Medication Development for Protracted Abstinence in Alcoholism: Suvorexant Versus Placebo

NCT04229095

Study Protocol -10/24/2019

Study Interview Application (Version 1.0)

1.0 General Information

***Please enter the full title of your study::**

Medication Development for Protracted Abstinence in Alcoholism: Suvorexent versus Placebo

***Please enter the Study Number you would like to use to reference the study:**

Suvorexent for Protracted Abstinence in Alcoholism
* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

Please identify the Research Type?

Substance Abuse and Addictions

Please identify the Study Phase:

II

2.0 Add departments

2.1 List departments associated with this study:

Is Primary?	Department Name
⦿	**Non Scripps** - The Scripps Research Institute (TSRI)

3.0 ■ Assign key study personnel(KSP) access to the study

3.1 * Please add a Principal Investigator for the study:

Name	Role	Training Record
Mason, Barbara J, Ph.D.	**Principal Investigator**	View Training Record

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

Name	Role	Training Record
Shadan, Farhad, M.D.	**Sub-Investigator**	View Training Record

B) Research Support Staff

Bess, Jessica Lynn, MSW	Study Coordinator	View Training Record
Quello, Susan B., B.A., B.S.	Clinical Research Assistant	View Training Record

3.3 *Please add a Study Contact:

Name	Role	Training Record
Mason, Barbara J, Ph.D.	Study Contact	View Training Record
Quello, Susan B., B.A., B.S.	Study Contact	View Training Record

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

4.0 Study Interview

Interview Tips:

- *All questions that require answers are preceded by an asterisk (*). After completing a section click on the 'Save and Continue to Next Section' button in the upper right. If you miss a required question, an error box will appear and the field you missed will be indicated in red.*
- *You do not have to complete this interview all at one time. If you wish to stop in the middle, any sections you have completed AND SAVED will be saved as a 'Draft' version. You can return to this 'Draft' version by going to the My Studies area of Study Assistant.*
- *If you are entering a long block of text copied from another source that requires editing, it will be easier to paste this into MS Word on your desktop and do the editing there, then paste into the text box or text editor within this application.*
- *If you want to go back to a prior section in the interview do NOT use the 'Back' button in the upper right or the 'Back' button in your browser. Click on the section you wish to go back to in the 'Sections' menu on the left. If the 'Sections' menu on the left is not visible, then use the 'Back' button in the upper right. If you do accidentally click on the 'Back' button you will go the Submissions section for your study. Click on the 'Application' link under 'Protocol Items' to return to the interview.*
- *Help for completing some sections will appear on the right side of the interview. Put your cursor over the bubble containing a question mark and click on the link that pops up to view HELPFUL TIPS.*
- *When calling or emailing with questions about or problems with this interview please refer to the section title in addition to the section number.*

4.1 ***How do you want your Institution, Department, Division, etc. to appear on official IRB Approval Notices?**

Scripps Research, Department of Molecular Medicine

5.0 Independent IRB

5.1 ***Are you using a Central/Independent IRB? (*If Yes, be sure to attach the IRB application, sponsor protocol, investigational drug brochure and approved consent/assent forms.*)**

○ Yes ◉ No

6.1 ***Is this a Humanitarian Use Device Registry (HUD)?**

○ Yes ◉ No

7.0 Exempt/Waived Research

7.1 ***Do you think this research may be Waived under 45 CFR 46.102(f) as '*Not Human Subjects*' research? [FOR CLARIFICATION/QUESTIONS, CALL THE IRB OFFICE BEFORE YOU COMPLETE THIS SECTION: 858-678-6402| Examples that may be Waived include:**

- **Use of human derived materials that are purchased from a commerical source**
- **Use of unidentifiable tissue or serum from a biorepository**

(Note: Using or deriving Human Stem Cell lines cannot be waived.)

○ Yes ◉ No

If Yes, please explain:

7.2 ***(Reminder: If you answered 'Yes' to Waived, please answer 'No' to Exempt.)* *Do you think your study may be Exempt from IRB review? (*This category is usually only applicable to basic scientists at the Research Institute. If you are not sure, select No. If you are using blood from the Normal Blood Donor service or using or deriving human stem cells, your study is NOT exempt.)***

○ Yes ◉ No

If Yes, please explain in detail:

8.0 TSRI Normal Blood Donor Services

8.1 ***Is your ONLY use of human subjects obtaining blood from the TSRI Normal Blood Donor program?**

Note: If you are obtaining any other specimens, answer No.

○ Yes ◉ No

9.0 Care Line/Co-Management Committee

9.1 ***Has your proposal been endorsed by a Scripps Health Care Line or Co-Management Committee?**

○ Yes ◉ No

9.2 **If NO, please indicate why not:**

N/A

10.0 Clinical Research Services

10.1 ***Is your study being conducted at or through**

- **Scripps Clinic**
- **Scripps Green Hospital**
- **Scripps Cancer Center**
- **Scripps Clinical Research Services**

◉ Yes ○ No

If you answer 'Yes' to this question, your submission will be automatically routed to CRS Director James Mason for sign off before it goes to the IRB.

11.0 Tissue/Blood from Scripps (Patients/Employees) OR Outside of Scripps

11.1 *Are you obtaining blood or tissue from Scripps employees or patients? (*May require informed consent.*)

IF USING THE NORMAL BLOOD DONOR PROGRAM, OR IF THIS IS A CLINICAL TRIAL, ANSWER "NO".

○ Yes ◉ No

If Yes, please describe:

11.2 *Is your only use of human subjects obtaining blood, tissue, saliva, etc. using collaborators outside of Scripps Health or TSRI? [Check "NO" if your study involves any intervention with human subjects such as drugs, devices, interviews, questionnaires, etc.]

○ Yes ◉ No

If Yes, please describe:

12.0 Privacy of Health Information and Confidentiality of Data

12.1 *Do you plan to obtain individual patient authorization (via patient consent) to use and/or disclose Protected Health Information? *(If NO, you MUST request a Waiver of Informed Consent and a Waiver of Privacy Authorization from the IRB, and submit a Confidential Data Request form to Audit/Compliance through the IS Service Now Portal, available under "Quick Links" on the Scripps intranet)*

◉ Yes ○ No

13.0 Privacy of Health Information and Confidentiality of Data - Detail

13.1 *Do you plan to use Scripps Health medical records or patient data to identify potential subjects? *(Note: If Yes, you need to complete a Confidential Data Request form [CDR]. Refer to Scripps policy.)*

○ Yes ◉ No

13.2 *What provisions have been made to maintain the confidentiality of the subject's data and/or samples? *(Important: Identifiable medical information may NOT be stored on non-Scripps electronic devices such as smartphones, laptops, tablets, personal computers, etc. NEVER email any personal identifiers such as name, MR#, etc.)*

☑ Limited access - IRB must be aware of anyone who has access to identifiable data
☑ Stored in secure folder on the Scripps network
☑ Research numbers will be assigned. Identification code will be kept separately from the data
☑ Password-protected database
☐ Other

If Other, please explain:

13.3 ***Will Non-Scripps personnel need to access any Scripps Information Systems to complete the research?** ***(Important: Any non-Scripps personnel will require orientation, employee health screening, name badge and IS coordination. They must also go through a vendor/volunteer process before accessing any Scripps data. Policy S-FW-EC-1157 is on the Scripps intranet.)***

○ Yes ◉ No

If Yes, list anyone who will have access to the data that is NOT part of the study staff or sponsoring organization.

13.4 ***Is there any specific hardware, software and/or transmission of data beyond the standard eCRF?** ***(This would include sponsor- required laptops or software to be loaded onto Scripps PCs, laptops or assets.)*** **If Yes, please complete the** Request for Software Installation or Third Party Application Service Provider **(ASP) form.** ***(Note: Modems are not acceptable.)***

○ Yes ◉ No

14.0 Research Sites and Administrative Review

14.1 ***Is this a multi-center trial?**

○ Yes ◉ No

If Yes, are you the Principal Investigator or Program Director for the multi-center trial?

○ Yes ○ No

If Yes, (*you are the Principal Investigator or Program Director*), list all non-Scripps sites.

14.2 **How will any Non-Scripps sites send data to Scripps Health?**

14.3 **What steps have been implemented to verify the integrity of Non-Scripps data prior to loading it into the Scripps network?** ***(Answer is required if Scripps PI is acting as lead site for multi-center study.)***

14.4 ***Is the research a project of Scripps Health or the Scripps Research Institute (TSRI)?**

☐ Scripps Health - (Conducted by Scripps employees, agents or in Scripps facilities)
☑ Scripps Research Institute - (Conducted by TSRI employees, agents or in TSRI facilities)

14.5 ***Indicate the sites(s) at which data will be collected and/or analyzed. (*Select all that apply.*)**

☐ MD Office
☐ Outside - Non Scripps Health
☐ Scripps Cancer Center (SCC) - Network
☐ Scripps Cancer Center - Mercy
☐ Scripps Cancer Center - Green
☐ Scripps Clinic - Carmel Valley
☐ Scripps Clinic - Mission Valley

- [ ] Scripps Clinic - Torrey Pines
- [x] Scripps Green Hospital
- [ ] Scripps Memorial Hospital - Encinitas
- [ ] Scripps Memorial Hospital - La Jolla
- [ ] Scripps Mercy Hospital - San Diego
- [ ] Scripps Mercy Hospital - Chula Vista
- [ ] TSRI - Florida
- [ ] TSRI - Normal Blood Donor Service (NBDS)
- [ ] Scripps Radiation/Oncology
- [ ] Scripps Proton Center
- [x] TSRI - The Scripps Research Institute
- [ ] Whittier Institute
- [ ] Scripps Clinical Research Center
- [ ] Other
- [ ] Anderson Medical Pavilion
- [ ] Prebys Cardiovascular Institute

If Other, enter site name.

14.6 Non Scripps and other collaborative research sites.

Please identify additional locations or facilities not listed above.

If using other sites, do they require additional IRB review?

○ Yes ○ No

If Yes, what is the status of this other IRB review?

○ Not yet submitted
○ Pending
○ Approved

15.0 Scripps Health Review

15.1 *Does this study involve any Scripps Health facility or Scripps Health patients?

◉ Yes ○ No

16.0 Scripps Health Review Detail

16.1 *Is this study Investigator-Initiated? *(A protocol designed by the investigator, even if it is supported by commercial funds.)*

◉ Yes ○ No

16.2 *What is the anticipated benefit to future patients or healthcare providers?

This is not a treatment study, so research subjects will not benefit personally, but their participation may help identify new medications to help others stop drinking

16.3 ***What is the anticipated benefit of this research to Scripps Health as an organization or to the patients who receive care from Scripps Health?**

This study may help identify a novel medication to help people suffering from alcoholism.

16.4 ***The topic of this study relates to which of the following:** ***(Select all that apply.)***

- ☐ Cost of Care
- ☐ Preventing hospital admission/Preventing readmission
- ☐ Care across the continuum
- ☐ Publicly reported quality metrics
- ☐ Nurse sensitive quality indicators
- ☐ Never-events
- ☐ Value based purchasing/Core Measures
- ☐ Strategic plan, goals or objectives
- ☐ Board reported quality metrics
- ☐ Patient satisfaction
- ☐ Delay to treatment
- ☐ Hospital aquired infection
- ☐ Mortality
- ☐ Patient safety
- ☐ Medication management and/or safety
- ☐ Decreased labor/staff time
- ☐ Improved operational efficiency
- ☐ Regulatory readiness
- ☐ Workplace or workforce safety
- ☐ Healthcare literacy
- ☐ General Wellness Monitoring
- ☑ Other

If Other, please explain:

Drug development of novel medications to treat alcoholism.

17.0 Clinical Trial

17.1 ***Is your project a Clinical Trial?** ***The NIH defines a clinical trial as a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.***

◉ Yes ○ No

17.2 **If not a clinical trial, does your project involve testing an assay or device of any sort?**

○ Yes ◉ No

17.3 ***Will your project involve informed consent from individual subjects?**

◉ Yes ○ No

17.4 **If this is a Clinical Trial, what is the NCT number that identifies the trial on www.clinicaltrials.gov?**

Note: All clinical trials must be registered in a national database at www.clinicaltrials.gov. Each trial is assigned a unique registry number, the "NCT" number, which begins with NCT followed by an 8-digit number. We must have this number to be able to identify clinical trials ongoing at Scripps, as required by Scripps Health leadership. For commercially-sponsored studies, get the number from the sponsor; for investigator-initiated studies, ask the Principal Investigator or search the clinical trials database to find it.

☐ N/A
☑ NCT Not Listed

If NCT number is not listed, explain why:

Our study has not been registered on Clinicaltrials.gov at the time of this application but will be posted and the NCT number will be provided to the IRB.

18.0 Study Procedures

18.1 ***Does your study involve any procedures or tests that are NOT considered routine care?**

◉ Yes ○ No

If Yes, describe all procedures that will be done for Research Purposes ONLY.

Please see study detail in Section 29.1.

18.2 ***Are any of these procedures or tests investigational?**

○ Yes ◉ No

If Yes, describe how the investigational procedure differs from standard therapy:

19.0 Study Procedures Detail

19.1 ***Is the Investigator certified/trained in the use of the procedure(s)?**

◉ Yes
○ No
○ N/A

19.2 ***Is the procedure allowed under the scope of practice for staff?**

◉ Yes
○ No
○ N/A

19.3 ***Do the principal and other physician investigators have privileges to perform the proposed procedure(s)?**

◉ Yes
○ No

19.4 *Does the proposed research staff have the education and training required to perform the proposed procedures?

- [x] Yes
- [ ] No
- [ ] N/A

20.0 Drugs

20.1 *Does your study involve the use of any drugs?

(•) Yes ( ) No

21.0 Drug Details

21.1 *Are any investigational drugs used in the study?

(•) Yes ( ) No

21.2 *List all investigational drugs and active comparator drugs to be used in this study:

View Details	Drug Name	FDA Approved	A new drug or a new use of an already approved drug:	IND Number
⊟	**Trade Drug Name:** Belsomra **Generic Drug Name:** **Investigational Drug Name:**	Yes	Yes	Requires initial IRB approval

Trade Drug Name:	Belsomra
Generic Drug Name:	
Investigational Drug Name:	
Is the drug supplied at no cost?	No
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	Yes
Is an IND necessary	Yes
IND Number	Requires initial IRB approval
Who holds the IND:	PI holds the IND
IND details:	After this submission has received approval from the Scripps Office for the Protection of Research Subjects, Dr. Mason will apply for an IND from the FDA (IRB approval of the protocol is required for IND submission).
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	
Dose Range:	15 mg
[illegible]	[illegible]

Will the investigational pharmacy be dispensing?	No
Identify who will be preparing the investigational drug /biologic for administration and describe in detail how it will be prepared:	The study drug will be purchased and over-encapsulated to match double-blind placebo by a local compounding pharmacy.
Indication(s) under Investigation:	Alcohol Use Disorder (AUD)
Where will the drug be stored	Scripps Research, Laboratory of Clinical Psychopharmacology
Drug Storage Restrictions (including temperature, etc.):	Room temperature
Administration Instructions:	15 mg to be taken orally at 9:30 pm
Possible Untoward Effects, Their Symptoms & Treatment:	Somnolence
Contraindications and Interactions, If Known:	Narcolepsy, CYP3A inhibitors and inducers, digoxin

21.3 *Describe your plan for storing, dispensing and accounting for the study drug(s).

The medication is stored in a locked cabinet in the medication room that is kept locked at the Laboratory of Clinical Psychopharmacology at Scripps Research. Our pharmacy technician will prepare and label an individual dose of double-blind medication (15 mg of suvorexent or matched placebo) per the computer-generated randomization code.The pharmacy technician will also keep the randomization code and maintain record of study medications dispensed throughout the study. The Study Coordinator will walk the subject to Scripps Green Hospital on day of admission and provide a labeled bottle containing a single dose to a designated hospital staff member. The subject will be given their single dose of double-blind study medication at Scripps Green Hospital at 9:30 pm by hospital staff.The Study Coordinator will document the names of the staff members at Scripps Green Hospital who receive the study medication.

21.4 *Name all persons who will dispense the study drug(s) and sign drug accountability records.

Sam Reed
Jessica Bess

21.5 *Has the investigational pharmacy been notified?

- ○ Yes
- ◉ No

If Not, please explain:

N/A

21.6

Check all drugs that will be paid for by the sponsor or study budget.

- ☑ Investigational Drugs
- ☑ Other Study Drugs (including placebo)

21.7 If applicable, offer a proposed mechanism of action for investigational drugs or approved drugs under study for a new indication:

Orexin antagonist

22.0 Medical Devices

22.1 *Does your study involve the use of any medical devices?

○ Yes ◉ No

23.0 Alternative Treatments

23.1 *Are there alternative drug(s), device(s) or procedure(s) that are approved for use in the United States?

○ Yes ◉ No

If Yes, describe.

This is not a treatment study.

23.2 *Is the study drug/device/procedure currently available without participating in the study?

◉ Yes ○ No

If Yes, describe:

Suvorexent is currently marketed for treatment of insomnia.

24.0 Data and Safety Monitoring

24.1 *Describe the plan for monitoring data and safety. *(A plan is REQUIRED.)*

Data and Safety Monitoring
Potential risks and benefits for participants
Stringent procedures will be followed to minimize the risk of adverse reactions to this single-dose study, including the following:
• Subjects will be excluded who are at increased risk through a thorough medical history, physical exam, including ECG, blood chemistry, complete blood count (CBC), liver function tests (LFT's), urinalysis, and urine toxicology screen for drug of abuse. Subjects with any conditions that would expose them to unusual risk (e.g., significant medical disorders or pregnancy) will be excluded.
• Subjects will be carefully monitored by the P.I. and Michael Skinner, M.D., PharmD, Safety Monitor, during weekly laboratory meetings with all personnel involved in the study.
• A menstrual history, negative pregnancy test, and birth control will be documented in women to avoid giving study drugs to women with unrecognized pregnancies.
• Female subjects of childbearing potential will be instructed to use an effective (i.e double barrier) form of birth control for the duration of the study and for 1 week thereafter.
• Study medication will be administered according to a protocol reviewed for safety by the FDA and conducted under an IND. The medication studied is considered safe when used in accordance with the procedures to be employed in the study.
•Pre and post treatment testing of motor coordination and mental alertness (e.g., the digit symbol test) will verfify the absence of any adverse drug effects (daytime somnolence) prior to leaving the lab.
• The clinical ratings and blood tests will be performed by experienced personnel to minimize complications and unnecessary fatigue and distress.
• At the follow-up visit, subjects who report significantly increased alcohol consumption or serious psychiatric/medical symptoms will be offered a referral to treatment specific to their

Every effort will be made to minimize the risk of clinical deterioration during the study and at the follow-up visit including the following:
• Participants will not receive the medication if they have any signs or symptoms that may contraindicate its administration.
• The subjects will be closely monitored and highly trained and experienced personnel will provide a degree of supervision that might not be available under usual treatment conditions.
• The study physician will evaluate any subject experiencing clinical deterioration and make a clinically-based decision regarding study discontinuation and referral for appropriate care in consultation with the P.I. Criteria for study termination include: development of intolerable side effects; development or worsening of a physical or psychiatric disorder that requires treatment that would be in violation of the protocol. If a subject is discontinued, every attempt will be made to perform the evaluations specified for the final visit at the time of discontinuation. Reason(s) for premature termination will be documented in the case report form.
•Participants will be evaluated for adverse events 1-day and 1-week post-treatment.
• Importantly, the research group has a well-established record of subject safety in the conduct of analogous clinical laboratory trials and they will receive monitoring of their overall health status while in the study.

Patient confidentiality will be preserved by the following measures:
• Keeping the subject case report forms in locked file cabinets.
• Case report forms and computerized data will be identified by numerical code so that the subject's name will not be used.
• No information will be released to non-study personnel regarding the identity or progress of subjects without written request by the individual subject to the P.I. In addition to the aforementioned protection of privacy, a Certificate of Confidentiality will be obtained to protect against involuntary disclosure of the identities of research participants.
• Electronic datasets will be password protected and accessible only to authorized personnel.

Collection and Reporting of AEs and SAEs
The P.I. will be responsible for monitoring the conduct of this single-site, single-dose human laboratory study to ensure the safety of participants. The P.I. will monitor subject side effect complaints in consultation with study physicians and Dr. Michael Skinner, MD, Pharm D, our independent Medical Safety Monitor, who has over 2 decades of experience as a Research Physician in the pharmaceutical industry involved in Phase I, II and III clinical trials. If a SAE occurs, the P.I., in consultation with the Study Physician, Farhad Shadan, M.D., and the Independent Clinical Safety Monitor, Michael Skinner, M.D., PharmD., will report it to the IRB, our NIAAA Project Officer and the US FDA within 48 hours of becoming aware of the event. The written report will capture all safety information including the date of SAE onset, a description of the event, action taken, and whether a relationship between the SAE and drug exists. In addition, a summary of all SAEs that occurred during the previous year, and their outcomes, will be included in the annual progress report to the FDA, NIAAA and our IRB. AEs will be documented at each study visit on the Adverse Event case report form by recording of each adverse event and onset, duration, severity, relation to study medication and any clinical action. These will be compiled and reported to the FDA, NIAAA and our IRB in the annual progress report.

Management of SAEs or Other Study Risks
The study physician will be responsible for managing a drug-related SAE and/or making referrals for appropriate care, as needed, until the problem has resolved or stabilized with no further change expected.

DSM Plan Administration
Responsibility for data and safety monitoring
The P.I. is responsible for monitoring this single-site, single-dose human laboratory trial. Dr. Mason will meet with members of her staff and the Study Safety Monitor, Dr. Skinner, on a weekly basis to discuss progress of the study, subject enrollment and retention, the clinical status of active subjects and any safety issues as they arise.

Frequency of DSM
All case report form data will be entered into an electronic file as they are completed. Data safety monitoring will be conducted by the P.I. and Safety Monitor who will review adverse events on a weekly basis. The Safety Monitor will advise the P.I. and the study physicians if any changes in the study plan may be needed to improve subject safety.

Data safety and monitoring reports will be provided annually to the IRB, NIAAA and the FDA. We will use pre-established criteria and procedures for reporting AEs, SAEs, issues potentially arising from conflicts of interest, significant protocol changes, and/or cause for trial termination to the

DSM board plan
Per NIAAA guidelines, no DSM board is required for this single-site, early Phase II trial.

24.2 *Has a data and safety monitoring committee been set up for this study?

○ Yes ◉ No

25.0 Blood Draw

25.1 *Will blood be collected specifically for this research?

◉ Yes ○ No

26.0 Blood Draw Details

26.1 *Source of Blood Samples (*Check all that apply.*)

☑ Subjects as part of a clinical trial
☐ Blood Donors with a condition or a disease that are NOT part of a clinical trial
☐ The Scripps Research Institute (TSRI) Normal Blood Donor Service (NBDS)
☐ OTHER normal blood donors NOT part of the Normal Blood Donor Service (NBDS)

If Other, please explain where the samples are coming from:

(If you are using TSRI NBDS, be sure to include an NBDS Donor Information Form with your submission.)

26.2 *Describe in simple language how this blood will be used.

Blood samples will be used for serum pregnancy test (if female), complete metabolic panel (CMP), that includes gamma glutamyl transferase (GGT), and complete blood count with differential (CBC w/diff) for general bodily functioning, suvorexent plasma level and plasma cortisol level.

26.3 *How frequently will the blood samples be collected?

○ Less Than 2 Times per Week
◉ More Than 2 Times per Week
○ N/A Outside Scripps

26.4 *How much blood (ml) will be collected each draw?

◉ Less Than 50 Mls (10 teaspoons)
○ More Than 50 Mls (10 teaspoons)
○ N/A Outside Scripps

26.5 *Who will draw the blood?

Jenny Miller, our Research Medical Assistant who is a certified phlebotomist, will draw the blood

26.6 If blood will be obtained outside of Scripps, will the samples be obtained with Informed Consent? (*Note: If Yes, attach a copy of the IRB approval and/or approved Informed Consent from the other site to the Inital Review Submission Form.)*

- ○ Yes
- ○ No
- ◉ N/A

If No, please explain why:

26.7 ***Will the blood be used for genetic analysis?**

○ Yes ◉ No

26.8 **If Yes, will the results of the genetic analysis be shared with subjects? (REMINDER: If you plan to share the results, consider adding the Genetic Information Nondiscrimination Act language to the consent. Please click on the grey 'Help' button in the upper right to view the genetic language template.)**

○ Yes ○ No

If Yes, explain how the results will be used:

26.9 ***Will ALL blood samples used in the study be de-identified?**

◉ Yes ○ No

26.10 ***Will leftover de-identified blood be used for other studies? (*Future plans must first be reviewed by a Scripps IRB.)***

○ Yes ◉ No

27.0 Subject Compensation

27.1 ***Will subjects receive any payment or compensation for participation in this study?**

◉ Yes ○ No

28.0 Subject Compensation Detail

28.1 ***Describe all payments/reimbursement being offered to subjects, such as transportation expenses, meals, gifts, and other out-of-pocket expenses.**

Subjects will be reimbursed at the following rates: $50 for the screening visit (Visit 1), $500 for randomization, overnight hospital stay, and next-day cue reactivity procedures (Visit 2), and $50 for the 1-week follow-up visit (Visit 3). The total compensation for completion of all 3 study visits is $600.00.

How will subjects be paid? (*Check all that apply.)*

- ☐ Cash
- ☑ Check from investigator, sponsor, CRO, or other outside entity
- ☐ Check request or payroll payment through Scripps (requires W-9 tax form)

☐ Through payroll (Scripps Health Employees)
☐ Scripps Greenphire Card
☐ Other

If Other, please explain:

28.2 *How much will each subject be paid per visit? And in total?

See 28.1

28.3 *Describe your plan for issuing subject payments: (For example: per visit, end of study, etc.)

Subjects will be paid with a check at the end of each visit that they complete.

28.4 *Will there be any costs (such as prolonged hospitalization, extra tests, co-payments) to subjects associated with their participation in research?

○ Yes ◉ No

If yes, please explain.

28.5 Who will pay for the treatment of a research related injury?

☐ Sponsor
☐ Subject or his or her medical insurance
☑ Other
☐ Not Applicable

If other, describe.

If a subject needs either medical care or urgent medical treatment as a result of their particpation in the study, TSRI general liability insurance will cover the costs.

29.0 Study Plan - Details

29.1 Research Methods - *Include the Schedule of Events or provide a precise description of the data collection methods. (Attach the Schedule of Events to the Initial Review Submission Form, if applicable)*

Overview of Study Design.
A total of 50 subjects will be randomly assigned to a single, double-blind, dose of suvorexent 15 mg (n = 25) or matched placebo (n = 25) to be administered at 9:30 pm on the Scripps Green Hospital inpatient unit. Subjects will meet the Diagnostic and Statistical Manual – 5th Edition (DSM V) criteria for alcohol use disorder of at least moderate severity (AUD-MS) and be non-treatment-seeking, to avoid exposing treatment-seeking individuals with AUD-MS to alcohol cues. Alcohol abstinence is required 2 days prior to dosing in order to test the effect of study drug when motivational symptoms of early abstinence are manifest. Human lab testing occurs at Scripps Research on the third day of abstinence.

Subjects will be escorted from Scripps Green Hospital to Scripps Research at noon following discharge from Scripps Green Hospital. Subjects will be tested in a validated model of risk factors for relapse in early abstinence that involves the following procedures: subjects are presented with 12 positive, negative or neutral affective images selected from the International Affective Picture System on a flatscreen monitor (IAPS). Each affective condition is followed by in vivo exposure to the subject's preferred alcoholic beverage or bottled water, which the subject is told to view and smell for 90 seconds and to not drink it. Endpoints selected assess the effects of

These methods inform the 3 stages of the addiction cycle: preoccupation/anticipation (craving), binge/intoxication (drinking quantity and frequency, binge drinking) and negative affect (mood, anxiety). Craving in response to alcohol cue exposure in the lab has been reliably predictive of subsequent drinking in alcoholics, and thus craving in response to in vivo alcohol cue exposure in the laboratory comprises the primary outcome for this study. Self-reported drinking data are collected as a secondary outcome during the week of post-treatment follow-up.

Subjects return 1 week after drug administration to assess any persisting effects on naturalistic measures of drinking, craving, sleep, and affect. A positive signal on such indices would lend support to the potential utility of the drug in the treatment of AUD-MS and identify endpoints likely to show a positive drug effect in clinical treatment trials.

Study Procedures:
Visit 1-Screening: After providing written informed consent, subjects complete the Screening Visit for initial evaluation of eligibility. A mini-cue session familiarizes subjects with the human lab setting and identifies non- cue-reactive subjects for study exclusion (Visual Analogue Scale [VAS] craving rating of alcohol cue < 3 points higher than water cue).

Visit 2-Randomization: Subjects complete the evaluation for eligibility. Medically cleared subjects complete baseline assessments and are randomized to receive a single-dose of the double-blind study drug. Study Coordinator will walk subject to Scripps Green Hospital for their overnight hospital stay and subjects will be administered their medication at 9:30 pm. The following day, Study Coordinator will return to Scripps Green Hospital at 12:00 pm to walk the subject back to the lab for their human laboratory testing session. Abstinence from alcohol will be assessed with breath alcohol concentration (BAC) and Timeline Followback Interview (TLFB) and confirmed retrospectively via urinary ethyl glucuronide and ethyl sulfate (EtG/EtS) testing, which can reliably detect alcohol metabolites in urine 80 hours after alcohol consumption. Upon confirmation of eligibility and completion of clinical assessments, subjects will be escorted to a lighting-controlled, sound-attenuated room for mood induction and alcohol exposure. Our alcohol cue reactivity methods have been described above. Upon completion of the study, subjects relax, are debriefed, and complete measures of craving and mood to verify a return to baseline. Post treatment testing of motor coordination and mental alertness (e.g., the digit symbol test) will verify the absence of any adverse drug effects (daytime somnolence) prior to the subject leaving our lab.

Visit 3 – Follow-Up: Subjects return 1 week after the lab session and discontinuation of study drug to assess persistence of any treatment effects and resolution of any adverse reactions. Motivational interviewing and potential treatment options are provided by a study clinician.

30.0 Study Plan - Clinical Trial

30.1 Clinical Trial Details

***Describe the design of the study (double blind, randomized, etc.)**
(Enter N/A if not applicable.)

Double-blind, random assignment

***Describe any preliminary data that supports or refutes the hypothesis to be tested.**

As of the date of this application's submission, there is no published preliminary data to provide.

Describe previous research, pre-clinical or clinical findings that led to the proposed research. (*In early phases of drug or device development where there is little human data, provide the type and number of patients who have received the drug, device or procedure to date.)

The orexin (Orx or hypocretin [Hcrt]) system regulates a range of physiological processes and is recruited by drugs of abuse (1). Two Orx receptors have been identified (OrxR1 [Hcrt-r1] and OrxR2 [Hcrt-r2]) [2-4]. Orexin neurons in the lateral hypothalamus become activated by stimuli that are associated with food, morphine, cocaine, and alcohol [5-8]. The blockade of OrxR1 decreases alcohol [9] and nicotine [10] self-administration and prevents cue- and stress-induced

of abuse than by natural non-drug reinforcers [8]. For example, although stimuli that were conditioned to cocaine, alcohol, and a conventional reinforcer (palatable food reward) were equally effective in eliciting reinstatement, blockade of OrxR1 selectively reversed conditioned reinstatement that was induced by a cocaine- or alcohol-related stimulus but had no effects on the same stimulus that was conditioned to a conventional reinforcer [14, 15]. One explanation for the preferential effects of OrxR blockade on conditioned reinstatement for drugs vs. non-drugs could be that drugs neuroadaptively alter the neural systems that regulate motivation that is normally directed toward natural rewards and is only revealed by pharmacological manipulations. There is evidence of the alcohol-induced dysregulation of Orx transmission. Earlier findings revealed that Orx mRNA is upregulated in the LH in inbred EtOH-preferring (iP) rats following chronic alcohol consumption [9]. Preliminary data suggest that a history of alcohol dependence downregulates LH Orx mRNA and, in turn, upregulates PVT Orxr1 rmRNA (and protein) during abstinence. This indicates that the Orx system, may acquire a preferential role in mediating the effects of stimuli that are conditioned to drugs vs. natural rewards over the course of repeated drug use. Thus, behavioral and functional evidence suggests a role for Orx signaling in the neurobehavioral and motivational effects of drugs of abuse [16-18] and strongly support the hypothesis that pharmacological manipulation of the Orx system, i.e., administration of an orexin antagonist, could prevent alcohol craving and relapse in abstinent individuals.

Suvorexant (Belsomra) is the only commercially available orexin antagonist. It received approval by the FDA in 2014 for treatment of insomnia, characterized by difficulties with sleep onset and /or sleep maintenance. While we recognize that such sleep problems are an important impediment to maintaining abstinence in patients with alcohol use disorder, that indication is not the focus of our study. Rather, in keeping with the overarching aims of our NIAAA-funded alcohol research center (AAXXXXX), we seek to clinically validate the above pre-clinical findings that orexin antagonism may have a role in decreasing alcohol craving and drinking relapse in participants with AUD, and thereby support recovery in early abstinence. Our center has found alcohol reinstatement to be blocked with same day administration of a single dose of orexin antagonist in rats (Remi Martin-Fardon, personal communication, 10/3/2019). Suvorexant has a mean 15 hour half-life in humans. It is to be taken orally, within 30 minutes of going to bed, in a single dose of 10 – 20 mg, based on clinical response. Risk of daytime somnolence has been associated with the 20 mg dose in pivotal sleep studies and alcohol interaction studies have shown increased risk of somnolence when the drug is combined with alcohol. Thus, we aim to balance scientific efficacy with protection of human safety by studying a single dose of 15 mg administered at 10pm on the Scripps Green Hospital inpatient unit where subjects will spend the night and be walked to our lab at Scripps Research at noon the following day, to complete testing in our validated lab model of risk factors for relapse in early abstinence. At no point will alcohol be consumed, and patients will have abstinence verified prior to hospital admission and prior to testing at Scripps Research. Pre and post treatment testing of motor coordination and mental alertness (e.g., the digit symbol test) will verify the absence of these adverse drug effects prior to leaving our lab.

***Describe and justify any withdrawal of standard medications or the inclusion of a placebo.**

Withdrawal of standard medications will not be allowed for inclusion into the study. Rather, if subjects are taking medications that are exclusionary, they will not be allowed to participate in the study.
A placebo group is necessary in order to effectively evaluate the effects of the target medication.

31.0 Recruitment and Advertising

31.1 *From where will subjects be recruited? Check all that apply:

- ☐ Outpatients
- ☐ Inpatients
- ☐ Your Own Patients
- ☐ Referrals from Other Physicians
- ☐ Hospital or Clinic - Logbooks, schedules, or any other institutional database
- ☐ Extramural data or tissue repository or disease database
- ☐ Commercial Company
- ☐ Advocacy Groups
- ☐ Private Practice
- ☑ Other

If other, describe.

We have a marketing firm, Dynamic Marketing, that creates social media content to advertise our study on Facebook and Instagram. Dynamic Marketing also utilizes sponsored posts on Facebook and Google Adwords. Every month, they write a blog post to create interest and drive traffic to our website. We also utilize our website, flyers, and Craigslist.

31.2 *How will subjects be recruited? Check all that apply:

- [ ] Direct contact in a medical setting
- [ ] Direct contact in a non-medical setting (explain)
- [ ] Newspaper Ad (include publication and date)
- [x] Broadcast media (television/radio/internet)(include details)
- [ ] Posted Notice (location(s))
- [ ] Dear Valued Patient Letter (use the template located in Help - Click on the '?' icon in the upper right and it appears in the list)
- [ ] Newsletters (attach copy or Web site)
- [x] Flyers
- [ ] Recruitment Organization(s)
- [ ] Dear Colleague Letters
- [x] Social Media
- [x] Other

Provide additional information for any items checked above (if applicable):

See above

31.3 *Do you already have a list of potential subjects for this study?

( ) Yes (•) No

31.4 *Who will do the recruiting? (*Check ALL that apply.*)

- [ ] Investigator
- [x] Study Staff
- [ ] Recruiting Agency
- [ ] CRO - Clinical Research Organization
- [ ] Sponsor
- [ ] Other

If other, describe.

31.5 If a patient qualifies for more than one study, how will the Principal Investigator determine which study will be offered to the patient?

N/A

31.6 What limit will be placed on the number of consent forms that a patient will be expected to read and understand at any one time?

Subjects will be expected to read and understand one consent form, the one attached to this submission.

32.1 ***Are you requesting alteration of the informed consent process?**

○ Yes ◉ No

32.2 ***Are you requesting permission to waive in-person consent?**

○ Yes ◉ No

If Yes, how will informed consent be obtained?

33.0 Consent Procedure

33.1 ***Who will conduct the initial informed consent discussion?**
(IMPORTANT: Only personnel who have been added to the protocol in iMedRIS/iRIS and have completed the required education in human subjects protections may obtain informed consent.)

Jessica Bess, the Study Coordinator or Susan Quello, if the Study Coordinator is not available.

33.2 ***Describe the experience and qualifications of the person(s) named above.**

Jessica Bess has been working in Dr. Mason's lab as a Study Coordinator since 7/2017 and Susan Quello since 2003.

33.3 ***Describe the process of obtaining subjects' consent (Include where, when and how the consent will be obtained).**

Subjects are first spoken to on the phone and given a description of the study and a brief screening to see if they may likely qualify. The subjects that meet basic eligibility requirements and are willing to come in for a screening are given an appointment for their Screening Visit in the laboratory. Subjects will then come into the laboratory and be given the informed consent form (ICF) to read. They will then be asked if they have any questions about the study. If the subject understands the ICF and agrees to participate, they will sign where appropriate, witnessed by the study Coordinator, then the Study Coordinator will sign the ICF as well.

33.4 ***Describe the method of documenting that informed consent was obtained.**

Documentation of ICFs will be by written signature in the ICF and it is also recorded in the Visit 1 progress note. Informed consent forms will be kept in a separate binder in a locked cabinet in a locked room.

33.5 ***List any and all consent/assent forms that will be used.**

One consent form will be used (attached)

33.6 ***Have the consent/assent forms been previously approved by a Non-Scripps IRB?**

○ Yes ◉ No

If Yes, which Non-Scripps IRB? (Including commercial/academic IRBs)

If new information emerges that might affect a subject's willingness to continue in the study, we will incorporate the new information in an addendum to the original consent form for enrolled subjects, and also submit a revised consent form for new subjects containing the new information,

(NOTE: We suggest that new information be incorporated into a simple addendum to the original consent form for enrolled subjects and a revised consent form for new subjects.)

33.8 **If the study involves minors, describe the process of parental permission and how the assent of the minor will be sought.**

N/A

33.9 ***Will non-English speaking people be approached to participate in this study?**

○ Yes ◉ No

33.10 **If you need written HIPAA authorizations from subjects, these documents must be retained for at least 6 years.**

Note: If research is conducted in a Scripps hospital, a copy of the consent form, including the Authorization, must be filed in the subject's hospital medical record.

*Check which of the following 3 methods you will use:

- ☐ Retain the entire consent form for 6 years
- ☐ Retain the Authorization separately for 6 years
- ☐ Copy the HIPAA Authorization page and send it to Health Information Services
- ☑ Not Applicable

34.0 Waiver of Privacy Rule Authorization

34.1 ***Are you requesting to waive individual Privacy Rule authorization?**

○ Yes ◉ No

35.0 Risks and Benefits

35.1

Describe all potential risks of participating in the study, *in simple terms.

Please include :

- **Risks to the subject's privacy and the confidentiality of data.**
- **The likelihood and seriousness of the most important risks. (Use %, if available, or range, such as 'likely', 'rare', etc.)**
- **If serious risks are involved, explain which risks are expected to be temporary and which might be permanent.**
- **Include the possible consequences of serious risks and possible treatment, if known.**

Subjects may experience fatigue and distress due to clinical evaluation by rating scales; increased urge to drink or feelings of depression or anxiety following cue exposure and/or stress induction procedures.

Subjects may feel pain or discomfort during blood draws when the needle pokes their skin. There may be bruising, swelling, pain or infection later at the puncture site, although this is unlikely. Dizziness and fainting are possible, but very unlikely.

Abnormal test results may cause subjects to experience anxiety and seek additional medical services, and therefore be a potential risk of their research participation.

Medication Side Effects:
The most common adverse reaction (reported in 5% or more of patients treated with suvorexent and at least twice the placebo rate) was somnolence or sleepiness.

35.2 ***Will radiation or radioactive substances be used in your research?** ***For more information on Radiation Safety, move your mouse over the help bubble to the right and click on the link that pops up.***

○ Yes ◉ No

If Yes, have you submitted the Protocol and Informed Consent form to the Radiation Safety Committee Officer?

○ Yes ○ No

If NO, be advised that you must submit to the Radiation Safety Committee Officer.

35.3 **Describe any use of radiation, including X-rays, fluoroscopy, radioisotopes or protons. Protocols that include any research use of radiation, radioisotopes or protons must be submitted to the Radiation Safety Committee for review.**

35.4 ***Does the research protocol involve the use of designated HAZARDOUS CHEMICALS in the clinical setting?**

○ Yes ◉ No

List chemical(s) requiring review.

35.5 **Describe procedures for minimizing any potential risks, including risks to confidentiality, and assess their likely effectiveness.**

Investigators and research personnel are trained in ethical standards for human research and are current with IRB requirements for training and certification. To insure that all research activities are in full compliance with IRB standards, Dr. Mason chairs a weekly meeting with the research team to provide oversight regarding recruitment, research procedures and the clinical status of all active subjects.

Protections Against Risk
Suvorexent will be administered according to a protocol reviewed for safety by the FDA and conducted under IND or waiver of IND, per the decision of FDA. Subjects will take the medication in an inpatient setting and be told not take any herbal, over-the-counter or prescribed drugs unless approved by the study physician. The 15 mg dosage is within the currently approved dose ranges for suvorexent. Suvorexant has a mean 15-hour half-life in humans. It is to be taken orally. Risk of daytime somnolence has been associated with the 20 mg dose in pivotal sleep studies and alcohol interaction studies have shown increased risk of somnolence when the drug is combined with alcohol. Thus, we aim to balance scientific efficacy with protection of human safety by studying a single dose of 15 mg administered at 9:30 pm on the Scripps Green Hospital inpatient unit where subjects will spend the night and be walked to our lab at Scripps Research at noon the following day, to complete testing in our validated lab model of risk factors

post treatment testing of motor coordination and mental alertness (e.g., the digit symbol test) will verify the absence of these adverse drug effects prior to leaving our lab.
Importantly, the research group has a well-established record of patient safety in the conduct of similar human laboratory studies and pharmacological trials. Suvorexent is considered safe when used in accordance with the procedures to be employed in the study and exposure to drug is of brief duration i.e., a single-dose administration. Subjects with any conditions which would represent increased risk, e.g. significant medical or psychiatric disorders or pregnancy, will not be admitted to the study. Stringent procedures will be followed to minimize the risk of adverse reactions. These include the following: 1.) a medical history; 2.) a physical exam, including EKG, blood chemistry, complete blood count (CBC), liver function tests (LFT's), urinalysis, and urine toxicology screen for drug of abuse; 3.) a menstrual history, negative pregnancy test prior to study admission, and birth control will be documented in women of childbearing potential, to avoid giving suvorexent to women with unrecognized pregnancies; 4.)Women of child bearing potential will advised to use an effective method of birth control for study duration and for 1 week thereafter; 5.) and close medical supervision. Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until a clinically stable endpoint is reached. The clinical ratings and blood tests will be performed by experienced personnel to minimize complications and unnecessary fatigue and distress.

All subjects are required to be abstinent a minimum of 3 days prior to the lab session. Depending upon the extent of alcohol use and individual tolerance some subjects may be at risk for alcohol withdrawal. To protect against these risks each subject will be carefully evaluated with the CIWA by an experienced study clinician at the randomization visit for potential withdrawal risk and symptoms, including vital signs, time of last drink, quantity consumed, pattern of drinking, and history of alcohol withdrawal. In the unlikely event that significant (CIWA > 8) withdrawal symptoms are present, subjects will not proceed with the study and will be referred to a nearby detox facility.

Subjects may benefit directly from study medications, evaluation of their medical status, and study participation. Prior follow-up of non treatment-seeking subjects in our human lab studies with alcohol dependence have shown no harmful effect and increased likelihood of entering treatment following participation. During the course of the study, subject care will be supervised by a physician. Medical and laboratory examinations will be conducted prior to drug administration or at any time the subject develops adverse reactions. Subjects are provided with phone numbers to call for 24/7 medical attention. Any subject who develops side effects or medical complications that cannot be satisfactorily treated within the parameters of the research protocol will be discontinued from the study and referred for the most appropriate medical care.

Confidentiality will be preserved by the following measures: keeping the subject case report forms (CRF) in locked cabinets; CRF's and computerized data will be identified by numerical code so that neither the subject's name will not be used; no information will be released to non-study personnel regarding the identity or progress of subjects without written request by the individual subject to the Principal Investigator. A Certificate of Confidentiality will be obtained to protect against involuntary disclosure of the identities of research participants.

35.6 **What provisions have been made for ensuring that medical or professional intervention is available to subjects if an adverse event occurs?**

Every effort will be made to minimize the risk of clinical deterioration. The subjects will be closely monitored. Highly trained and experienced personnel will provide a degree of supervision that may not be available under usual treatment conditions. A study physician is available 24 hours a day, 7 days per week in the case of clinically significant adverse events. The study physician will evaluate any subject experiencing clinical deterioration and make a clinically-based decision regarding study discontinuation and referral for appropriate care in consultation with the P.I.

35.7 ***Is there potential for direct benefit to the subject?**

(•) Yes ( ) No

If yes, describe.

Subjects may benefit directly from study medication, evaluation of their medical status, and study participation.

***Will there be benefit to the class of subjects or to society?**

(•) Yes ( ) No

If yes, describe.

Alcohol use disorder is a chronic relapsing disorder characterized by repeating cycles of pathological alcohol use, acute withdrawal and protracted abstinence. The cost to society is enormous with estimates in excess of 220 billion dollars per year related to medical costs, lost productivity and premature death. To date, 3 medications have FDA approval for alcohol dependence, disulfiram, naltrexone, and acamprosate. However, all current drugs for alcohol dependence are underutilized and have modest effect sizes, underscoring the critical need for the development of pharmacotherapies with larger effect sizes to move the alcohol dependence treatment field forward.

We anticipate that alcohol dependent subjects treated with suvorexent will report significantly decreased craving for alcohol following alcohol cue exposure in the laboratory and report fewer symptoms of protracted abstinence (e.g., craving, relapse to drinking, mood and sleep disturbances) under naturalistic conditions, relative to those treated with placebo. This will allow future development of suvorexent as a potential treatment option for alcohol dependence, which will benefit society as a whole.

35.9 ***Describe why you think the risks to subjects are reasonable in relation to the anticipated benefits?**

The risks to subjects are reasonable in relation to the anticipated benefits because all measures will be taken to minimize risks to research participants. The health and safety risks associated with being a research subject are far outweighted by the potential direct benefit of reducing heavy alcohol consumption, and contributing to research that may reduce alcohol use disorder in society.

36.0 Surveys and Questionnaires

36.1 ***Does the project involve the use of Surveys, Questionaires or Interviews?**

(•) Yes ( ) No

37.0 Surveys and Questionnaires Detail

37.1 ***Will subjects be identified in any way?**

( ) Yes (•) No

38.0 Study Population

38.1 ***Briefly describe your targeted population. (*Patients with a condition or disease, healthy control subjects, etc.*)**

We are looking to recruit 50 paid, non-treatment seeking, alcohol-dependent but otherwise healthy male and female volunteers between the ages of 18-70.

38.2 ***Explain rationale for using human subjects.**

The purpose of this study is to evaluate the efficacy of suvorexent as a potential treatment for alcohol use disorder of moderate or greater severity; therefore, use of humans is essential to determining the efficacy of suvorexent as a potential treatment in this disorder.

☐ Age Range Not Applicable

Enter the specific age range for study population.

From:

18

To:

70

38.4 *Gender

○ Male
○ Female
◉ Both male and female

38.5 *How many subjects are you planning to enroll at this institution/site?

50

If this is a chart review, indicate the number of charts: ***(If this is not a chart review, enter 0.)***

0

If necessary, provide explanation below.

38.6 *How many subjects will be enrolled at ALL sites? (Include Scripps and NON-Scripps)

50

If necessary, provide explanation below.

38.7 To achieve your needed number of subjects, how many subjects do you estimate will need to give informed consent? *(Allowing for screen failures)*

100

38.8 *Justification for the number of subjects required:

Previous studies in our lab have shown that we need to give informed consent to 100 subjects in order to enroll the 50 subjects required for the study.

38.9 Please check all potentially vulnerable populations that are included:

* *Regulated*

☐ Children / Minors (subjects less than 18 years) *

- ☐ Economically or educationally disadvantaged persons
- ☐ Non-ENGLISH speaking
- ☐ Diminished mental capacity
- ☐ Physically disabled
- ☐ Students
- ☐ Scripps Health Employees
- ☐ Scripps Research Institute Employees
- ☐ Other

If other, describe.

If including vulnerable subjects, explain why. Explain what safeguards are included to protect against coercion or undue influence.

38.10 Inclusion Criteria

***Use the link below to add inclusion criteria.**

Order Number	Criteria
1	• Male or female volunteers, 18-70 years of age. • Meets DSM-5 criteria for current alcohol use disorder of moderate or greater severity (AUD-MS). • In the month prior to screening, reports drinking ≥ 21 standard drinks per week if male, ≥ 14 if female, with at least one heavy drinking day (≥ 5 males, ≥ 4 females) per week. • Subjects will not be seeking treatment because the medication studies are not treatment trials, and to avoid exposing treatment-seekers to alcohol cues • Subjects must be abstinent a minimum of 3 days (but not more than 7 days) prior to the human lab session. • Negative BAC and a CIWA score of < 8 at time of randomization and lab session to eliminate acute alcohol or withdrawal effects on dependent measures. • In acceptable health in the judgment of the study physician, on the basis of interview, medical history, physical exam, EKG, routine urine and blood chemistry. • Subjects with a history of depression, who have been on a stable dose of anti-depressant medication for at least 3 months, and do not meet current DSM-V criteria for depression or anxiety. • Females with childbearing potential must have a negative pregnancy test on the screening and randomization visits and agree to use effective birth control for the duration required by a given study. • Able to provide informed consent and understand questionnaires and study procedures in English. • Willing to comply with the provisions of the protocol and take oral medication.

38.11 Exclusion Criteria

***Use the link below to add exclusion criteria.**

1	• Meets DSM-5 criteria for a major psychiatric disorder, including mood or anxiety disorders or substance use disorders other than alcohol or nicotine, or ,ild cannabis use disorder • Has a urine drug screen (UDS) positive for substances of abuse other than alcohol or marijuana • Significant medical disorders that will increase potential risk or interfere with study participation as determined by the study physician. • History of seizure disorders. • Liver function tests more than 3 times the upper limit of normal or elevated bilirubin. • Metabolism by CYP3A is the major elimination pathway for suvorexent, therefore, subjects taking CYP3A inhibitors or inducers will be excluded • Subjects taking digoxin • Treatment within the month prior to screening with (1) an investigational drug, (2) medications which may negatively interact with study medications, or (3) drugs that may influence study outcomes (e.g., disulfiram [Antabuse], naltrexone [ReVia], acamprosate [Campral], or anticonvulsants). • Ongoing treatment with medications that may increase risk, including prescribed, over-the-counter, and herbal preparations, as determined by the study physician. • Sexually active female subjects with childbearing potential who are pregnant, nursing, or refuse to use effective methods of birth control for the duration required by a specific protocol. • No fixed domicile and/or no availability by home or mobile telephone. • History of hypersensitivity to the study drug or the ingredients. • Failure to take double-blind medication as prescribed.

38.12 Provide justification for inclusion or exclusion of any group (gender, race, ethnicity or other):

All gender, race and ethnicity groups will be included.
Excluded groups include children and pregnant or breast-feeding women.

38.13 Subject Debriefing

Describe any debriefing procedure(s).

Following the cue reactivity procedures, subjects are debriefed and complete rating scales to assure that mood and craving have returned to baseline.

When will participants be given experimental results and the key to any study blinding?** ***(If not known, request this information from the Sponsor.)

Once the last randomized subject has completed the study and follow-up visit, the blind will be broken on drug assignment. At that time, subjects requesting the identity of their medication group assignment will be notified as to which group they were in during the study. Results will be available within one year of study completion.

39.0 Nursing, Allied Health and Health Services Research

39.1 *Is this Nursing, Allied Health or Health Services Research ? ***(Note: Health Services research is the study of the organization, delivery and financing of health care. Some projects of this type may be considered Qualitiy Assurance, Quality Improvement or Process Improvement but NOT research.)***

○ Yes ◉ No

40.0 Human Specimens and Cell Lines

40.1 *Will ANY specimens, other than blood, be obtained for this study?

◉ Yes ○ No

41.0 Human Specimens and Cell Lines Detail

41.1 Human Specimens

**With regard to human specimens, check all that apply.*

- ☐ Identifiable (patient identifiers (Name, Medical Record Number), Family History (Pedigree), Treatment and Outcome Data)
- ☑ Unidentifable (Demographics (Race, Gender, Age), Diagnosis, Histopathology, Specimen Descriptors (Type, Condition, Amount) - if Yes, may meet criteria for Exempt, Category 4
- ☐ Genetic Analysis
- ☐ Genomic Analysis
- ☐ Proteomic Analysis

41.2 *Specimen Type (*Check all that apply)*

- ☐ Cells
- ☐ Stool
- ☐ Hair / Nails
- ☐ Saliva
- ☐ Semen
- ☑ Urine
- ☐ Tissue
- ☐ Fluid
- ☐ Bone Marrow Aspirate
- ☐ Other

If fluid, tissue or other, describe.

41.3 *Will the specimens come from samples originally obtained for clinical purposes?

○ Yes ◉ No

41.4 If Yes, describe how the samples were obtained and if informed consent was required.

41.5 If No, where will the specimens come from?

The samples will be obtained for research purposes only during a subject's study visit at the lab. Subjects will provide saliva samples, urine samples, and will undergo blood draws all of which will be obtained at the lab. Informed consent will be required before any of the above-listed procedures are undertaken.

***Will specimens be maintained in such a way that the subjects can be identified?**

○ Yes ◉ No

If Yes, how will confidentiality be preserved?

Subjects initials, study number and age are used as sample identifiers. No name-identifying information will be used in sample collection, documentation, analysis, or storage.

41.7 ***Will specimens be transferred to or from a Scripps Health facility?** ***(If Yes, please complete a Materials Transfer Agreement.)***

○ Yes ◉ No

If Yes, how will specimens be identified?

If Yes, to which institution will specimens be transferred?

☐ TSRI
☐ Other:

41.8 ***Will this study involve human stem cells?** ***(If 'Yes', attach a copy of the ESCRO approval to the Initial Review Submission Form)***

○ Yes ◉ No

If Yes, are the human stem cells derived from human embryonic tissue?

○ Yes ○ No

If not from embryonic tissue, are the cells pluripotent or capable of being de-differentiated into pluripotent cells?

○ Yes ○ No

41.9 ***Does this study involve established human cell lines?**

○ Yes ◉ No

If Yes, name the cell lines:

If Yes, will human cell lines be obtained from a public repository or a public source?

○ Yes ○ No

Will these cell lines or data be linked directly to the subject from whom they were obtained?

○ Yes ○ No

41.10 ***Will saved samples or their derivatives have the potential to produce profits for the investigators or Scripps?**

○ Yes ◉ No

○ Yes ◉ No

41.12 ***Does this study involve gene transfer or recombinant DNA use in INDIVIDUAL SUBJECTS in a CLINICAL TRIAL?**

○ Yes ◉ No

If Yes, then review by an Institutional Biosafety Committee will also be required. To view information on Institutional Biosafety Review of Protocols Involving Gene Transfer Or Recombinant DNA (Appendix M of the NIH Guidelines), click on the Help bubble to the right.

41.13 **If Yes, explain.**

41.14 ***Does the research protocol involve the use of RECOMBINANT DNA TECHNOLOGY or BIOLOGICAL AGENTS or materials that may be infectious in the clinical setting?**

○ Yes ◉ No

List infectious agent or rDNA vector.

42.0 **Funding Source** (*If you are a Principal Investigator receiving a Federal funded grant for collaborative sites to conduct Human Subjects Research, contact the IRB office. You will need to submit IRB documents from the collaborating institution.)*

IMPORTANT: **If ANY funding for this project is coming from a Federal source (federal agency, federal government, National Institutes of Health, National Science Foundation, US military - such as Department of Defense, etc.), the source(s) MUST be entered in this section.**

42.1 ***Is this study funded by a commercial sponsor?**

○ Yes ◉ No

42.2 ***Is this study funded by a grant?**

◉ Yes ○ No

***Is this an SCMG grant?**

○ Yes ◉ No

If this study is funded by a grant, are you the PI receiving the grant?

◉ Yes ○ No

If you are the PI receiving the grant, will any other projects in the grant use human subjects?

◉ Yes ○ No

**If you are the PI for the entire grant, and checked 'Yes' to 'Human Subjects', please submit a copy of the entire grant.*

Please select one.

- ○ Applied/Pending
- ◉ Approved
- ○ Not Applicable

42.4 **Sponsor Protocol Number:**

N/A

42.5 **Grant Number:**

5P60AA006420-36

42.6 ***Granting Agency/Sponsor (You can select more than one agency.)**
(If your agency is not in the list, click on the help bubble to the right.)

If Departmental Funds are being used, click on 'Private' and choose 'Departmental Funds'.

Note: All studies must have an identifiable source of funding or they cannot be reviewed. Fill in the matrix below.

	Sponsor	Funding	Protocol Control	Data Coordination	Monitoring	Auditing	Pass Through Funding
Commercial							
Federal or State	National Institute on Alcohol Abuse and Alcoholism	■	□	□	□	□	□
Private							
CRO							
Department funds							

42.7 **Proposed Funding Date - BEGIN**

01/01/2018

42.8 **Proposed Funding Date - END**

42.9 **Are part of or all activities in this proposal funded by a training grant?**

(•) Yes ( ) No

Medication Development for Protracted Abstinence in Alcoholism: Suvorexant Versus Placebo

NCT04229095

Study Protocol Amendments-03/26/2020-06/22/2022

Suvorexant Amendments

Submitted on 09/30/20-Approved on 11/03/20

1. Adding COVID-19 nasal swab test for each study participant to be performed 72 hours prior to overnight stay in order to comply with UCSD-ACTRI's current "COVID Free" guidelines/requirement for overnight visits.
2. Changing suvorexant half-life from 15 to 12 hours.
3. Changing dose time of administration from 9:30 pm to 1:00 am.
4. Changing post-treatment testing of motor coordination and mental alertness (i.e, digit span test) to administration of The Epworth Sleepiness Scale. Subjects with a total score of greater than or equal to 10, will be taxied home.
5. Changing Visit 3 from an in person visit to a virtual visit.
6. Minor editorial changes to the Study Interview Application and including the previously IRB-approved addition to the Exclusion Criteria (ACQ less than or equal to 30 at Visit 1) and newly added Exclusion Criteria of VAS craving severity rating of alcohol cue less than or equal to 3 points at Visit 1.

General Review and Notification submitted on 05/27/21:

Notice of UCSD IRB deferral to Scripps IRB for oversight of this clinical trial

Submitted on 06/16/21-Approved on 07/06/21

We request approval to modify the time that subjects will be administered the 20 mg dose of suvorexant during their one-night, inpatient stay at USCD's CCR. This revision follows Eugene Sato, Operations Manager at the ACTRI CCR Clinic, making us aware that the clinic is currently experiencing a shortage of clinical and overnight staff. Based on those conversations, we have determined that it will be necessary for us to run 2 subjects simultaneously during the one-night, inpatient stay at the CCR. The study medication, suvorexant, has a 12-hour half-life, so we propose staggered dosing from 12:30 am-3:30 am based on the subject's appointment time for their cue reactivity procedure the following day at Scripps Research.

Submitted on 06/22/22-Approved on 07/06/22

Revise UCSD's COVID-19 testing policy.
Amend ECG procedure may be conducted at Visit 1 or Visit 2.

UCSD's ACTRI policy for the required COVID-19 nasal swab test has been revised from having the test completed 3 days prior to the overnight stay at a drive-thru testing site to having an at-home test administered the day of the overnight stay. We have amended the IFC to reflect the change in policy.

A total of eleven amendments were submitted for the protocol to receive approval for additional staff and study advertisements.