination to further determine eligibility. 3) If eligible they will participate in the baseline ADP in the Hospital Research Unit (HRU) of Yale New Haven hospital (YNHH), 4) they will be randomized to receive 0 mg or 125 mg/day of Saracatinib for a 7-10 day outpatient medication treatment period (depending on ADP scheduling) with daily medication/adverse event recording appts 5) they will complete the second ADP on the last medication day in the Hospital Research Unit (HRU) of Yale New Haven hospital (YNHH), after taking the last dose of study medication, 6) they will be scheduled for one-week and one-month follow up appointments. At the one week follow up, adverse events and drinking will be recorded and a clinical psychologist or social worker will provide a motivational enhancement session to motivate these non-treatment seeking drinkers to consider treatment. They will also be given the option to participate in an fMRI at the one-month follow-up appointment.

Justification for choice of Saracatinib dose: Saracatinib has been extensively studied in healthy individuals and patients with solid tumors (Dalton et al., 2010; Baselga et al., 2010; Fujisaka et al., 2013; Hannon et al., 2012) and more recently in patients with Alzheimers disease. For our "proof-of-concept" trial, we chose to use a higher dose of 125 mg, which have most commonly been tested in most trials (including those by our collaborator Dr. Strittmatter with AD patients) and shown to be safe. AZ has completed 7 Phase I studies in healthy volunteers and 5 Phase I studies in patients with solid tumors and advanced solid malignancies. AZD0530 doses of 60 mg to 185 mg were well tolerated, and although adverse events were more frequent at and above 250 mg, no major safety issues were identified at any of the doses studied. In patients with advanced cancer, the MTD was 175mg. In clinical oncology, the duration of AZD0530 treatment has been 2-12+ weeks in most trials. Importantly, with AZD0530 monotherapy no serious hematologic adverse events have been documented in doses lower than 175 mg. In the phase 1 trials, no major safety issues were identified in any of the doses studied, up to 250 mg daily. There is a potential for mild decreases in values for both white cell count and platelets at doses of above 125 mg, but these abnormalities never fell below reference levels, and levels normalized while patients remained on the drug. Thus, the dose proposed in this study, 125 mg, has not only been used safely in healthy volunteers and patients with cancer and AD, but have also been used for longer periods than the six days proposed in the current project.

We have completed a pilot trial (HIC # 0602001068) to examine if there any interactions between AZD0530 (at the highest dose proposed in the current project i.e. 125 mg/day) and a moderate dose of alcohol (0.08 mg/dl; similar to the blood alcohol levels usually achieved by drinkers in our ADP paradigms) following 8 days of AZD0530 treatment (similar to the current protocol) in social drinkers. Five subjects have participated and no unanticipated adverse effects have been noted; findings were presented to the FDA, and HIC.

Justification for length of treatment phase: We chose to study the effect of Saracatinib on alcohol drinking following eight days' pretreatment to allow sufficient drug to accumulate. Per information in the AZ brochure, the PK profile of Saracatinib supports once-daily oral administration, with peak levels seen 3-4 hours after administration, and a mean t1/2 of about 40 hours. This treatment period also allows us to generate clinically relevant information on adverse events observed beyond an acute dose in heavy drinkers.

Eligibility Determination, Physical Exam, Baseline Assessments

Intake appointments will be scheduled at the Substance Abuse Center in the Connecticut Mental Health Center, New Haven, CT. After informed consent, the intake battery will be administered to assess study eligibility. This appointment should approximately 1 ½ hours. The research assistant (RA) will schedule potentially eligible participants a physical exam with an APRN which will include a detailed medical history, EKG's, blood draws for routine CBC tests and hepatic, kidney and thyroid function tests as well as pregnancy tests from female participants (50cc). This appointment will last approximately 1 ½ hours. All tests and medical history will be reviewed by the PI and the study physician (Dr. Julia Shi). All participants will complete the core battery of assessments (See CTNA Clinical Core for details) and if they have consented for genetic studies, then blood samples will be drawn (30cc).

Medication Treatment Period and Blood Sample for Drug Levels

Participants will be randomized to receive Saracatinib 125 mg/day or placebo. Study medication will be dispensed by the Investigational Pharmacy of YNHH. During the first seven outpatient treatment days, participants will be asked to come in daily to take their medication. Adverse events, vitals, alcohol drinking and craving will also be monitored by the RA and study APRN. On the ADP day, participants will take their 8th dose of medication upon arrival to the Hospital Research Unit (HRU).

Alcohol Drinking Paradigm (ADP)

The procedures for both ADP's will be similar and will follow the NIAAA guidelines for administering alcohol to humans (http://www.niaaa.nih.gov/research/guidelines-andresources/administering-alcohol-human-studies). Participants will arrive at the HRU of YNHH at 10 am for ADP1 and 10:30am for ADP2. They will be told not to consume any alcohol after 10 pm on the earlier evening. We will assess breath alcohol levels and urine drug tests. If the breath alcohol levels are positive but below 0.05 and decreasing, the participant will be allowed to continue. If the urine drug tests are positive and/or breath alcohol levels are 0.05 or greater, the session will be rescheduled. The drinking sessions will be conducted in a private room in the HRU. Because caffeine is a weak phosphodiesterase inhibitor (Nehlig et al., 1992), caffeine users will be limited to one serving of their usual caffeinated beverage with lunch at 12 pm. This will also help to avoid caffeine withdrawal.

The ADP will start at 3 pm with the priming dose period, which will be followed by 3, 1 hour drinking periods (4-5 pm, 5-6 pm and 6-7pm) and will conclude at 7 pm (see Table 1 for detailed list of procedures).

a. *Exposure to Alcohol Cue:* Ten minutes prior to the start of the priming dose period (i.e. 2:50 pm), the RA will enter the participant's room with the alcohol dose and the preferred

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mixer. The RA will then proceed to mix the priming drink in front of the participant. When done, he/she will leave the drink on the table, instruct the participant not to drink the priming drink yet, and leave the room. At 2:59 pm the RA will reenter the room, ask the subject to report on how much they are craving alcohol, and then tell the participant that they have five minutes to consume the priming drink and will then again leave the room.

b. *Priming Dose (PD) Period:* This dose provided at 3 pm will raise blood alcohol levels to 0.03mg% and subjects will have 5 minutes to drink it. The purpose of the PD is to provide a standard dose for evaluating the effects of medications and to model a “lapse” situation. A 40-minute absorption period will follow during which the subjective and physiological effects of this priming dose of alcohol in combination with Saracatinib will be monitored. Using this procedure, we will be able to closely monitor changes in subjective effects of alcohol during the rising and falling limbs of the blood alcohol curve.
c. *Alcohol Self-Administration (SA) Periods:* Following the PD, there will be 3, 1-hour SA periods. During each SA period, participants will be offered a choice between 4 alcoholic drinks designed to raise BALS by 0.015 mg% of alcohol), or cash (equivalent to the price of each drink that is not consumed). The first SA period will begin at 4:00 pm when the RA will take 4 prepared drinks into the room along with a "tab" sheet worth $12. The participant will be informed that these 4 drinks will be available to him/her for the next 60 minutes (i.e. until 5 p.m.). S/he can either choose to drink or keep the money; each drink will cost $3. The money will be given to them the next morning before they leave the hospital. The second and third SA period will begin at 5 p.m. and 6 p.m. respectively will be similar to the SA period. Thus, participants can choose to consume up to 12 additional drinks over these 3 SA periods or receive up to $36. *Given the possibility that a participant could consume more alcohol during the ADP than what they might normally consume, all subjects will be closely monitored and the ADP will be stopped if 1) The subjects requests to stop, 2) In the judgment of trained research personnel conducting the study and monitoring subject behavior the study needs to be stopped, or 3) If the subject’s heart rate exceeds their maximum heart rate (220 minus age).*
d. *Beverage Content and Mixers:* The YNHH Investigational Pharmacy will calculate the alcohol dose based on the age, weight and gender of the participant (Watson, 1989) and deliver the doses to the HRU. The PD will raise blood alcohol levels to 0.03 mg% and each drink in the SA periods will raise BAL by 0.015 mg%. Alcoholic beverages administered during this study will consist of 1 part 80 proof liquor of the subject's choosing to 3 parts mixer chosen from a selection of equicaloric noncaffeinated noncarbonated beverages. The RA will prepare the drinks using the alcohol doses prepared by the YNHH pharmacy. Participants would have already chosen their mixers on an earlier day, thereby providing a closer approximation to their own drinking experiences. Frozen plastic cubes will be used to chill each drink without diluting them and the prepared drinks will be covered with saran wrap to avoid any evaporation of alcohol.

Assessments during and after the three choice periods:
During the second, third and fourth hour of the laboratory session, drinking behavior will be videotaped for later analysis, and craving and stimulation/sedation will be assessed every thirty minutes. **The frequency of assessments is limited to avoid interfering with the evaluation of drinking behavior.**

Blood samples to monitor blood alcohol levels will be obtained every 10 minutes during the PD and every 60 minutes thereafter (total of 5cc). On the morning after the second ADP, all of the laboratory tests that were completed at baseline will be repeated.

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End of ADP and overnight stay in HRU

After the end of the ADP, breath alcohol levels will be assessed until they fall below 0.02. Participants will be given dinner and will stay in the hospital overnight in order to ensure that 1) they do not continue to drink following exposure to alcohol in ADP, 2) they are safe and are not discharged while intoxicated and, 3) they are motivated to drink during the ADP since they will not have access to more alcohol later that same day. The next morning participants will complete assessments, blood draws (50cc), be given breakfast and then discharged.

Follow up interview

Subjects will participate in a 1-week follow-up appt. during which drinking over the past week and remaining adverse events will be monitored and a **blood sample to for safety laboratory tests will be obtained** (50cc). A brief motivational intervention will be provided by a licensed clinical psychologist or licensed social worker to encourage subjects to address their alcohol problem and an immediate referral to treatment will be made if they are interested. Even though participants are not seeking treatment for their drinking, we feel that their presence in the hospital provides a "teaching moment" to address their drinking behavior (Sinha et al., 1997). Subjects will also participate in a 1-month follow up during which information about their drinking since their prior appointment will be assessed.

Motivational intervention: A brief motivational intervention will be provided at the one-week follow-up to encourage the subject to address their alcohol problem. For Study 1, this session will be audiotaped if the subject agrees to sign consent for audiotaping. Tapes will only be used for training purposes and will be identified by code numbers and erased within 7 years of study completion. Even though the subjects participating in this study are not seeking treatment for their drinking, we feel that participation in this study is an opportunity to address their heavy drinking behavior. This brief motivational interview is based on the principles of Miller's Motivational Enhancement Therapy (MET) [133]. We will provide subjects with personalized feedback regarding their physical exam and laboratory findings, and on the influence of drinking on their health. We will also review with them the potential benefits of quitting drinking. We have found that similar brief advice resulted in decreases in alcohol drinking behavior and increased motivation to quit drinking [132]. If interested, an immediate referral to treatment will be made. Also, subjects will also be given the option of participating in one of our alcohol treatment studies.

Functional Magnetic Resonance Imaging

Described learning and/or memory paradigms will be used involving functional neuroimaging. If the participant agrees to complete this portion of the study, he/she will be carefully screened for contraindications to participation in an fMRI study. The screening process involves a phone interview with the participant coordinator who goes through a set of screening questions. At the scanner, before entering the scanner environment, the participants fill out a number of forms, including a MRI screening form and are questioned verbally by the experimenter giving informed consent. Following this screening, acceptable participants will lie on their back in the MRI machine for 2 – 3 hours.

During the fMRI session participants will be asked to perform a series of tasks involving learning, attention and memory similar to the ones they may complete during the behavioral assessment. Participants will be given detailed instructions by the experimenter explaining the task instructions. During some of the cognitive tasks participants may see various distracting images some of which will be photographs. The photographs that participants will see may cover a broad range of contents, including slides of flowers, children, families, people's faces, insects, animals, sports, and graphic slides similar to those that might be seen in a documentary of war footage (including

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mutilated individuals and dead bodies). Some people experience some degree of distress when viewing the most graphic pictures. If participants will be shown these graphic images they will have an opportunity to view some sample pictures to make certain that they understand the types of slides you will see during our study. Subjects will be able to elect which level of pictures they are willing to view and they will be informed that they can stop viewing the emotional pictures at any time.

Assessments

- Socio-demographic/General Information: At intake, demographic data, medical history and family psychiatric history will be assessed with interviews and self-report forms that provide data on age, race, socioeconomic status, marital status, educational and occupational levels, and significant medical history.
- SCID5: The Structured Clinical Interview for DSM5 (SCID5) (First et al., 2015) will be used to determine psychiatric diagnoses. This interview assesses DSM-V current and lifetime psychiatric diagnoses for anxiety, mood, psychotic, alcohol and substance use, somatoform, and eating disorders.
- Psychiatric Family History by Interview, the FHAM: As a source of pedigree information, the psychiatric status (including substance abuse/dependence, mood disorder, ASPD, etc.) of all first- and second-degree biological relatives will be obtained from each subject (including parents) using the family history method (FHAM-Family History Assessment Module) developed by COGA. DSM-IV criteria will be used to diagnose all biological family members.

  The FHAM is a reliable method for obtaining family history information and the specificity and sensitivity of the FHAM for the diagnosis of substance dependence is quite good (Rice et al., 1995). We will administer the FHAM in three steps. First, the structure of the family pedigree is drawn and reviewed with the informant. Next, psychiatric screening questions are asked about all relatives in the pedigree. Then, based on the responses to the screening questions, symptom checklists are completed for each first-degree relative, spouse, or other relative well known to the informant.
- Time-Line Follow-Back Assessment Method (TLFB: Sobell and Sobell, 1992): We will obtain quantity /frequency alcohol consumption for each day during 30-days prior to the study, the 7day outpatient medication and follow-up periods. The TLFB has good test-retest reliability and validity for verifiable events.
- Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar): A 10-item scale that assesses alcohol withdrawal signs (nausea/vomiting, tremor, headache, anxiety, agitation, orientation, sweating, and auditory, visual/tactile disturbances). It is used for the clinical management of alcohol withdrawal (Sullivan et al., 1989; Saitz and O'Malley, 1997) and in research (Sellers et al., 1991; Saitz et al.,1994).
- SAFTEE (Levine and Schooler, 1986). A tool for systematic assessment of adverse effects in clinical trials which includes 1) open-ended questions about any changes in physical or health problems, appearance, or activity level, and 2) yes/no responses to a specific list of symptoms (which correspond to anticipated adverse events associated with Saracatinib). For each symptom reported, the date of onset, severity (minimal, mild, moderate, severe), whether it was drug-related, and action taken, is recorded. The SAFTEE will be administered daily during the outpatient period, on the ADP day and at follow ups, to monitor and document rates of adverse events.
- Yale Craving Scale (YCS; Rojewski et al., under review; Krishnan-Sarin et al., in press)*:* The YCS is a five-item measure that employs a generalized Labeled Magnitude Scale (gLMS) to assess the intensity of craving for alcohol relative to the intensity of the strongest imaginable sensation. A psychometric evaluation of the YCS suggests that it evidenced: 1) good internal consistency, 2) scalar measurement invariance which makes it well suited for between group

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comparisons, and 3) concurrent relationships with drinking outcomes. The training exercise and the full 5-item YCS will be administered at baseline. During the ADP, the first item ("desire to drink right now") will be used at each time point. To confirm that use of the single item scale was psychometrically justifiable, we conducted a series of bivariate correlations (using data from 111 participants in earlier CTNA trials) between the YCS item assessing current alcohol craving, the total YCS score, and the Alcohol Urge Questionnaire (Bohn et al., 1995). The YCS single item on current craving correlated strongly with the YCS total score ($r=0.78$, $p<0.001$) and the AUQ ($r=0.59$, $p<0.001$). The YCS had superior psychometric properties relative to the AUQ in measuring craving in dependent and non-dependent drinkers.

- Biphasic Alcohol Effects Scale (BAES; Martin et al., 1993): This scale is used to measure the stimulant and sedative effects of alcohol and has been found to be sensitive to memantine and naltrexone's effects (Krishnan-Sarin et al., in press; Kranzler et al., 2000; Swift et al., 1994). We and others have validated the use of a shorter 6-item BAES (Rueger and King, 2013; Krishnan-Sarin et al., in press), which will be used.
- Alcohol Urge Questionnaire *(AUQ)* (Bohn et al., 1995)*:* The AUQ is an 8 item questionnaire, derived from a larger 49 item "Questionnaire of Alcohol Urges," that assesses *desire for a drink, expectation of positive effect from drinking,* and *inability to avoid drinking if alcohol was available.* The AUQ is a reliable and valid scale for the measurement of self-reported alcohol urges, and scores have been shown to be strongly related to alcohol dependence severity (as measured by ADS scores) and to cognitive preoccupation with alcohol. Its brevity and time frame for ratings (i.e., right now) makes it suitable for administration during the alcohol drinking period.
- Padua Inventory (Sanavio, 1988): consists of 60 items describing common obsessional and compulsive behavior and allows investigation of the topography of such problems in normal and clinical symptoms.
- The Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) (Carver and White, 1994; Gray, 1981) will assess behavioral activation and inhibition, which have been proposed as biological systems underlying behavior and affect. This measure has been shown to have good convergent, discriminant, and predictive validity in which it measures sensitivity rather than the person's typical experience. The BIS will be used to tap the component of impulsivity related to decreased sensitivity to the negative consequences of behavior.
- Barratt Impulsiveness Scale (BIS)(version 11) (Patton et al.,1995)*:* This 30 item self- report instrument provides a trait measure of impulsiveness and yields four scores: a total score, nonplanning activity, cognitive impulsivity, and motor impulsivity. Cronbach alpha coefficients range from .79-.83.
- Short Inventory of Problems (SIP) [153a]: A brief version of the Drinker Inventory of Consequences (DrInC), this is a 15-item test that measures physical, social, intrapersonal, impulsive, and interpersonal consequences of alcohol consumption. Subjects indicate whether each item occurred in the previous 12 months.
- Self-Rating of Effects of Alcohol (SRE) [153b]: This 5-item self-report contains questions related to the number of drinks required for up to four different effects early in the drinking career.
- Alcohol Expectancy Questionnaire (AEQ) [153d]: This 68-item questionnaire is an empirically derived self-report form designed to measure the degree to which individuals expect alcohol to produce a variety of general and specific positive effects.
- Negative Alcohol Expectancy (NAEQ) [153e]: This 60-item self-report provides assesses the current level of motivation to restrain/stop drinking and the constituent components of the current level of motivation. The NAEQ also identifies negative expectancies that may serve as a deterrent and represent motivation to stop or restrain drinking.

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- Sensation Seeking Scale (SSS) [153f]: 40-item self-report measures individual differences in optimal levels of stimulation and arrival.
- Depression Anxiety Stress Scale (DASS) [153g]: This 42-item self-report which measures the negative emotional states of depression, anxiety and stress.
- Childhood Trauma Questionnaire (Bernstein, et al. 1994): This 28-item self-report inventory that provides brief, reliable, and valid screening for histories of abuse and neglect. It inquires about five types of maltreatment - emotional, physical, and sexual abuse, and emotional and physical neglect. Also included is a 3 item Minimization/Denial scale for detecting falsenegative trauma reports.
- Drinking Motives Questionnaire (DMQ)(Cooper et al. 1992): contains 15 reasons why people might be motivated to drink alcoholic beverages. Participants rate on a 4-point scale how frequently each of the 15 listed reasons motivate them to drink alcoholic beverages. The measure yields three scale scores reflecting different motives for drinking alcohol.
- Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ)(Torrubia et al., 2001): consists of 48 yes-no items that included questions about habitual behaviours in response to cues of punishment, frustrative non-reward and novel stimuli as well as stimuli related to reward and approach-related tendencies.
- The Self-Report Habit Index (SRHI) (Verplanken & Orbell, 2003).: a 12-item index of habit strength developed on the basis of features of habit; that is, a history of repetition, automaticity (lack of control and awareness, efficiency), and expressing identity.
- UPPS Impulsive Behavior Scale (Whiteside & Lynam, 2003): a 45-item self-report questionnaire which distinguishes four facets of impulsivity: urgency, lack of premeditation, lack of perseverance, and sensation-seeking. It is scored on a 4-point scale from Strongly Agree to Strongly Disagree.
- Alcohol approach-avoidance task (AAT) (Wiers et al., 2009): We chose to use the AAT to assess automatic alcohol-affect associations since it has been used to show that heavy drinkers with a G allele of the OPRM1 gene have stronger automatic approach tendencies for alcohol. The AAT is an alcohol variety of the Approach Avoidance task developed by Rinck and Becker (2007) and measures approach bias for alcohol related stimuli. The subject pushes or pulls computer presented stimuli according to a content irrelevant feature, the tilt of the stimulus. Pushing the joystick gradually decreases stimulus size, while pulling gradually increases stimulus size. The zooming feature also generates a sense of approach or avoidance (Neumann, 2000). Reinout Wiers will provide consultation to our group on the AAT.
- The Implicit Association Test (IAT) (Greenwald et al., 2003): This task measures implicit affective asssociations with the alcohol. Using a computerized sorting task, individuals simultaneously classify two target conditions, ‘alcohol’ (ie., wine, beer, pint, vodka, whiskey, wine cooler) versus ‘soft drink’ (coca cola, juice, orange soda, root beer, sparkling water, 7- up) , and two affective categories relevant to drinking, ‘pleasant’ (ie. talkative, excited, cheerful, happy, funny, lively), versus ‘unpleasant’ (i.e., nauseous, listless, awful, miserable, sad, annoying). IAT effects will be calculated with the D600 scoring algorithm. Internal consistency for biploar alcohol-related affective IAT was .79 in (Houben, in press); the bipolar IAT predicted drinking above explicit measures and outperformed five other variants of the IAT(e.g., unipolar positive, uniplor negative IAT).
- Ratings of Drinking Behavior during the Alcohol Self-Administration Period: Subjects will be videotaped during the self-administration portion of the study. These videotapes will be rated by two independent raters who will indicate the onset and offset of each sip of alcohol. Using this data, dependent measures will be constructed including time until the first sip and average time to consume each drink.
- Psychophysiological Measures will include heart rate and blood pressure monitored using a Critikon Dinamap while skin temperature will be measured using Yellow Springs Instruments

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4600 precision thermometer. The cuff of the Dinamap will be on subject's dominant arm while the probe of will be attached to the middle finger of the subject's non-dominant arm. These data will be further used to examine the safety of combining Saracatinib with alcohol during the ADP.Blood Alcohol Levels: Blood samples will be stored at -4°C and will be analyzed using gas chromatographic techniques at the HRU laboratory.

- Patient-Reported Outcomes Measurement Information System (PROMIS Alcohol Use – Short Form): The PROMIS adult Alcohol Use item bank assesses drinking patterns (e.g. quantity and frequency of consumption, time spent drinking, episodes of heavy drinking), cue-based drinking (internal states and external contexts), cravings to drink (e.g. urgency, compulsivity), and efforts to control drinking (e.g. difficulty in limiting drinking) that indicate problematic drinking, particularly at the high end of the severity continuum. This bank, however, also provides good precision at moderate and low severity drinking levels (unlike many traditional measures of alcohol use and abuse). Although negative consequences are often associated with problem drinking, these consequences are assessed by a separate bank.
- Ethylglucuronide (EtG): The ethanol metabolite, ethylglucuronide (EtG) will be assayed in urine samples collected at the initial screening visit. EtG is a biomarker of recent alcohol consumption that provides an objective measure of abstinence (Jatlow et al-2014). We will use this to validate any self-report of heavy drinking within 80 hours of the appointment.
- Baseline Predictors of Drinking Behavior and Saracatinib response: We will focus on important predictors identified in earlier CTNA (impulsivity) and new predictors based on hypotheses regarding habitual behavior.
- ***Habit:*** One of the goals of our alcohol center which funds this proposal is to understand the relationship between goal-directed and habitual drinking and in earlier work we observed correlations between drinking and measures of habit. Thus, we will assess propensity for habit using The *Self-Report Habit Index (*SRHI; Verplanken and Orbell, 2003) is a 12-item index of the degree to which a behavior, in this case, alcohol drinking, is habitual based on features of habit (a history of repetition, automaticity, lack of control and awareness, efficiency), and expressing identity. In an earlier project we observed that this scale predicts alcohol problems, coping motives and medication response
- ***Learning in response to rewards and punishments****:* Alcohol dependence may be related to differential learning in response to positive and negative reward outcomes which may reflect differential dopamine sensitivity (i.e. those with higher D1 sensitivity may be more likely to learn from positive prediction errors, and those with higher D2 sensitivity may learn from the lack of expected reward). We will use the *Probabilistic Selection Task* (PST; Frank et al., 2004) to probe the tendency to learn from positive outcomes or reward (direct pathway) versus negative outcomes or punishment (indirect pathway. During training, participants are presented with pairs of symbols (AB, CD, EF) and asked to select one of the two stimuli. Feedback then indicates if the choice was correct or incorrect. Participants then learn to perform accurately (that is, learn to select A, C and E) by learning, which stimulus is associated with positive feedback (Go learning), and which one is associated with negative feedback (NoGo learning) or both. Participants are then presented with novel pairs of stimuli consisting of either an A or a B paired with each of the other stimuli (C through F, which on average had a 50% probability of positive feedback during training). If participants perform better on the pairs that include A then they learn better from positive feedback (Go learning). If they perform better on the pairs that include B, they learn better from negative feedback (NoGo learning).

3. Genetic Testing N/A ☐

A. Describe

i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned
We plan to use the samples to conduct pharmacogenomics studies related to the targeted neurochemical systems. For example, since we are exploring the use of Fyn kinase inhibitor, we will explore if medication response on drinking is related to the various FYN SNP's. The samples may also be stored for future research to examine genes related to alcohol drinking. For this we may look through genetic markers throughout the participant's genomes to identify one or more markers near, or within genes, influencing risk of alcohol drinking. We will decode all or part of the sequence of their DNA. We may also study genes that influence other behaviors and characteristics that may be related to alcohol drinking, such as smoking or impulsivity. We may also study other substances in the blood to help us learn more about genetic variation, gene effects, characteristics, and different population groups. The DNA will also be used to study differences in genes and sequences between individuals. Results from these genetic studies will be shared with public databases (per our data sharing agreement with NIH) but no personal identifying information will be shared.

ii. the plan for the collection of material or the conditions under which material will be received
The genetics samples will be collected at the time of physical exam from those who have consented to providing these samples. The samples will be stored in a -70 freezer prior to being de-identified and transported to Dr. Gelernter's lab.

iii. the types of information about the donor/individual contributors that will be entered into a database
The PI will retain identifiable information about each sample that is collected. The samples identified by code and stripped of any identifiers prior to being transported to Dr. Gelernter's lab.

iv. What are the methods to uphold confidentiality
The identifiers will be stored in a locked file cabinet at the PI's Office.

B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects? Genetic testing will only be conducted for research purposes and the results will be available to investigators on this study. Eventually, DNA extracted may be available to any qualified researcher; so will some of the genetic information from the DNA.

C. Is widespread sharing of materials planned? Yes

D. When and under what conditions will materials be stripped of all identifiers? The PI will retain identifiable information about each sample that is collected. The samples identified by code and stripped of any identifiers prior to being transported to Dr. Gelernter's lab. All samples are made anonymous prior to distribution. Some of the investigators may have commercial interests.

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E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials? Donors will be told during the consenting process that they can choose to withdraw their materials at any time.

i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)? Donors will be told to contact the PI directly to request withdrawal of participation

F. Describe the provisions for protection of participant privacy. The PI will retain identifiable information about each sample that is collected. The samples identified by code and stripped of any identifiers prior to being transported to Dr. Gelernter's lab.

G. Describe the methods for the security of storage and sharing of materials. The identifiers will be stored in a locked file cabinet at the PI's office.

4. Subject Population: Provide a detailed description of the types of human subjects who will be recruited into this study.

Approximately 90 male and female non-treatment seeking alcohol dependent volunteers will be recruited and evaluated for eligibility. We anticipate that 60 will complete the baseline ADP and be randomized to one of two medication groups. Based on our current experience, we anticipate a final completer sample of 50 heavy drinkers will complete the baseline ADP, the drug administration period and the second ADP.

5. Subject classification: Check off all classifications of subjects that will be <u>specifically recruited</u> <u>for enrollment</u> in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐ ☐ Children ☐ ☐ Healthy ☐ ☐ Fetal material, placenta, or dead fetus
☐ Non-English Speaking ☐ Prisoners ☐ Economically disadvantaged persons
☐ Decisionally ☐ Impaired Employees Pregnant women and/or fetuses
Yale Students Females of childbearing potential

NOTE: Is <u>this</u> research proposal designed to enroll children who are wards of the state as potential subjects? ☐ Yes ☒ No (If yes, see Instructions section VII #4 for further requirements)

6. Inclusion/Exclusion Criteria: What are the criteria used to determine subject inclusion or exclusion? <u>Inclusion criteria:</u>

1) Ages 21-50
2) Able to read English at 6th grade level or higher and to complete study evaluations
3) Meet DSM-5 criteria for alcohol use disorder assessed using the SCID and the psychological evaluation.
4) Average weekly alcohol consumption of 30-70 standard drinks for men and 20-65 drinks for women, thus, an average of 4.3 standard drinks/day for men and 2.87 standard drinks/day for women, which defines a high-risk drinker based on World Health Organization (WHO, 2000) Risk Levels

<u>Exclusion Criteria:</u>

1) Individuals who are seeking alcohol treatment or have been in alcohol treatment within the past 6 months

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2) Current DSM-V criteria for substance use disorder, except for tobacco use disorder or mild cannabis use disorder.
3) Positive test results at more than one baseline appointment on urine drug screens conducted for opiates, cocaine, benzodiazepines and barbiturates.
4) Psychotic or otherwise severely psychiatrically disabled; as determined by psychological evaluation.
5) Medical conditions that would contraindicate the consumption of alcohol including hepatic dysfunction.
6) Clinically significant abnormalities in screening laboratories, including Aspartate aminotransferase (AST) >3 times ULN; Alanine aminotransferase (ALT) > 3 times ULN; Total bilirubin >1.5 times ULN; Serum creatinine >2.0 times ULN, and in TFT's (Using values in the "mild- (Grade 1)" range listed on page 6 of the 2007 FDA Guidance for Industry brochure).
7) Any neurological trauma or disease, delirium, or hallucinations, hepatic, cardiovascular, metabolic, endocrine or gastrointestinal disease. Clinically significant or unstable medical conditions, including uncontrolled hypertension or diabetes, or significant cardiac, pulmonary, renal, hepatic, endocrine, or other systemic diseases which in the opinion of the study physician and PI, may put the patient at risk because of participation in the study.
8) Anemia or Neutropenia (defined as absolute neutrophils count of <1500/microliter) or Thrombocytopenia (defined as platelet count <150,000/microliter). 9) Self-reporting of GI bleeding
10) Current blood clotting or bleeding disorder, or significantly abnormal PT or PTT at screening.
11) History of interstitial lung disease
12) Current use of any strong CYP3A4 inhibitors (because Saracatinib is CYP3A4 inhibitor) including: atazanavir, indinavir, ritonavir, saquinavir, nelfinavir, ketoconazole, itraconazole, clarithromycin, telithromycin, and nefazodone, rifampicin, phenytoin, phenobarbital, and carbamazepine; certain CYP3A4 substrates including colchicine, cyclosporine, disopyramide, fluticasone, quinidine, vinblastine, vincristine or phosphodiesterase inhibitors like sildenafil, tadalafil, and vardenafil.
13) Regular use of psychoactive drugs including anxiolytics and antidepressants and other medications (for e.g. typical neuroleptics, narcotic analgesics, antiparkinsonian medications, systemic corticosteroids, medications with significant central anticholinergic activity, or drugs with psychotropic activity or drugs which cause excessive sedation).
14) Current use of warfarin
15) Subjects with CIWA-r scores of 8 or greater, or a history of significant repeated alcohol withdrawals, to reduce the likelihood of withdrawal symptomatology if subjects reduce their drinking.
16) Women who are pregnant or nursing
17) Participants (males and females) who refuse to use a reliable method of birth control.
18) Subjects who report disliking spirits will be excluded because hard liquor will be provided during the alcohol administration components of the study.
19) Subjects who have taken any investigational drug within 4 weeks of medication treatment and/or participated in another study, which involves additive blood sampling, and/or interventional measures that would be considered excessive in combination with the current protocol within 4 weeks immediately preceding admission to the treatment period. Investigational amyloid lowering therapies are prohibited two months prior to screening and for the duration of the trial. Other investigational agents are prohibited one month prior to screening and for the duration of the trial.
20) Subjects who have donated blood within the past six weeks.

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21) Report any heavy drinking of alcohol within three days on TLFB prior to initial screening and have a negative result on EtG urine test
22) Subjects going through chemotherapy or on any chemotherapy drugs like anastrozole.

7. How will **eligibility** be determined, and by whom?
All potential participants will be screened over the phone and if they appear to be eligible, will be brought in to be consented by Suchitra Krishnan-Sarin, Ph.D., Dana Cavallo, Ph.D., Tricia Dahl, Thomas Liss, Nicholas Franco, Heather LaVallee, Asti Jackson, or Alissa Goldberg. If no exclusion criteria are determined, a physical exam will be scheduled and reviewed by our Study Physician.

8. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

Risks Associated with Study Drug, AZD0530

Previous animal studies that have tested the effects of AZD0530 at doses that were higher than those used in the current project, or for longer periods of time, have shown that the drug can cause problems with the heart, liver, blood cells, and digestive system (including the stomach and intestines). These harmful effects have included irritation of the digestive system (which can lead to symptoms of vomiting and diarrhea). Other side effects include lower blood pressure, higher heart rate, lower white blood cell counts (infection-fighting cells), and higher liver enzymes (which can be a sign of damage to the liver). It is not known for sure if AZD0530 would produce the same harmful effects in humans that it has with long-term doses in animals. In addition, animal studies suggest that taking AZD0530 during pregnancy could result in eye defects in the fetus.

AZD0530 has been extensively studied in human subjects, including published studies with healthy individuals [25,26], and patients with solid tumors [27,28]. AstraZeneca has extensive safety data of this drug in human subjects, described in detail in the Investigator Brochure (IB), and described in detail below. Notably, in a multiple ascending dose study, AZD0530 doses of 60 mg to 185 mg were well tolerated, and although adverse events were noticeably more frequent and severe at the 250 mg dose, no major safety issues were identified from adverse events at any of the doses studied.

To date, 187 healthy volunteers and 421 patients with advanced cancer have received single or multiple once-daily oral doses of AZD0530. In a single ascending dose study, the maximally tolerated dose (MTD) was considered 1000mg. In a multiple ascending dose study, the MTD was considered 250mg, although a toxicity- limiting dose was not pursued. In patients with advanced cancer, the MTD was 175mg. What follows is a detailed review of the effects of AZD0350 in both healthy volunteers and patients with advanced cancer on various organ systems and systemic function.

Existing preclinical toxicology in two species demonstrates safety through 6 months, supporting chronic administration for this duration in humans. In clinical oncology, the duration of AZD0530 treatment has been 2-4 weeks in most trials.

The dose proposed in this study, 125 mg, has generally been well tolerated in both healthy volunteers, and in patients with advanced solid tumors. The most common adverse events at this dose have included rash, headache, and diarrhea. Less common adverse events have included nausea, vomiting, anorexia, palpitations, fatigue, influenza-like symptoms, and

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abnormal liver function tests. Other adverse effects at higher doses have included upper respiratory infection, myalgia, abdominal pain and tenderness, and epididymitis.

Importantly, with AZD0530 monotherapy, febrile neutropenia or other serious hematologic adverse events have not been documented in doses equal to or lower than 175 mg. In a total of 7 phase 1 trials, including 187 healthy volunteers, no major safety issues were identified from adverse events in any of the doses studied, up to 250 mg daily (AZ Investigator's Brochure). There is a potential for a mild decrease in values for both white cell count and platelets with doses of 125 mg and above, but these abnormalities never fell below reference levels, and levels normalized while patients remained on (AZ Investigator's Brochure). The timing for hematologic effects of AZD0530 is within 14 days of drug initiation, providing the rationale for the 30-day monitoring period in the phase 1 study (AZ Investigator's Brochure). It should be noted that 2/3 of the safety data have been generated from patients with solid tumors, and some of these patients were included in the study despite mild baseline pancytopenia.

In studies where AZD0530 was used to treat patients with cancer the following side effects were noted: GI disorders: nausea, vomiting, diarrhea, decrease appetite, General disorders: flu-like syndromes, asthenia, Hematologic disorders: neutropenia, lymphopenia, thrombocytopenia, leukopenia, anemia, bleeding, bruising, Investigations: increases in serum, creatinine, positive findings on urine dipstick testing for protein and/or blood, elevations in serum transaminases, Respiratory Disorders: pneumonitis, Skin and Sub-cutaneous tissue: rash (general popular).

Healthy Volunteers

- *Vital signs, ECG parameters, and physical findings*: No clinically relevant changes seen with AZD0530.
- *Systemic:* Flu-like symptoms have been reported in healthy volunteers exposed to a single dose of AZD0530, and at doses of 125mg and higher.
- *CNS:* Headache and myalgia were reported in volunteers exposed to a single dose of AZD0530 of 1000mg.
- *Pulmonary:* Upper respiratory tract infection has been reported in healthy volunteers exposed to a single dose of AZD0530. No clinically relevant changes in pulmonary function seen in doses up to 500mg.
- *Renal:* While a rise in plasma and serum creatinine due to reduction in tubular secretion of creatinine was reported, multiple dosing of AZD0530 has no effect on renal function as shown in a dedicated study[26].
- *Hematologic*:
- Bleeding: Events consistent with bleeding occurred in 33/187 volunteers after receiving AZD0530, and in 6/57 receiving placebo. The majority of events involved epistaxis or venipuncture site bleeding. All events related to AZD0530 were grade 1 (CTCAE).
- Neutropenia: One volunteers experienced neutropenia considered a grade 2 adverse event. The dose was 200 mg daily. In doses of 125 mg and 200 mg a decrease in neutrophil count was noted in some patients but did not fall below the normal reference range.
- Thrombocytopenia: In doses of 125mg and 200mg a decrease in platelet count was noted in some patients but did not fall below the normal reference range.
- *Anemia:* Hemoglobin and hematocrit are not changed with AZD0530. While a reduction in these values was seen in healthy volunteers, it was also observed in subjects receiving placebo.
- *Death:* No deaths occurred in studies in healthy volunteers.

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- *Genitourinary:* One healthy volunteer experienced epididymitis while on 200 mg AZD0530 daily.
- *Liver function:* Isolated increases in AST, ALT, and GGT have been seen in a multiple ascending dose study of AZD0530. Two healthy volunteers discontinued intervention – one received 60mg of AZD0530, the other placebo.
- *Endocrine:* There is a trend for lowering estradiol levels in AZD0530 doses of 125, 185, and 250mg. However, none of these changes are statistically significant compared to placebo. At the 185mg dose there may be a small reduction in testosterone levels, but this is not thought to be clinically relevant.
- *Dermatologic:* Rash has been reported in healthy volunteers exposed to a single dose of AZD0530.

Patients with advanced cancer:

AZD0530 was developed for the treatment of solid tumors, and a significant amount of safety data exist in patients with advanced cancer. The rate of adverse events, as expected, is higher in this group than in healthy volunteers.

- *Vital signs, ECG parameters, and physical findings*: No clinically relevant changes seen.
- *Systemic:* Nausea (37%), Anorexia (36%), Vomiting (27%), Diarrhea (26%). Drug discontinuation was rare, and typically in doses of 200mg and higher. Other reported symptoms include abdominal pain, constipation (up to 16%), dry mouth, melena, fatigue (up to 15%), and peripheral edema.
- *CNS:* Dizziness, headache, somnolence, up to 10%.
- *Pulmonary: Rare cases of pneumonitis-type events, including fatal events. These were cases involving advanced cancer; however, AZD0530 could not be excluded as the causative agent.*
- *Renal:* No clinically relevant renal dysfunction related to AZD0530.
- *Hematologic*:
- Bleeding: Up to 27% of subjects. Hematuria, GI bleeding, epistaxis, and hemoptysis reported, but majority mild (grade 1). Not clear that bleeding events were directly related to AZ0530.
- Neutropenia: Occurred in up to 17% of patients with doses of 175-200. There are reported cases of febrile neutropenia in patients with renal cancer and liver metastases. Rarely caused the need for dose change or drug discontinuation.
- Thrombocytopenia: Reduction in platelets seen across doses except 50mg, up to 20% of subjects. No patient required a dose interruption or supportive therapy.
- Anemia: Up to 30% of patients, but majority continued study without need for dose interruption or reduction. Seen in doses of 175mg and higher.
- *Death:* No deaths directly caused by AZD0350.
- *Genitourinary:* no events noted
- *Liver function:* Isolated increases in AST, ALT, GGT reported. None requiring drug discontinuation.
- *Endocrine:* No significant dysfunction reported.
- *Dermatologic:* Erythema reported (rare)

In a recent 4-week multiple ascending dose, randomized, double-blind, placebo-controlled trial of AZD0530 in 24 patients with Alzheimer ’s disease, AZD0530 was found to be safe. Patients received doses of 50 mg, 100 mg, 125 mg, or placebo daily for 4 weeks with primary endpoints of safety, tolerability, and cerebrospinal fluid (CSF) penetration of AZD0530. AZD0530 was generally safe and well tolerated across doses. [29]

Overall, the safety profile of the dose of AZD0530 proposed in this project is very good.

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Alcohol:

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

Alcohol may also cause nausea in high doses; however, nausea is not expected at the dose being used in this sample of heavy drinkers. Subjects will not be drinking to levels more than they typically consume in their own drinking context, and, with the exception of the priming dose, they determine the amount of alcohol consumed.

Another area of potential risk to subjects under the influence of alcohol involves their safety during the experimental procedures. Although impairment of gross motor coordination in heavy drinkers is rare at the alcohol dose used in this study, all subjects will be under the supervision of the experimenters to prevent possible accidents such as falls. Subjects will not leave the laboratory during the self-administration procedure. By staying in the HRU overnight, the possibility that the subject might leave the session and continue to drink alcohol, thereby placing themselves at risk for accidents, is prevented.

Alcohol is a reinforcing agent, which may cause changes in behavior including repetitive or excessive alcohol consumption. Because of this, the administration of alcohol to alcoholics in treatment could potentially impede the progress of their recovery. In addition, the administration of alcohol to sober alcoholics living in the community presents a possible risk of relapse. As a result, we will be recruiting **non-**abstinent **non-**treatment-seeking alcoholics in keeping with the National Advisory Council on Alcohol Abuse and Alcoholism's recommended guidelines (1989) on ethyl alcohol administration. At completion of the study, we will make a serious and concerted effort to link the subject with treatment for their alcohol problems. This will be done by giving the subject objective feedback about the fact that their drinking exceeds standards for avoiding hazardous drinking, providing a brief one-session motivational intervention for their drinking, and by arranging for alcohol treatment services if they are interested. In our previous and ongoing work, several participants quit drinking and many others reduced their drinking in the three months following this intervention.

Interactions of Saracatinib and Alcohol:

There are no known interactions of co-administering Saracatinib and alcohol. We are completing a pilot study (HIC 0602001068) examining the effect of administering up to 80 mg/dl of alcohol which is close to the maximum BAC that participants in our ADP paradigms achieve and 125 mg/day of AZD (administered for eight days; similar to what is being proposed in the current study). We have had two subjects participate in this protocol to date and have not observed only minimal and anticipated adverse events.

Intravenous Access:

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

Blood and Urine Collections:

Screening blood and urine collections are performed primarily as safeguards to subjects and should add no risks other than those normally associated with these procedures. Subjects will have approximately 50 cc of blood drawn at the intake, second self-administration, and at one week follow up appointments to determine liver and kidney functioning. In addition, a total of 10 cc of blood will be drawn at the lab sessions to determine alcohol levels. Therefore, the total amount of blood drawn during the study (160 ml) is well within the HIC guidelines of 450 cc

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within eight research weeks, and the blood loss poses minimal risk in healthy subjects. We will advise subjects against donating blood for six weeks following study participation.

Rating Scales and Questionnaires:
These are all noninvasive and should add no risk. The major disadvantages are the time taken to complete them, and possible breach of confidentiality. Our past experience with these measures indicates that they are acceptable to subjects. Careful efforts aimed at maintaining confidentiality will be made.

Functional Neuroimaging (fMRI):
Magnetic resonance (MR) is a technique that uses magnetism and radio waves, not x-rays, to take pictures and measure chemicals of various parts of the body. The United States Food and Drug Administration (FDA) has set guidelines for magnet strength and exposure to radio waves, and we carefully observe those guidelines. Those who participate will be watched closely throughout the MR study. Some people may feel uncomfortable or anxious. If this happens to the patient, he/she may ask to stop the study at any time and we will take you out of the MR scanner. On rare occasions, some people might feel dizzy, get an upset stomach, have a metallic taste or feel tingling sensations or muscle twitches. These sensations usually go away quickly but we will instruct the patient to please tell the research staff if this occurs. There are some risks with an MR study for certain people. If a person has a pacemaker or some metal objects inside your body, he/she may not be in this study because the strong magnets in the MR scanner might harm them. Another risk is the possibility of metal objects being pulled into the magnet and hitting a participant. To reduce this risk, we require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. We also ask all people involved with the study to walk through a detector designed to detect metal objects. It is important to know that no metal can be brought into the magnet room at any time. Also, once a participant is in the magnet, the door to the room will be closed so that no one from outside accidentally goes near the magnet. We will make sure the participants read and answer very carefully the questions on the MR Safety Questionnaire related to their personal safety. We will ask each participant to take a moment and be sure that they have read the MR Safety Questionnaire and be sure to tell us any information they think might be important.

This MR study is for research purposes only and is not in any way a clinical examination. The scans performed in this study are not designed to find abnormalities. The primary investigator, the lab, the MR technologist, and the Magnetic Resonance Research Center are not qualified to interpret the MR scans and are not responsible for providing a diagnostic evaluation of the images. However, hi-resolution de-identified structural images may be shared with referring clinicians if requested for select patients to rule out gross anatomical markers or findings. Moreover, if a worrisome finding is seen on a scan, a radiologist or another physician will be asked to review the relevant images. Based on his or her recommendation (if any), the primary investigator or consulting physician will contact the participant, inform them of the finding, and recommend that they seek medical advice as a precautionary measure. The decision for additional examination or treatment would lie solely with the participant and their physician. The investigators, the consulting physician, the Magnetic Resonance Research Center, and Yale University are not responsible for any examination or treatment that they receive based on these findings.

Genetic Samples:
Donation of 30 ml of blood for genetics studies will be part of every Informed Consent document. Subjects will be informed of possible risks and benefits of participation in genetics research will be informed of the potential genomewide scope of the genotyping effort, and will

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be informed that their DNA samples will be retained indefinitely (banked). A Certificate of Confidentiality from NIAAA has been obtained to further protect the confidentiality of this information.

9. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

Saracatinib:

Effective screening will exclude all subjects who would be at greater risk for complications because of medical, neurological or psychiatric illnesses or who have any of the other exclusion criteria (described above). Individuals currently dependent on other drugs will be screened out. Subjects maintained on study medication will be issued "keyed" cards which allow health professionals to break the double blind by calling the Yale-New Haven pharmacy switchboard, which answers 24 hours a day. Subjects will also be monitored daily for frequency and severity of adverse events using the SAFTEE. These adverse events will be reviewed daily by the study physician, Dr. Julia Shi or the APRN, Denise Romano. We will also repeat blood draws for routine CBC tests and hepatic, kidney and thyroid function tests at the end of the treatment period and at one week follow up (51cc).

The Investigator's Brochure states that Saracatinib should not be administered to pregnant or breast-feeding women and it is recommended that non-childbearing status should be confirmed by a negative pregnancy test before administration of Saracatinib in women of childbearing potential. Conception must be avoided during maternal or paternal exposure to Saracatinib.

Therefore, the following precautions will be taken for women: 1) Urine pregnancy tests will be performed at intake, prior to starting the medication, and on the day of the alcohol self administration sessions. Pregnant or nursing women will be excluded from participation and encouraged to seek advice about the risk of heavy drinking, encouraged to seek alcohol treatment, and, if interested, referred to other cessation programs. 2) Women and men must agree to use a reliable method of birth control while they are in the study. Each female subject will be asked to alert the principal investigator if she departs from her birth control plans or if, in spite of adherence to these plans, she thinks she might be pregnant. Each male subject will be asked to alert the principal investigator if he departs from his birth control plans or if, in spite of adherence to these plans, he thinks his partner might be pregnant.

Confidentiality Safeguards

Right to privacy for participation in this research will be protected through anonymous coding of data and proper storage of research records. A list of numbers and the corresponding names will be maintained by the Project Director. Access will be limited to the PI and her designates involved in the study. Data from CTNA projects will be maintained by the Data Management and Biostatistics Component (DMBC) and/or Investigator. Data will be available on request after the completion of analyses by the Investigators and after publication of results. Requests should be submitted to the Investigator with details about the type of information needed and plans for use. After review between the Requestor and Investigator, and approval by the Executive Committee, the agreed-upon list of files will be submitted to the DMBC for preparation and delivery to the Requestor.

A certificate of confidentiality has been obtained from the NIAAA, which will protect the confidentiality of all research records generated by this study. Other safeguards include screening by experienced professionals in order to ensure that the inclusion and exclusion criteria are met before patients are entered in the study, including physical exam and laboratory tests.

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Subjects will be informed about possible risks from participating in genetics research. They will be informed that DNA will be stored indefinitely. They will be informed that genotyping (possibly extending to genomewide extent) will take place on their donated DNA. They will also be told that under some circumstances, it can be a risk for genetic information about to be known but that we will keep the results of the genetic testing confidential. We will not make any of our results available to them or add it to their medical records. If they want to know their risk of a genetic disease, we will refer them to a genetic counselor. Finally, they will also be informed that this genetic data may be subject to sharing with other investigators, and that if data are shared, it will be in anonymous form, that is, with no personal identifiers.

Alcohol challenges

The alcohol challenges will be conducted by personnel experienced in alcohol challenge research. We provide a number of safeguards to reduce the risk of physical injury by supervising all sessions and having subjects stay in a safe environment overnight. We also exclude subjects for whom physical or psychological problems contraindicate alcohol consumption. By selecting non-treatment-seeking subjects who are currently drinking heavily on a regular basis, we are not exposing subjects to alcohol consumption levels that differ from their normal drinking context. Although we have never had a subject chose to leave a session early, should a subject insist on leaving the research setting prematurely, we will provide transportation back to their residence. This contingency is explicitly addressed in the consent form. Clearly, subjects are free to discontinue the experiment at any time, although we would strongly encourage them to remain in the research setting until their blood alcohol level is below .02. Because subjects are not in treatment, participation in an alcohol challenge study will not interfere with efforts to achieve abstinence. At the end of the study, however, a potential benefit is that subjects will be provided with a professional evaluation and a motivational intervention to encourage them to seek treatment.

Functional Neuroimaging (fMRI)

Participants will be appropriately screened for metals as will all personnel who enter the room that contains the MRI scanner. This screening will involve a self-report questionnaire, an interview with a trained radiographer and assessment with a ferromagnetic metal detector. Subjects will also be monitored physiologically throughout the scanning session using pulse oximetry. Their heart rate and blood pressure will be monitored at all times while they are in the MRI scanner.

10. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) For more information, see the Instructions, page 24.
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? This protocol is a greater than minimal risk protocol and therefore requires a data safety and monitoring plan.

    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? N/A

    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://www.yale.edu/hrpp/forms-templates/biomedical.html for
        i. Minimal risk ii. Greater than minimal

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1) Plan for Grading Adverse Events and Attribution of Adverse Events

Side effects/adverse experiences are collected on standardized forms, using the SAFTEE (Levine and Schooler, 1986). The SAFTEE includes 1) open-ended questions about any changes in physical or health problems, appearance, or activity level, and 2) yes/no questions on a specific list of symptoms (which correspond to anticipated adverse events associated with Saracatinib) for a specified time period. For each symptom reported on the SAFTEE a rater also records the date of onset, severity (minimal, mild, moderate, severe), whether it was drug-related, and action taken. The SAFTEE is administered at baseline, during the inpatient periods, and every other day during the outpatient treatment periods. We will monitor the number of patients experiencing symptoms and the severity of symptoms.

2) Plans for unanticipated and anticipated serious adverse events reporting to the IRB/HIC, funding agency, and regulatory agency

2.a. Definition of Serious Adverse Events: The FDA's definition of serious adverse events (21 CFR 312) will be used. SAEs include any untoward medical occurrence that at any dose results in death or the immediate risk of death, hospitalization or the prolonging of an existing hospitalization, persistent or significant disability/incapacity, or a congenital anomaly/birth defect (NIH Guide-6/11/99)

2.b. Plans for reporting serious adverse events: Adverse events that meet the criteria for a Serious Adverse Event will be reported to the IRB, MAC, and NIAAA within 24 hours by phone and in writing within 1 week.

3) Plans for reporting non-serious anticipated and unanticipated adverse events

The number of subjects (and percentage) reporting each anticipated adverse event would be reported on an annual basis to the IRB, MAC, and NIAAA as part of annual progress report (NIAAA) and annual reapproval (IRB). These will be reported for the overall sample and not by treatment condition in order to maintain the blind. However, if anticipated adverse events occur in greater magnitude or frequency than expected, then these will be reported to the IRB and NIAAA.

3.a. Anticipated Adverse Events:

*3.a.1.*Saracatinib-induced side effects: Studies to date suggest relatively few adverse events of Saracatinib and that it is safe and well tolerated across doses. Diarrhea, headache, fatigue and nausea were the top adverse events observed at 100 and 125 mg dose of Saracatinib in Alzheimer's patients, but the incidence rates were low and did not differ from the rates observed with placebo. The 50 mg dose was associated increased headache in one individual.

3.b.1. Blood Drawing: Possible adverse events include feeling lightheaded, bruising at the withdrawal site, fainting, and pain.

4) Identification of who will perform the safety review and with what frequency

4.a. Establishment of a DSMB to perform the safety review

We will be accessing the Data and Safety Monitoring Board (DSMB) developed for the Center. The DSMB is multi-disciplinary and includes representatives with expertise in the primary components of the proposed trial. The following individuals will be on the DSMB as voting members:
Robert Swift, MD, PhD, Prof. Psych (Brown)/ VAMC Chmn., DSMB
Robert Stout, PhD, Director, Decision Sci. Int., Statistician, DSMB

Howard Zonana, MD, Dir., Dept. Psychiatry Ethics Committee, IRB Rep., DSMB
Lisa Newton, PhD, Prof. Applied Ethics, Fairfield Univ. Ethicist, DSMB

This DSMB will follow the operational guidelines outlined in the YCCI plan for DSMB.

4.b. Frequency of Review of Safety Reports

Subjects are recruited at a maximum rate of 2 per month; thus, the DSMB will review safety reports two times a year. More frequent meetings will be scheduled if indicated by interim findings.

d. For multi-site studies for which the Yale PI serves as the lead investigator: N/A
   i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed?
   ii. What provisions are in place for management of interim results? iii. What will the multi-site process be for protocol modifications?

11. **Statistical Considerations:** Describe the statistical analyses that support the study design.

Power Calculations: We will to recruit up to 90 subjects and randomize 40 subjects to the 125 mg Saracatinib dose and 20 subjects to placebo. We will use the number of drinks consumed at the baseline session (5 or less, 6 or more) and gender as stratification variables in the randomization. 6 drinks is half the total number of drinks they are allowed to drink in the self-administration period and will allow the participant to reach a BAC of 0.07 or higher which is the threshold for heavy drinking. We anticipate that we will obtain complete data on 52 subjects in approximately 2:1 ratio on active vs. placebo. This would give us 80% power to detect large effects of drug (d=0.8 or greater) at two-sided alpha level of 0.05. Such an effect size is considered clinically meaningful and is consistent with our pilot data where we observed large effects of the 125 mg dose (administered over eight days) on alcohol-induced stimulation and feeling intoxicated and feeling good (all >0.8) following exposure to a fixed dose of alcohol (0.8 mg/kg) in heavy social drinkers. Randomizing more subjects on active drug will allow us to explore relationships between potential predictors (e.g. gender, smoking status) and outcome in the treatment group. Thus, we will be well powered with our proposed sample to detect clinically relevant effects of Saracatinib.

Statistical analyses: All data will be transcribed onto teleforms, checked for completeness and clarity, and sent to the data manager, Ms. LaVelle. All outcomes will be summarized descriptively and assessed for normality prior to analysis using normal probability plots and Kolmogorov test statistics. Transformations or nonparametric analyses will be performed as necessary. In the mixed models described below, the correlation between repeated measures on an individual will be modeled using random effects and/or structured variance-covariance matrices. The best fitting variance-covariance structure will be determined by information criterion. The mixed effects approach is advantageous in that it is unaffected by randomly missing data and allows greater flexibility in modeling the correlation structure of repeated measures data (Gueorguieva & Krystal 2004). All tests will be two-sided and considered statistically significant at alpha=.05. Significance levels for secondary comparisons will be adjusted for multiple tests using the Bonferroni correction, basing the adjustment on the number of conceptually related statistical tests within each hypothesis.

Aim 1: Scores on the Yale Craving Scale will represent the dependent variable in a linear mixed model with treatment (0 or 125 mg Saracatinib) as a between-subjects factor and time (see time points, Table 1) and session (baseline, post-treatment) as within-subject factors. All multilevel interactions will be modeled and interpreted by plotting and comparing least squares means. We anticipate a significant treatment by time by session interaction explained by greater posttreatment reductions in craving with Saracatinib compared to placebo. We will also explore the influence of

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treatment on alcohol craving in response to the alcohol cue exposure just prior to the start of the drinking session using a similar model. In the above models, treatment will be considered as a categorical predictor but linear and quadratic effects of dose will also be tested. **Aim 2:** Total number of drinks consumed during the ADP will be compared among treatment conditions using linear mixed models as above with treatment (0 mg or 125 mg Saracatinib) as a between-subjects factor and session (baseline, post-treatment) as a within-subject explanatory factor. We anticipate a significant treatment by session interaction owing to reduced drinking following Saracatinib treatment, but not placebo. We will also consider change from baseline as the outcome measure and compare the treatment groups using ANOVA.
Secondary Aim 1: Alcohol-induced stimulation and sedation during ADP will be evaluated using the same linear mixed models outlined in Specific Aim 1, with BAES subscale scores as the dependent variables.
Secondary Aim 2: Adverse events will be recorded and summarized qualitatively by treatment group. Total and severe adverse event frequencies will be compared between groups using chisquare or Fisher's exact test. Similar to what our collaborators, Drs. Strittmatter and Nygaard observed among AD subjects (see preliminary data), we anticipate AE profiles of the two active Saracatinib groups will be similar to placebo. Vital signs and blood alcohol levels and plasma Saracatinib levels assessed during the ADP will also be evaluated using linear models to examine alcohol-Saracatinib interactions.
E**xploratory Aims**: All measures (e.g., PST, Habit, genetic markers, neural markers) will be evaluated using the same models outlined in Specific Aim 2.

SECTION VI: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, state N/A and delete the rest of the section.

A. DRUGS, BIOLOGICS and RADIOTRACERS

1. **Identification of Drug, Biologic or Radiotracer:** What is (are) the **name(s)** of the drug(s) biologic(s) or radiotracer(s) being used? Identify whether FDA approval has been granted and for what indication(s).
AZD0530, or Saracatinib, is a selective inhibitor of Src family kinases, with high specificity for Fyn kinase. The drug was developed for the treatment of solid tumors and has been found safe and well tolerated in both phase 1 and phase 2 clinical trials (AZ Investigator's Brochure). AZD0530 has not been approved for clinical use by the FDA.

All protocols, which utilize a drug, biologic, or radiotracer **not** approved by, but regulated by, the FDA, or a radiotracer regulated by the RDRC, must provide the following information:

a. What is the Investigational New Drug (IND) **number** assigned by the FDA?
We have already received an IND (Holder: John Krystal; # 124428) for the use of AZD0530 for neuroimaging study (PI: Godfrey Pearlson) and for a safety study with alcohol administration (HIC protocol 0602001068; PI Krishnan-Sarin); this IND is attached. We submitted the report from our safety study to the FDA on November 29, 2016 along with modifications to the same IND to allow us to conduct the current study in heavy drinkers. We heard back from the FDA on Dec 22, 2016 requesting us to modify the IND to add information about the criteria and procedures for

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discontinuing or delaying access to additional alcohol during the self-administration session. We responded with a modification that included stopping language (as highlighted in the section titled "Alcohol Drinking Paradigm" earlier in this protocol) on February 7th, 2017. As of March 8, 2017, no further queries were made by the FDA, clearing the IND for use on this study.

b. Who holds the IND? John Krystal, a Co-I will hold the IND

c. All protocols which utilize a radiotracer not approved by, but regulated by the FDA must provide the IND number: _____

Alternatively, use of the investigational radiotracer may be under RDRC/RSC oversight: (check if appropriate)_____

For all investigational radiotracers, attach a copy of the RDRC/RSC application (for radioisotopes used in the PET Center, PET Center personnel may complete this step)
Go to http://rsc.med.yale.edu/login.asp?url=myApps.asp. When you have logged in, complete the application and attach a copy to this submission.

Alternatively, an **exemption from IND filing requirements** may be sought for a clinical investigation of a drug product that is lawfully marketed in the United States. If there is no IND and an exemption is being sought, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

Exempt Category 1
The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:

i. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug. Yes ☐ No ☐
ii. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product. Yes ☐ No ☐
iii. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product. Yes ☐ No ☐ iv. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56). ☐ Yes ☐ No
v. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs. ☐ Yes ☐ No

Exempt Category 2 (all items i, ii, and iii must be checked to grant a category 2 exemption)
☐ i. The clinical investigation is for an *in vitro* diagnostic biological product that involves one or more of the following (check all that apply):
☐ Blood grouping serum
☐ Reagent red blood cells
☐ Anti-human globulin

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☐ ii. The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and

☐ iii. The diagnostic test is shipped in compliance with 21 CFR §312.160.

Exempt Category 3

☐ The drug is intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.60

Exempt Category 4

☐ A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

AZD0530, or Saracatinib, is a selective inhibitor of Src family kinases, with high specificity for Fyn kinase. The drug was developed for the treatment of solid tumors and has been found safe and well tolerated in both phase 1 and phase 2 clinical trials (AZ Investigator's Brochure). AZD0530 has been extensively studied in human subjects, including published studies with healthy individuals[78,94], and patients with solid tumors[95,96]. AstraZeneca has extensive safety data of this drug in human subjects, described in detail in the Investigator Brochure (IB). Notably, in a multiple ascending dose study, AZD0530 doses of 60 mg to 185 mg were well tolerated, and although adverse events were noticeably more frequent and severe at the 250 mg dose, no major safety issues were identified from adverse events at any of the doses studied. To date, 187 healthy volunteers and 421 patients with advanced cancer have received single or multiple once-daily oral doses of AZD0530. More recent evidence also suggests that AZD at 100 mg and 125 mg was safe and well tolerated when used for up to 4 weeks in patients with Alzheimers disease (Nygaard et al., 2015).

Animal studies that have tested the effects of AZD0530 at higher doses than those used in the current project, or for longer periods of time, have shown that the drug can cause problems with the heart, liver, blood cells, and digestive system (including the stomach and intestines). These harmful effects have included irritation of the digestive system (which can lead to symptoms of vomiting and diarrhea). Other side effects include lower blood pressure, higher heart rate, lower white blood cell counts (infection-fighting cells), and higher liver enzymes (which can be a sign of damage to the liver). It is not known for sure if AZD0530 would produce the same harmful effects in humans that it has with long-term doses in animals. Animal studies also suggest that taking AZD0530 during pregnancy could result in eye defects in the developing baby.

3. **Source:** a) Identify the source of the drug or biologic to be used.

AZD0530 and matching placebo will be provided by Astra Zeneca; Astra Zeneca will not provide any other support for the current protocol. Study medication will be dispensed by the Investigational Drug Service.

b) Is the drug provided free of charge to subjects? ☒ Yes ☐ No If yes, by whom?

4. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.

Check applicable Investigational Drug Service utilized:

- ☒ **YNHH IDS**
- ☐ **CMHC Pharmacy**
- ☐ **VA PET Center**
- ☐ **Other:**
- ☐ **Yale Cancer Center**
- ☐ **West Haven**
- ☐ **None**

Note: If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.

5. **Use of Placebo:** ☐ **Not applicable to this research project**

If use of a placebo is planned, provide a justification, which addresses the following: a. Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this. This is not a treatment trial or a treatment seeking population of heavy drinkers. We need a placebo to confirm the effects of Saracatinib.

b. State the maximum total length of time a participant may receive placebo while on the study. 8 days
c. Address the greatest potential harm that may come to a participant as a result of receiving placebo. Not a treatment seeking population, thus no harm is anticipated
d. Describe the procedures that are in place to safeguard participants receiving placebo. Not a treatment seeking population.

6. **Use of Controlled Substances:**

Will this research project involve the use of controlled substances in human subjects?
☐Yes ☒ No *See HIC Application Instructions to view controlled substance listings*.

If yes, is the use of the controlled substance considered:
☐ Therapeutic: The use of the controlled substance, within the context of the research, has the potential to benefit the research participant.
☐ Non-Therapeutic: *Note, the use of a controlled substance in a non-therapeutic research study involving human subjects may require that the investigator obtain a Laboratory Research License. Examples include controlled substances used for basic imaging, observation or biochemical studies or other non-therapeutic purposes. See Instructions for further information.*

7. **Continuation of Drug Therapy After Study Closure** ☒ **Not applicable to this project** Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?
☐ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access.

☐ No If no, explain why this is acceptable.

B. DEVICES

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☒No *If Yes, please be aware of the following requirements*:

a. A YNHH New Product/Trial Request Form must be completed via EPIC: **Pull down the Tools tab in the EPIC Banner, Click on Lawson, Click on "Add new" under the New Technology Request Summary and fill out the forms requested including the "Initial Request Form," "Clinical Evidence Summary, " and attach any other pertinent documents. Then select "save and submit" to submit your request**; and

c. Your request must be reviewed and approved **in writing** by the appropriate YNHH committee before patients/subjects may be scheduled to receive the investigational device or investigational procedure.

2. What is the name of the device to be studied in this protocol?

Has this device been FDA approved? ☐Yes ☐ No
If yes, state for what indication.

3. **Background Information:** Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.

4. **Source:**
   a) Identify the source of the device to be used.
   b) Is the device provided free of charge to subjects? ☐ Yes ☐ No

5. What is the PI's assessment of risk level (significant or non-significant) associated with the use of the device?

☐ **Significant Risk (SR) Device Study:** A study of a device that presents a potential for serious risk to the health, safety, or welfare of a participant and 1) is intended as an implant; 2) is used in supporting or sustaining human life; or otherwise prevents impairment of human health; 3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or 4) otherwise presents a potential for serious risk to the health, safety, or welfare of a participant.

Significant Risk Devices require an Investigational Device Exemption (IDE) issued by the FDA.

What is the **IDE number** assigned by the FDA?
Did the FDA approve this IDE as **Category A** (experimental/investigational) or as **Category B** (nonexperimental/investigational)?

Who holds the IDE?

☐ **Non-Significant Risk (NSR) Device Study:** A study of a device that does not meet the definition for a significant risk device and does not present a potential for serious risk to the health, safety, or welfare of participants. Note that if the HIC concurs with this determination, an IDE is not required.

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6. **Abbreviated IDE or Exempt IDE:** There are abbreviated requirements for an IDE and there also are exemptions to the requirement for an IDE. *See the criteria in the HIC Application Instructions,* Section VI.B.4 at http://www.yale.edu/hrpp/resources/docs/100FR1aHICProtocol_Application_Instructions5-2511.pdf *to determine if these pertain to this study.*

☐ **Abbreviated IDE or Exempt IDE** – *If criteria set forth in the HIC Application Instructions are met, copy and paste the completed relevant section from the Instructions into this application.*

7. **Investigational device accountability**:
   a. State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:

      Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable):

Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number):

Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations:

Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements:

Distributes the investigational device to subjects enrolled in the IRB-approved protocol:

SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. **Targeted Enrollment: Give the number of subjects:**
   a. targeted for enrollment at Yale for this protocol 50 completers
   b. If this is a multi-site study, give the total number of subjects targeted across all sites N/A

2. **Indicate recruitment methods below.** Attach copies of any recruitment materials that will be used.

☒ Flyers ☒ Internet/Web Postings ☒ Radio
☐ Posters ☐ Mass E-mail ☐ Solicitation Telephone ☒ Letter
☐ Departmental/Center Website ☐ Television ☒
☐ Medical Record Review ☐ Departmental/Center Research Boards Newspaper
☐ Departmental/Center ☒ Newsletters Web-Based Clinical Trial Registries
☐ YCCI Recruitment database Clinicaltrials.gov Registry (do not send materials to HIC) Other (describe):

3. **Recruitment Procedures:**
   a. Describe how potential subjects will be identified.
      Participants will be recruited through advertisements in local newspapers, community locations (bars, coffee shops, grocery stores), listings on Craig's list and social

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networking sites or through our Facebook page or our url "www.paidalcoholstudy.com" which links subjects to confidential surveys and provides preliminary information about the project.

b. Describe how potential subjects are contacted.

Potential subjects will be contacted using the telephone number or other contact information that they provide.

c. Who is recruiting potential subjects?

Potential participant's eligibility will be assessed by an approved research staff member who will then set them up for the initial intake appointment. We do not anticipate problems recruiting these subjects since their profile is similar to that of participants in earlier projects and we have been very successful in our earlier recruitment efforts.

4. Screening Procedures

a. Will email or telephone correspondence be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? ☒ Yes ☐ No

b. If yes, identify below all health information to be collected as part of screening and check off any of the following HIPAA identifiers to be collected and retained by the research team during this screening process.

HEALTH INFORMATION TO BE COLLECTED:

HIPAA identifiers:

☒ Names

☐ All geographic subdivisions smaller than a State, including: street address, city, county, precinct, zip codes and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly-available data from the Bureau of the Census: (1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people, and (2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.

☒ Telephone numbers

☐ Fax numbers

☒ E-mail addresses

☒ Social Security numbers

☐ Medical record numbers

☐ Health plan beneficiary numbers

☐ Account numbers

☐ All elements of dates (except year) for dates related to an individual, including: birth date, admission date, discharge date, date of death, all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older

☐ Certificate/license numbers

☐ Vehicle identifiers and serial numbers, including license plate numbers

☐ Device identifiers and serial numbers

☐ Web Universal Resource Locators (URLs)

☐ Internet Protocol (IP) address numbers

☐ Biometric identifiers, including finger and voice prints

☐ Full face photographic images and any comparable images

☒ Any other unique identifying numbers, characteristics, or codes (medical diagnosis, medications, substance use)

5. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐ Yes, all subjects

☐

☒

Yes, some of the subjects No

If yes, describe the nature of this relationship.

6. **Request for waiver of HIPAA authorization:** (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.) **Choose one:**

☐ For entire study

☒ For recruitment purposes only

☐ For inclusion of non-English speaking subject if short form is being used

Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data; Subjects are screened over the phone and voluntarily complete the Qualtrix Survey

i. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data;

It would be impractical to obtain the subject's authorization (for recruitment purposes only) because potential participants will be calling in to be screened over the phone before any face-to-face meeting, therefore will not be able to sign the HIPAA authorization at that time.

By signing this protocol application, the investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

7. **Required HIPAA Authorization:** If the research involves the creation, use or disclosure of protected health information (PHI), separate subject authorization is required under the HIPAA Privacy Rule. Indicate which of the following forms are being provided:

☒ Compound Consent and Authorization form

☐ HIPAA Research Authorization Form

8. **Consent Personnel:** List the names of all members of the research team who will be obtaining consent/assent. *see IRES for list
9. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

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

10. E**valuation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.
Subjects with limited decision-making capacity will not be enrolled in this study. Since we are recruiting a population of heavy drinkers, we will evaluate breath alcohol levels at the start of the intake session and will not continue obtain consent if the individuals breath alcohol level is positive.

11. Documentation of Consent/Assent: Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects. Adult Compound Authorization Form

12. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use. Due to the intensity and complexity of the design of this study we will only enroll Englishspeaking subjects.

12(a) As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment?

YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are found on our website at: http://www.yale.edu/hrpp/forms-templates/biomedical.html. If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via amendment prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

13. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐ **Not requesting a consent waiver**
☒ **Requesting a waiver of signed consent**
☐ **Requesting a full waiver of consent**

A. Waiver of **signed** consent: (Verbal consent from subjects will be obtained. **If PHI is collected, information in this section must match Section VII, Question 6**)

☒ **Requesting a waiver of signed consent for Recruitment/Screening only** If requesting a waiver of signed consent, please address the following:

a. Would the signed consent form be the only record linking the subject and the research?
Yes No

☐ ☐
b. Does a breach of confidentiality constitute the principal risk to subjects?
☐ Yes ☐ No

OR

c. Does the research activity pose greater than minimal risk?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity
☒ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☒ No

☐ **Requesting a waiver of signed consent for the <u>Entire Study</u> (**Note that an information sheet may be required.)

If requesting a waiver of signed consent, please address the following:

a. Would the signed consent form be the only record linking the subject and the research?
☐ Yes ☐ No

b. Does a breach of confidentiality constitute the principal risk to subjects?
☐ Yes ☐ No

OR

c. Does the research pose greater than minimal risk? ☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** ☐ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

B. <u>Full waiver</u> <u>of consent:</u> (No consent from subjects will be obtained for the activity.)

☐ **Requesting a waiver of consent for <u>Recruitment/Screening</u> only**

a. Does the research activity pose greater than minimal risk to subjects?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity
☐ No

b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No

c. Why would the research be impracticable to conduct without the waiver?

d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

☐ **Requesting a full waiver of consent for the <u>Entire Study</u> (Note: If PHI is collected, information here must match Section VII, question 6.)**

If requesting a full waiver of consent, please address the following:

a. Does the research pose greater than minimal risk to subjects?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.***
☐ No

b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No

c. Why would the research be impracticable to conduct without the waiver?

d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

SECTION VIII: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

a. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

Name, address, telephone number, email address SS #, and birth date, medical/psychological diagnosis and current medications will be collected from subjects

b. How will the research data be collected, recorded and stored?

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

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

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

c. How will the digital data be stored? ☐ CD ☐ DVD ☐ Flash Drive ☐ Portable Hard Drive ☒ Secured Server ☐ Laptop Computer ☐ Desktop Computer ☐ Other

d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

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

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

Do all portable devices contain encryption software? ☒ Yes ☐ No
If no, see http://hipaa.yale.edu/guidance/policy.html

a. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.
Study data will be archived in a secure storage facility, data will not be destroyed until at least 7 years after completion of the study, at which point it will be shredded in accordance to university policy.

b. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, FDA, Data and Safety Monitoring Committee (DSMC), SSC, etc.)? (please distinguish between PHI and de-identified data)
The PI and research staff will have access to all data. The DSMB, FDA, DHHS, Yale HRPP/HIC, Yale EMR, and NIAAA will only have access to de-identified data. A CMHC record containing PHI will also be kept in a locked file at CMHC.

c. If appropriate, has a Certificate of Confidentiality been obtained?
Because this study contains sensitive information and drug testing and is funded by the NIH, per the Notice of Changes to NIH Policy for Issuing Certificates of Confidentiality (NOT-OD-17-109), effective October 1, 2017, this study is assumed to now have a Certificate of Confidentiality, subjects are anticipated to be protected, and the consent form Privacy and Confidentiality section reflect this.

d. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g. HIV testing – reporting of communicable diseases; parent interview - incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported.
Any voluntary reports of child abuse, elder abuse and intent to harm self or others will be reported to the appropriate authorities and if appropriate treatment will be recommended.

SECTION IX: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)
This study will not directly benefit the participants but will help advance knowledge in the area of development of pharmacotherapies for alcohol drinking. Subjects will be offered feedback about their drinking and active referral to treatment for their alcohol drinking behavior should they so desire. The proposed study may be a conduit for some to receive treatment and for others to reduce their drinking on their own.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?
   N/A

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.
   Subjects will have the opportunity to receive up to $1277 for completing all phases of the study. Payment for the intake interview will be $50, and they will receive an additional $50 for the physical examination. Subjects will also receive $200 for participating in the first drinking paradigm, $160 for taking the study medication ($10/day of travel, and $300 for participating in the second alcohol drinking paradigm. Subjects will earn a $250 bonus for completing both drinking paradigms. Subjects will have the opportunity to earn up to $36 during the self-administration period at each overnight. Subjects will be paid $10/day for travel during the outpatient medication phase and $30 for completing each of the two follow-up appointments (one week and one month). Subjects will be reimbursed $18 per overnight for parking.
   Lastly, if the subject agrees to participate in the fMRI portion of the study, he/she will earn an additional $75. Transportation will be provided if necessary.
   We have also included a referral bonus of $50 if a participant refers someone to our study that successfully completes their first overnight (randomized).

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.
   The subject has no costs associated with participation in this research since all research procedures are provided at no cost.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk.
   a. Will medical treatment be available if research-related injury occurs? It is unlikely that a participant will incur injury as a result of participation in this research. However, should an injury occur, treatment will be provided. However, the participant or their insurance company will have to cover the costs of treatment; this will be specified in the consent form.
   b. Where and from whom may treatment be obtained? Participants may receive treatment wherever they wish.
   c. Are there any limits to the treatment being provided? No
   d. Who will pay for this treatment? The participant or their insurance carrier will be expected to pay for the cost of the treatment.
   e. How will the medical treatment be accessed by subjects? Subjects will have a 24-hour emergency phone number to contact in the event of an emergency.

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