NCT04466215

Medication Development in Alcoholism: CORT118335 versus Placebo

IRB Study Protocol Date-10/01/2020

1.0

Scripps Office for the Protection of Research Subjects

Submission Packet to the Review Board

NOTE: YOUR FINISHED APPLICATION IS ATTACHED TO THE SECOND SECTION OF THIS INITIAL REVIEW SUBMISSION PACKET.

All required documentation is marked with a red askerisk.

Use this form to attach all supporting study documents along with the application interview you completed to assemble a packet which will be submitted to the IRB.

If you are using an independent IRB, attach the Investigational Drug Brochure and Draft Contract Budget in the Study Documents section.

1.1 Study Title:

Medication Development for Protracted Abstinence in Alcoholism: CORT118335 versus Placebo.

1.2 Principal Investigator:

Barbara J Mason, Ph.D.

1.3 *Lay Summary:

(500 words or less)

Please note that this summary must be in lay language, as this summary is reviewed by all members of the Insitutional Review Board (IRB), including our non-technical/non-medical members. Summaries not provided in lay language will be sent back for revision, which may possibly result in a delay of the protocol's review.

In your summary, please include the following information:

- **Include any pertinent information about the development of the drug/device/procedure**
- **Describe how the drug/device/procedure is thought to work. Include the rationale for testing the drug/deviceprocedure in the proposed population, if applicable.**
- **Comment on how use of the proposed drug/device/procedure differs from usual or standard care.**
- **Describe any possible advantages of the new drug/device/procedure that would make us eager to test it in our patients at Scripps.**
- **Comment on the need for new treatments for this disease under study.**
- **Justify the use of placebo, if applicable.**

The primary hypothesis under test is that treatment with CORT118335, a GR/MR antagonist that modulates the activity of cortisol and aldosterone, will result in significant improvements in subjective craving following alcohol-cue exposure in the lab and in naturalistic measures of protracted abstinence that include relapse to drinking, craving and disturbances in sleep and mood. Support for this hypothesis is provided by pre-clinical and clinical studies of GR and MR antagonists in AUD. Preclinical studies of the GR antagonist, mifepristone, showed reduced alcohol intake in alcohol-dependent rats, but not in non dependent animals, and a double-blind study of 56 non treatment-seeking alcohol dependent subjects showed 1-week of treatment with mifepristone 600mg/d significantly reduced alcohol craving and consumption compared to

placebo in the above human lab model (*Vendruscolo et al., 2015*). We recently completed a randomized, double-blind trial of 1-week of mifepristone 1200 mg/d, 600 mg/d or matched placebo followed by 8-weeks of counseling in 103 treatment-seeking outpatients with AUD. Preliminary analyses replicated the earlier effects of mifepristone found in the lab model involving non treatment seekers with AUD, i.e., significantly decreased drinking for the week on drug and for the following 2 weeks in individuals who did not have abstinence as a treatment goal. Effectiveness in this group was linearly related to mifepristone plasma level, with equivalent efficacy in men and women. Consistent with the half life of the drug, effects were not detected after 2 weeks post treatment. Individuals who entered treatment with abstinence as a treatment goal did well with counseling, regardless of whether their assigned drug was mifepristone or placebo. Mifepristone significantly ($p < 0.05$) improved ALT and GGT relative to placebo. Taken together, the preclinical, human lab model and clinical trial results lend support to the therapeutic potential of GR antagonism as a treatment strategy for AUD.

A relationship between the aldosterone-MR pathway and alcohol drinking also has been found in studies across 3 species: rats, monkeys and humans (*Acun et al., 2018*). Of note, non-abstinent AUD patients had significantly higher circulating aldosterone levels than abstinent AUD patients, and aldosterone levels were positively correlated with the quantity of alcohol consumed, as well as with craving and anxiety scores.

Spironolactone is an aldosterone/MR antagonist that has been shown to significantly reduce alcohol self-administration in rodent models of AUD, and an analysis of data from patients with AUD from the Veteran Birth Cohort, found those treated with spironolactone (for any reason, n=10,726) showed a significant reduction in Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) score, relative to AUD patients not treated with spironolactone (*Farokhnia et al., RSA 2020*, attached with permission).

One week of treatment with mifepristone, a GR antagonist, was well tolerated with no evidence of abuse potential, and no serious, severe, or unexpected adverse events or treatment discontinuations due to adverse events in 53 non treatment-seeking participants with AUD of moderate or greater severity in our human lab study (*Vendruscolo et al., 2015*). Similarly, in our recently completed clinical trial of 103 treatment-seeking outpatients with AUD of moderate or greater severity, 1-week of treatment with mifepristone was well tolerated, with headache (Mif=19.7%, placebo=12.5%) and fatigue (Mif=7.0%, placebo=12.5%) the only adverse events reported during treatment in ≥ 5% of subjects. Only one adverse event, headache, was rated as severe, and it resulted in study discontinuation in Week 5 of counseling, i.e., 4 weeks after the last dose of mifepristone, and it was rated as unrelated to study drug (mifepristone 1200 mg). One other subject discontinued treatment on Day 3 complaining of moderately severe nausea, sweating, loss of concentration and depression that was rated as possibly drug-related (mifepristone 600 mg). One SAE occurred that was rated as unrelated to study drug; a subject fell off a horse and was hospitalized 50 days after the last dose administration. Other than significant improvement in GGT and ALT in mifepristone-treated subjects, there were no treatment-related changes in ECG, lab values or vital signs.

Spironolactone is an aldosterone/MR antagonist that has been FDA-approved since 1960 for cardiovascular indications; the most common adverse reaction is gynecomastia after 1 or more months of chronic treatment. Spironolactone has been widely used in veterans with AUD with no safety concerns specific to AUD noted (*Farokhnia et al., RSA 2020*, attached with permission).

Taken together, the ability of CORT118335 to antagonize GR, and also possibly MR, combined with the preclinical and clinical safety and efficacy found in studies of GR and MR antagonists in AUD, lend support to the safety and potential efficacy of a proof-of -concept evaluation of the GR /MR antagonist, CORT118335, as a novel treatment for AUD.

1.4 **Include any appropriate comments for the submission.**

2.0 Application

2.1 ***Verify that the application you completed for this protocol is attached below. (If not, use the green link to attach.)**

Study Title:

Medication Development for Protracted Abstinence in Alcoholism: CORT118335 versus Placebo.

Edit/ View	Version	Title
	1.0	Study Interview Application (Version 1.0) - Attached

3.0 Informed Consent

3.1 *Attach the informed consent document(s) for this protocol. (*If a Normal Blood Donor Service Consent is necessary, attach that here also*).

Version	Title	Category	Language	Expiration Date	Consent Outcome	Checked Out	View Document
1.0	CORT118335 for Protracted Abstinence in Alcoholism [READ LEVEL = 9.8]		English				49.64 KB

4.0 Other Study Documents/Conflict of Interest Disclosure

4.1 Attach any other review board forms or study documents associated with the initial review submission.

Examples would include:

- ***entire grant application***
- ***sponsor protocol***
- ***investigational drug brochures***
- ***package inserts***
- ***questionaires***
- ***patient diaries***
- ***curriculum vitae***
- ***current California medical license***
- ***FDA letter***
- ***1572 - Statement of the Investigator - (Note: Be sure that any investigator on the 1572 is also on this application.)***
- ***Patient Info Booklet/Brochure (HDE)***
- ***FDA letter (HDE)***

(If you are using an Independent IRB be sure to attach Investigation Drug Brochure and Draft Contract Budget.)

Version	Sponsor Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
1.0		Annual NIH Progress Report	Annual Report				13.22 MB
1.0		CORT118335 IB	Investigator brochure				1.75 MB
1.0		Farokhnia et	Publications				

	al., RSA 2020		52.87 KB
1.0	Aoun et al., 2018	Publications	403.02 KB
1.0	Venditto/Simo et al., 2015	Publications	522.87 KB
1.0	FDA Form 1572	Other	12.71 MB
1.0	Concept Letter of Authorization to FDA for IND#142502	Investigator brochure	75.25 KB

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: CORT118335 versus Placebo.

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

CORT118335 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
Beneze, Alan	Sub-Investigator	View Training Record
Shadan, Farhad, M.D.	Sub-Investigator	View Training Record

3) Research Support Staff

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

6.0 HDE/HUD

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?**

N/A

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.)***

N/A

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 - Rancho Bernardo
- [ ] Scripps Genomic Medicine (STSI)
- [ ] Scripps Clinic - Torrey Pines
- [ ] 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.

N/A

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 Clinical Trial

16.1 ***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

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

○ Yes ○ No

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

◉ Yes ○ No

16.4 **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.

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☐ N/A
☐ NCT Not Listed

If NCT number is not listed, explain why:

17.0 Study Procedures

17.1 ***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 Section 18.0

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

◉ Yes ○ No

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

All procedures are for research purposes only.

18.0 Study Procedures Detail

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

◉ Yes
○ No
○ N/A

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

- (•) Yes
- ( ) No
- ( ) N/A

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

- (•) Yes
- ( ) No
- ( ) N/A

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

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

19.0 Drugs

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

(•) Yes ( ) No

20.0 Drug Details

20.1 *Are any investigational drugs used in the study?

(•) Yes ( ) No

20.2 *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:** CORT118335 **Generic Drug Name:** **Investigational Drug Name:**	No	Yes	Cross-referencing #142502

Trade Drug Name:	CORT118335
Generic Drug Name:	
Investigational Drug Name:	
Is the drug supplied at no cost?	Yes
Is the Drug FDA Approved:	No
Is this a new drug or a new use of an already approved drug	Yes
Is an IND necessary	Yes

IND Number	Cross-referencing #142502
Who holds the IND:	PI holds the IND
IND details:	Please see the Letter of Authorization (attached to this submission) from Corcept allowing Dr. Mason to cross-reference their IND for this study. Dr. Mason will hold the Investigator-initiated IND for this project.
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	
Dose Range:	900 mg
Frequency:	1x per day for 14 days
Route of administration:	Orally
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:	CORT118335 150 mg tablets and matched placebo tablets will be provided by Corcept Therapeutics. The daily dose of six 150 mg tablets will be packaged in wallet cards provided by Corcept Therapeutics that contains a 2-week supply of double-blind medication, plus a 1-wwek extra supply for rescheduling purposes if needed.
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:	900 mg (6 tablets) my mouth each morning with food
Possible Untoward Effects, Their Symptoms & Treatment:	Excessive glucocorticoid or mineralocorticoid receptor antagonism symptoms: Unusual tiredness or weakness Nausea and/or vomiting Dizziness when standing Aches and pains Loss of appetite or weight loss Dehydration Diarrhea Feeling depressed Participants reporting symptoms of excessive glucocorticoid or mineralocorticoid receptor antagonism during treatment will be discontinued from the study drug and seen promptly for medical evaluation
Contraindications and Interactions, If Known:	Chronic systemic steroid use and use of and drugs that are strong inhibitors and inducers of CYP2C9 will be exclusionary.

20.3 ***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. Our pharmacy technician will prepare and label a box containing a 2-week supply of double-blind medication (CORT118335 and placebo), plus a 1-week extra supply for rescheduling purposes if needed. They will also keep the randomization code and maintain record of study medication dispensed and returned throughout the study. The Study Coordinator or Clinical Research Assistant will monitor medication compliance by recording the number of pills dispensed at randomization (Visit 2) and returned at the cue session (Visit 3) on a drug dispensation case report form.

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

Sam Reed
Jessica Bess
Susan Quello

20.5 *Has the investigational pharmacy been notified?

○ Yes
◉ No

If Not, please explain:

N/A

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

☑ Investigational Drugs
☑ Other Study Drugs (including placebo)

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

Glucocorticoid receptor (GR)/ mineralocorticoid receptor antagonist

21.0 Medical Devices

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

○ Yes ◉ No

22.0 Alternative Treatments

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

◉ Yes ○ No

If Yes, describe.

Acamprosate, naltrexone and disulfram

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

○ Yes ◉ No

If Yes, describe:

23.0 Data and Safety Monitoring

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

Stringent procedures will be followed to minimize the risk of adverse reactions, including the following:

• Subjects will be excluded who are at increased risk as determined by the study physicians, Farhad Shadan, MD, PhD, and Alan Beneze, MD, based on a thorough medical history, physical exam, ECG, comprehensive metabolic panel (CMP) that includes potassium levels, complete blood count (CBC), liver function tests (LFT's), urinalysis, and urine toxicology screen for drug of abuse (UDS). Subjects with any conditions that would expose them to unusual risk (e.g., significant medical disorders or pregnancy) will be excluded. The CMP, CBC, LFT's, urinalysis, UDS, ECG and vital signs also will be obtained after the last dose administration.
• Subjects will be carefully monitored by the P.I. and Michael Skinner, M.D., PharmD, our independent Medical Safety Monitor, during weekly laboratory meetings with all personnel involved in the study.
• A menstrual history, negative pregnancy tests, and birth control will be documented in women to avoid giving study drugs to women with unrecognized pregnancies.
• All subjects of childbearing potential and their opposite sex partners will be required to use a double barrier form of birth control for the duration of the study and for one month thereafter.
• Subjects will be instructed to carry a wallet card at all times identifying the potential risk for excessive glucocorticoid receptor antagonism and excessive mineralocorticoid receptor antagonism and potential need for hydrocortisone in the settings of shock or surgery. The card will also contain contact information for the PI and study physician.
• Subjects will be advised neither to drive a car nor operate complex machinery until they have gained sufficient experience on drug to gauge whether or not it affects their mental and/or motor performance adversely.
• 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 needs.
• There are procedures for emergency unblinding of the medication.

Every effort will be made to minimize the risk of clinical deterioration during the study and at the follow-up virtual visit including the following:

• Participants will not receive the medication if they have any signs or symptoms that may contraindicate its administration, e.g., abnormal potassium levels.
• The subjects will be closely monitored.
• Participants will be asked about adverse events and concomitant medications at each visit.
• Participants will be instructed about signs and symptoms of adrenal insufficiency and how to contact the study physician in case they occur. The following language will be used in the informed consent:

Tell your doctor right away if you have any of these symptoms:
* Unusual tiredness or weakness
* Nausea and/or vomiting
* Dizziness when standing
* Aches and pains
* Loss of appetite
* Dehydration
* Diarrhea
* Feeling depressed

• Participants reporting symptoms of excessive glucocorticoid receptor antagonism during treatment will be discontinued from study drug and seen promptly for medical evaluation.
• Participants will repeat the CMP, CBC, LFT's, urinalysis, UDS, ECG and vital signs after the last dose administration to verify health status and rule out signs and symptoms of excessive glucocorticoid receptor antagonism and hyperkalemia.
• The study physician will evaluate any subject experiencing clinical deterioration and make a clinically-based decision regarding appropriate care in consultation with the P.I.
• Participants will be evaluated for resolution of adverse events 2-weeks post-treatment.
• Importantly, the research group has a well-established record of subject safety in the conduct of analogous clinical laboratory trials and subjects 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.
• 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 human laboratory study to ensure the safety of participants. The P.I. will monitor subject side effect complaints, clinically significant lab abnormalities and findings on physical exam in consultation with study physicians and Dr. Michael Skinner, MD, Pharm D, our Independent Medical Safety Monitor, who has over two 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., Ph.D., and the Independent Clinical Safety Monitor, Michael Skinner, M.D., PharmD., will report it to the Scripps-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 an indication 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, or results in death.

DSM Plan Administration

Responsibility for data and safety monitoring
The P.I. is responsible for monitoring this single-site 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 daily 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 IRB, NIAAA and the FDA.

DSM board plan
Per NIAAA guidelines, no DSM board is required for this single-site, early Phase 2 proof-of-concept study.

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

○ Yes ◉ No

24.0 Blood Draw

24.1 ***Will blood be collected specifically for this research?**

◉ Yes ○ No

25.0 Blood Draw Details

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

- [x] 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.)

25.2 *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 (CBC w/diff) for general bodily functioning. In addition, blood will be drawn for drug concentration and to measure plasma cortisol, aldosterone, and selected cytokines.

25.3 *How frequently will the blood samples be collected?

- (•) Less Than 2 Times per Week
- ( ) More Than 2 Times per Week
- ( ) N/A Outside Scripps

25.4 *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

25.5 *Who will draw the blood?

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

25.6 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:

25.7 *Will the blood be used for genetic analysis?

- ( ) Yes (•) No

25.8 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:

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

◉ Yes ○ No

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

○ Yes ◉ No

26.0 Subject Compensation

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

◉ Yes ○ No

27.0 Subject Compensation Detail

27.1 ***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), $75 for the randomization visit (Visit 2), $50 for an interim virtual visit between Visits 2 and 3, $275 for the cue reactivity visit (Visit 3), and $50 for the virtual follow-up visit (Visit 4). The total compensation for completion of all 4 study visits is $500.00.

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)
- ☐ Gift certificate
- ☐ Through payroll (Scripps Health Employees)
- ☐ Scripps Greenphire Card
- ☐ Other

If Other, please explain:

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

Subjects will be reimbursed at the following rates: $50 for the screening visit (Visit 1), $75 for the randomization visit (Visit 2), $50 for an interim virtual visit between Visits 2 and 3, $275 for the cue reactivity visit (Visit 3), and $50 for the virtual follow-up visit (Visit 4). The total compensation for completion of all 4 study visits is $500.00.

27.3 ***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. The payment

following the final, virtual visit will be mailed to the subject following completion of the visit.

27.4 ***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.

27.5 **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 particpiation in the study, TSRI general liability insurance will cover the costs.

28.0 Study Plan - Details

28.1 **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)***

This is a randomly assigned, double-blind, placebo-controlled outpatient study of the effectiveness of 2-weeks of oral CORT118335 (900 mg/d) for decreasing alcohol cue-induced craving for alcohol in subjects with alcohol use disorder of moderate or greater severity (AUD-MS). Alcohol cue reactivity procedures will be conducted on the last day of dosing (Day 14), with endpoints selected to assess the effects of drug on alcohol cue-induced craving in the lab, as well as on naturalistic measures of protracted abstinence involving sleep, mood, craving and relapse to drinking. A positive signal on such indices would lend support to the potential utility of the drug for the treatment of alcohol use disorder.

Initial Phone Screening

Clinically trained study personnel provide information about the study. Interested individuals who meet initial eligibility criteria are scheduled for a face-to-face intake evaluation.

Visit 1, Screening

After providing written informed consent, subjects complete a Screening Visit for evaluation of eligibility (see Table 1). The Mini-International Neuropsychiatric Interview (MINI; Sheehan & Lecrubier, 2015) for DSM-5 will be administered to determine the inclusion criteria of current AUD with ≥ 4 symptoms and to rule out major psychiatric disorders that would warrant study exclusion. The subject's demographic information, medical and alcohol use history, adverse events and use of concomitant treatments will be recorded using standardized forms. Vital signs and BAC will be assessed, and specimens for urinalysis, serum pregnancy test (if female), urine drug screen, blood chemistry that includes liver function tests (LFTs) and GGT, and complete blood count with differential (CBC w/diff) will be collected by the medical assistant and prepared for same day pick up by LabCorp for analyses. A mini-cue session familiarizes subjects with the cue reactivity lab setting and identifies non- cue-reactive subjects for study exclusion (Visual Analogue Scale [VAS] craving severity rating of alcohol cue ≥ 3 points higher than water cue).

Visit 2, Randomization

Subjects complete the evaluation for eligibility, including ECG, repeat negative pregnancy test and physical exam. Medically cleared subjects complete baseline clinical assessments and are randomized to receive a 2-week supply of double-blind study medication.

Visit 3, Alcohol Cue Session

Subjects return 2 weeks after randomization to complete the alcohol cue session. The alcohol cue session will last for two hours (Table 2).

Table 2. Alcohol Cue Session Procedures

Baseline
1:00 pm: Subject arrives: BAC, vital signs; adverse events and concurrent drug therapy; urine Etg/Ets screen for alcohol and uds for illicit drug use; blood samples obtained; TLFB; CIWA; clinical assessments (i.e., ACQ, PSQI, BDI, STAI).
1:40 pm: Subject prepped for cue session: electrodes attached, and impedance checked; baseline VAS obtained. Subject given instructions and cue-reactivity practice trial.

Cue-Reactivity Trials
2:00 pm: Step 1- Mood induction: subject exposed to block of 12 affective images (pleasant, unpleasant or neutral), psychophysiological recording.
Step 2- In vivo beverage cue: alcohol or water in front of subject for 90 s while recalling picture-induced mood, psychophysiological recording.
Step 3- Ratings: subjects complete VAS craving, and manipulation check in presence of beverage cue.
Step 4- Beverage removed from testing area after completion of ratings.
2:15 pm: Repeat Steps 1–4 for remaining affect-beverage trial combinations (six trials total).

End of Lab Study Procedures
2:45 pm: Debriefing and relaxation period, subject completes ACQ, and BDI-II to verify return to baseline.

Visit 4, Follow-up

Subjects will participate in a scheduled virtual visit 2-weeks after the cue session and discontinuation of study drug to assess persistence of treatment effects and resolution of any adverse reactions. Motivational interviewing and potential treatment options are provided by a study clinician. The study physician conducts a virtual review with all subjects of Week 3 lab results, ECG, status of any adverse events, and at-home Week 4 pregnancy test results with female subjects.

29.0 Study Plan - Clinical Trial

29.1 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.**

Our study is based on positive studies of mifepristone, a mixed glucocorticoid receptor (GR) antagonist and progesterone antagonist, in preclinical and human laboratory models of AUD (Vendruscolo et al., 2015) and a recently completed clinical trial of mifepristone in 103 outpatients with AUD (IND #114497, NCT02179749). This project also builds on positive preclinical studies of the GR/mineralocorticoid receptor (MR) antagonist, CORT118335, in rodent models of AUD, that found CORT118335 significantly reduced alcohol self-administration without affecting water self-administration or the consumption of a non-alcoholic saccharin-sweetened solution, indicating that CORT118335 did not suppress consummatory behaviors in general.

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 theoretical rationale for GR/MR as novel targets for reducing craving in AUD is based on the neurobiology of abstinence in AUD which involves activation of brain stress systems, which CORT118335 is hypothesized to normalize. This stress response is initiated by activation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to increases in glucocorticoid release. Glucocorticoids bind to GR and mediate adaptation to stress and regulate termination of the glucocorticoid stress response through negative feedback at the level of the HPA axis. Chronic stress, AUD, and the consequent impaired GR feedback have been proposed to lead to the dysregulation of HPA axis activity. Additionally, activation of GR drives MR activation of other stress-related neuropeptides, e.g., corticotropin releasing factor and norepinephrine, thereby further contributing to increasing stress, anxiety and compulsive-like ethanol drinking (Vendruscolo et al., 2012). Thus the activity of CORT118335 as a GR/MR antagonist may have significant therapeutic potential for AUD. A key rationale for the study of modulators of the brain emotional systems in AUD treatment is that medications that normalize the dysregulation or balance of the reward and stress systems may protect against relapse during protracted abstinence. For example, acute withdrawal and protracted abstinence from alcohol is associated with not only decreased dopaminergic function but also increased extrahypothalamic corticotrophin releasing factor function which is driven by GR. The GR is also involved in mediating inflammation, which has been identified as a potential treatment target for AUD; an ancillary benefit of CORT118335 may be a reduction in several inflammatory cytokines and chemokines that may be upregulated in AUD (e.g., TNF-alpha, IL-1, IL-2, IL-6, and chemokines CCL2 and CCL19) and have a positive feedback to reactivate and perpetrate a dysregulated HPA axis.

The primary hypothesis under test is that treatment with CORT118335, a GR/MR antagonist that modulates the activity of cortisol and aldosterone, will result in significant improvements in subjective craving following alcohol-cue exposure in the lab and in naturalistic measures of protracted abstinence that include relapse to drinking, craving and disturbances in sleep and mood. Support for this hypothesis is provided by pre-clinical and clinical studies of GR and MR antagonists in AUD. Preclinical studies of the GR antagonist, mifepristone, showed reduced alcohol intake in alcohol-dependent rats, but not in non dependent animals, and a double-blind study of 56 non treatment-seeking alcohol dependent subjects showed 1-week of treatment with mifepristone 600mg/d significantly reduced alcohol craving and consumption compared to placebo in the above human lab model (Vendruscolo et al., 2015). We recently completed a randomized, double-blind trial of 1-week of mifepristone 1200 mg/d, 600 mg/d or matched placebo followed by 8-weeks of counseling in 103 treatment-seeking outpatients with AUD. Preliminary analyses replicated the earlier effects of mifepristone found in the lab model involving non treatment seekers with AUD, i.e., significantly decreased drinking for the week on drug and for the following 2 weeks in individuals who did not have abstinence as a treatment goal. Effectiveness in this group was linearly related to mifepristone plasma level, with equivalent efficacy in men and women. Consistent with the half-life of the drug, effects were not detected after 2 weeks post treatment. Individuals who entered treatment with abstinence as a treatment goal did well with counseling, regardless of whether their assigned drug was mifepristone or placebo. Mifepristone significantly ($p<0.05$) improved ALT and GGT relative to placebo. Taken together, the preclinical, human lab model and clinical trial results lend support to the therapeutic potential of GR antagonism as a treatment strategy for AUD.

A relationship between the aldosterone-MR pathway and alcohol drinking also has been found in studies across 3 species: rats, monkeys and humans (Aoun et al., 2018). Of note, non-abstinent AUD patients had significantly higher circulating aldosterone levels than abstinent AUD patients, and aldosterone levels were positively correlated with the quantity of alcohol consumed, as well as with craving and anxiety scores.

Spironolactone is an aldosterone/MR antagonist that has been shown to significantly reduce alcohol self-administration in rodent models of AUD, and an analysis of data from patients with AUD from the Veteran Birth Cohort, found those treated with spironolactone (for any reason, n=10,726) showed a significant reduction in Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) score, relative to AUD patients not treated with spironolactone (Farokhnia et al., RSA 2020, attached with permission).

***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, then 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.

30.0 Recruitment and Advertising

30.1 *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
- [x] 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; Craigslist, and local newspapers like the San Diego Reader.

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

- [ ] Direct contact in a medical setting
- [ ] Direct contact in a non-medical setting (explain)
- [x] Newspaper Ad (include publication and date)
- [ ] 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

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

- ( ) Yes
- (•) No

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

- [ ] Investigator
- [x] Study Staff

- ☐ Recruiting Agency
- ☐ CRO - Clinical Research Organization
- ☐ Sponsor
- ☐ Other

If other, describe.

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

Currently there are no competing studies. Should our pending suvorexant study begin and overlap with recruitment for the CORT118335 study, we will alternate enrollment between the 2 studies as they are both under the aims of our P60 alcohol center grant. However, the suvorexant study involves an overnight inpatient stay that may not be possible for some subjects, e.g., due to pet or childcare responsibilities. Thus, we will try to keep enrollment balanced across studies while allowing for subjects' real-world constraints, should there be an overlap in recruitment.

30.6 **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?**

There is only 1 consent a subject will be expected to read and understand at any one time.

31.0 Alteration of Informed Consent

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

○ Yes ◉ No

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

○ Yes ◉ No

If Yes, how will informed consent be obtained?

32.0 Consent Procedure

32.1 ***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, MSW or Susan Quello, BA, BS

32.2 ***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 2017. Susan Quello has been working in Dr. Mason's lab since 2003.

32.3 ***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 in to 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.

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

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

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

1 consent form will be used (attached)

32.6 ***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)

32.7 ***How do you plan to inform subjects of new information that might affect their willingness to continue in the study?**

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.)

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

The study does not involve minors.

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

○ Yes ◉ No

32.10 **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

33.0 Waiver of Privacy Rule Authorization

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

○ Yes ◉ No

34.0 Risks and Benefits

34.1

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 or distress due to clinical evaluation by rating scales: increased urge to drink or feelings of depression or anxiety following cue exposure procedures.

Subjects may feel pain or discomfort during blod 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:
Given the small number of subjects studied, no adverse events specific to CORT118335 have been identified.
However, we have given extensive thought and consideration to the safety of CORT118335, a GR /MR antagonist, in subjects with AUD. There is no evidence of similar drugs having abuse potential or alcohol X drug interaction effects on psychomotor coordination or cognitive functioning. We base our conclusions about safety on our own experiences with mifepristone, a GR antagonist, in two studies involving a total of 156 subjects with AUD. In our first study, a human lab study involving 53 non treatment-seeking participants with AUD of moderate or greater severity (AUD-MS) mifepristone was well tolerated, with no evidence of alcohol X drug interactions or abuse potential, and no serious, severe, or unexpected adverse events or treatment discontinuations due to adverse events (*Vendruscolo et al., 2015*). Similarly, in our recently completed clinical trial of 103 treatment-seeking outpatients with AUD-MS, 1-week of treatment with mifepristone was well tolerate, with headache (Mif=19.7%, placebo=12.5%) and fatigue (Mif=7.0%, placebo=12.5%) the only adverse events reported during treatment in ≥ 5% of subjects. Only one adverse event, headache, was rated as severe, and it resulted in study discontinuation in Week 5 of counseling, i.e., 4 weeks after the last dose of mifepristone, and it was rated as unrelated to study drug (mifepristone 1200 mg). One other subject discontinued treatment on Day 3 complaining of moderately severe nausea, sweating, loss of concentration and depression that was rated as possibly drug-related (mifepristone 600 mg). One SAE occurred that was rated as unrelated to study drug; a subject fell off a horse and was hospitalized 50 days after the last dose administration. Other than significant improvement in GGT and ALT in mifepristone-treated subjects, there were no treatment-related changes in ECG, lab values or vital signs.

Spironolactone is an aldosterone/MR antagonist that has been FDA-approved since 1960 for cardiovascular indications; the most common adverse reaction is gynecomastia after 1 or more months of chronic treatment. Spironolactone has been widely used in veterans with AUD with no safety concerns specific to AUD noted (*Farokhnia et al., RSA 2020*, attached with permission).

Taken together, the ability of CORT118335 to antagonize GR, and also possibly MR, combined with the preclinical and clinical safety and efficacy found in studies of GR and MR antagonists in AUD, lend support to the safety and potential efficacy of a proof-of-concept evaluation of the GR /MR antagonist, CORT118335, as a novel treatment for AUD.

CORT118335 may cause excessive glucocorticoid or mineralocorticoid receptor antagonism.

Subjects will be told in the informed consent form to notify their doctor or study physician right away if they have the following symptoms:
* Unusual tiredness or weakness
* Nausea and/or vomiting
* Dizziness when standing
* Aches and pains
* Loss of appetite and weight loss
* Dehydration
* Diarrhea
* Feeling depressed

Subjects be given a wallet card to keep with them, to identify the potential risk of excessive glucocorticoid and mineralocorticoid receptor antagonism and potential need for hydrocortisone in the settings of shock or surgery. The card will also contain contact information for the study physician.

Subjects will be cautioned about operating machinery, including automobiles, until they are certain that taking CORT118335 does not affect their ability to drive or work with machinery.

34.2 ***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.

34.3 **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.**

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

○ Yes ◉ No

List chemical(s) requiring review.

34.5 **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 ensure 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
CORT118335 will be administered according to a protocol reviewed for safety by the FDA and cross-referenced under Corcept's IND #142502. Subjects will be advised to avoid driving or performing hazardous tasks until they know how thy will react to the medication, and to not take any herbal, over-the-counter or prescribed drugs unless approved by the study physician. The 900 mg daily dosage is currently under study for non-alcoholic liver disease and anti-psychotic-induced weight gain. Dosing regimens and durations were chosen to provide the minimum total duration of drug exposure that is still compatible with achieving optimal drug effects and maintaining subject safety.

Importantly, the research group has a well-established record of patient safety in the conduct of similar human laboratory studies and pharmacological trials. CORT118335 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., 2 weeks of 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 suvorexant 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 > 9) 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 use disorder 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.

34.6 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.

34.7 *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.

34.8 *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 use disorder, disulfiram, naltrexone, and acamprosate. However, all current drugs for alcohol use disorder are underutilized and have modest effect sizes, underscoring the critical need for the development of pharmacotherapies with larger effect sizes to move the alcohol use disorder treatment field forward.
We anticipate that subjects with an alcohol use disorder that are treated with CORT118335 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 CORT118335 as a potential treatment option for alcohol use disorder, which will benefit society as a whole.

34.9 ***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 out weighted by the potential direct benefit of reducing heavy alcohol consumption and contributing to research that may reduce alcohol use disorder in society.

35.0 Surveys and Questionnaires

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

(•) Yes ( ) No

36.0 Surveys and Questionnaires Detail

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

( ) Yes (•) No

37.0 Study Population

37.1 ***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 male and female volunteers with alcohol use disorder (AUD) of greater than or equal to moderate severity.

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

The purpose of this study is to evaluate the efficacy of CORT118335 as a potential treatment for alcohol use disorder of greater than or equal to moderate severity; therefore, use of humans is essential to determining the efficacy of CORT118335 as a potential treatment in this disorder.

37.3 ***Age**

[ ] Age Range Not Applicable

Enter the specific age range for study population.

From:

18

To:

75

37.4 ***Gender**

- ○ Male
- ○ Female
- ◉ Both male and female

37.5 ***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.)***

N/A

If necessary, provide explanation below.

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

50

If necessary, provide explanation below.

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

100

37.8 ***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.

37.9 **Please check all potentially vulnerable populations that are included:**

* *Regulated*

- ☐ Children / Minors (subjects less than 18 years) *
- ☐ Pregnant Women *
- ☐ Prisoners *
- ☐ 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.

37.10 Inclusion Criteria

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

Order Number	Criteria
1	• Male or female volunteers, 18-75 years of age. • Meets DSM-5 criteria for current alcohol use disorder of moderate or greater severity (AUD-MS, ≥ 4 symptoms). • 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 drinks/d if male, ≥ 4 drinks/d if female) per week. • Subjects will be non treatment-seekers because the study is not a treatment trial, 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 alcohol cue reactivity lab session. • Negative BAC and EtG/EtS and a CIWA score of ≤ 9 at the time of the lab session. • In acceptable health in the judgment of the study physician, on the basis of interview, medical history, physical exam, ECG, routine urine and blood chemistry. • Females with childbearing potential must have a negative pregnancy test on the screening and randomization visits. • All subjects must agree to use double barrier contraception for the duration of the study and one month thereafter, i.e., males must use condoms and females must use spermicide and/or a non hormonal barrier method, and their opposite sex partner must likewise use an effective non hormonal form of contraception. • 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.

37.11 Exclusion Criteria

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

Order Number	Criteria

- Medical conditions that could be aggravated by glucocorticoid and/or mineralocorticoid antagonism, such as: autoimmune disease, hypotension, or postural hypotension.
- Clinically significant findings on physical exam, ECG, urine or blood tests that may increase risk, e.g., serum potassium outside of the normal range.
- Meets DSM-5 criteria for a current major psychiatric disorder, including mood, anxiety or substance use disorders, other than alcohol, nicotine, or mild cannabis use disorders. However, 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 DSM-5 criteria for current depression or anxiety disorders may be admitted.
- Has an ACQ total score of ≤ 30 and/or is non cue reactive., i.e., VAS craving severity score < 3 points higher to alcohol cues than to water cues, at Visit 1 (screening).
- Cannot provide a urine drug screen negative for substances of abuse other than alcohol or cannabis.
- Liver function tests more than 3 times the upper limit of normal or elevated bilirubin.
- Pregnant or lactating.
- Treatment within the month prior to screening with (1) an investigational drug, (2) drugs 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.
- Chronic systemic steroid use
- Using drugs that are strong inhibitors and inducers of CYP2C9.
- No fixed domicile and/or no availability by home or mobile telephone.

1

37.12 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.

37.13 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.

38.0 Nursing, Allied Health and Health Services Research

38.1 *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

39.0 Human Specimens and Cell Lines

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

(•) Yes ( ) No

40.0 Human Specimens and Cell Lines Detail

40.1 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)
- [x] 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

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

- [ ] Cells
- [ ] Stool
- [ ] Hair / Nails
- [ ] Saliva
- [ ] Semen
- [x] Urine
- [ ] Tissue
- [ ] Fluid
- [ ] Bone Marrow Aspirate
- [ ] Other

If fluid, tissue or other, describe.

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

( ) Yes (•) No

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

40.5 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-referenced procedures are undertaken.

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

( ) Yes (•) No

If Yes, how will confidentiality be preserved?

40.7 *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:

40.8 ***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

40.9 ***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

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

○ Yes ◉ No

40.11 ***Does this study involve the storage of genetic data in electronic form?**

○ Yes ◉ No

40.12 *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.

40.13 **If Yes, explain.**

40.14 ***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.

41.0 **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.**

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

○ Yes ◉ No

41.2 ***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.*

41.3 ***Status of funding:**

Please select one.

○ Applied/Pending
◉ Approved
○ Not Applicable

41.4 **Sponsor Protocol Number:**

N/A

41.5 **Grant Number:**

P60 AA006420

41.6 ***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	NIH	■					
Private							
CRO							
Department funds							

41.7 **Proposed Funding Date - BEGIN**

01/01/2018

41.8 **Proposed Funding Date - END**

12/31/2022

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

○ Yes ◉ No

NCT0446615

Medication Development in Alcoholism: CORT118335 versus Placebo

IRB Summary of Amendments-11/11/2020-04/04/2022

Miricorilant Amendments

Amendment

Submitted on11/11/20-Approved on 12/09/2020

In obtaining our IND, the FDA requested that we add the following language to our exclusion criteria (Section 37.11 study application):
Based on the in vitro studies conducted for IND 142502, CORT118335 is
• exclusively metabolized by CYP2C19 (94%)
• concentration dependent inducer of CYP3A4 mRNA
• modest inhibitor of CYP3A4 (IC50, 3.9 μM), CYP2C9 (IC50, 5.1 μM) and CYP2C8 (IC50, 7.5 μM)
• potent inhibitor of BCRP (IC50, 0.2 μM) and UGT1A1 (IC50, 1.4 μM).
Given that the in vivo drug-drug interaction of CORT118335 and substrates or inhibitors of CYP enzymes or drug transporters have not been evaluated, in the proposed study, subjects taking substrates of CYP3A4, CYP2C9 and CYP2C8 will be carefully monitored for increased adverse effects of these substrate-drugs and those narrow therapeutic index drugs that are primarily metabolized by these cytochrome enzymes will be excluded.

Thus, subjects will be excluded who are taking:
• strong CYP2C19 inhibitors
• substrates metabolized primarily by CYP3A, CYP2C9 and CYP2C8 with narrow therapeutic index
• BCRP and UGT1A1 substrates

The FDA also asked us to provide criteria that would terminate the study. The following study stopping criteria was added and approved by the FDA:

Criteria to temporarily suspend the study have been established when either of the following specific safety thresholds are met:

• One participant with a Common Terminology Criteria for Adverse Events (CTCAE) Grade 4 treatment related SAE, or
• ≥ 2 participants with a CTCAE Grade 3 treatment related SAE

If the safety threshold is met, the independent Medical Safety Monitor along with a panel of qualified experienced physicians will meet to discuss and assess the severity and relationship of the SAE(s) to CORT118335 and provide a recommendation to the Principal Investigator whether the nature, frequency, and severity of adverse events associated with study treatment warrant the early termination of the study in the best interest of the participants, whether the study should continue as planned, or the study should continue with modifications. Regardless of this decision, FDA will be notified by the Principal Investigator and provided with a summary of the above AEs, as well as the panel's recommendation regarding study continuation and safety monitoring modifications, within 2 days of receipt of the recommendation from the panel.

We have amended the language in the medication supply section of the study application (Section 20.2) from: "The daily dose of six 150 mg tablets will be packaged in wallet cards

provided by Corcept Therapeutics that contain a 2-week supply of double-blind medication, plus a 1-week extra supply for rescheduling purposes if needed" to "The daily dose of six 150 mg tablets will be packaged in wallet cards provided by Corcept Theraputics. Each wallet card can support 7 days at 900mg/day. Subjects will be provided with 3 wallet cards: 2 cards to support the 2-week dosing duration and 1 additional card to permit rescheduling the cue reactivity testing if necessary. Corcept Therapeutics asked us to make this change for clarification.

We have submitted the study instructions and the study participant information card for approval.

We have partnered with Citrus Labs, a commercial company, to help us with our recruitment efforts for this study. Citrus Labs owns and operates the leading health app network, Mind Mates. Through the Mind Mate app, potential candidates will have already received education on clinical trials (risks, benefits, commitment required, etc.) and requested to participate in a relevant clinical trial. The app will be used to identify, pre-screen (we are requesting approval for the attached pre-screener questionnaire) and refer potential study candidates. The referrals will be delivered via a study dashboard provided by Citrus Labs. We have contracted with Citrus Labs to receive 40 guaranteed referrals.

We will also resume our social media advertising campaign on 12/1/2020 with Dynamic Marketing. Attached are examples of prior social media campaigns (November and December 2019). Since the study procedures and research methods are the same for all of Dr. Mason's Medication Development for Protracted Abstinence in Alcoholism studies, the attached examples will be updated with minor editorial changes.

Amendment

Submitted on 02/11/21-Approved on 03/15/2021

We received a safety Addendum (1) to the Investigator's Brochure Edition 5 from Corcept Therapeutics and modified the protocol accordingly.

We will obtain an additional blood draw for liver function tests at 9 days after the last dose of medication. Any subject with LFT's that are twice that of baseline and >2X the ULN will be followed to a return to baseline and until the subject is stable.

Subjects will be compensated $75 for the additional blood draw. The total compensation for the study is $575.00.

We have amended the name of the study drug from CORT118335 to miricorilant, now that it is being studied in humans under that name.

We request to add the Brief Irritability Test (BITe) to the self-report battery. It is a short 5-item questionnaire to assess irritability and, therefore, administration should not increase subject burden.

The EtG/EtS urine sample in the text of the IFC on page 3 was added to the Visit Schedule on page 4.

Dynamic Marketing will create brief videos (15-30 seconds), in place of written blog posts, advertising the study, or providing useful/helpful information to create interest and drive traffic to our social media posts. We request approval for the two attached videos for February.

We request approval for proposed Dynamic Marketing February social media content that is attached.

We request approval for the attached wallet card that will be given to subjects in case of suspected excess glucocorticoid blockade.

We request approval for Scripps Research COVID-19 procedures that have been added to a subject's email confirmation and driving directions and COVID screening questions to be administered prior to coming to the campus. Language was developed with and approved by Scripps Research's legal department.

Minor editorial changes were made to the IFC (removed abbreviations,) to foster readability and clarity for subjects.

We request approval to have subjects come to our lab, instead of going to Lab Corp, for the blood draw that takes place nine (9) days (plus or minus 2 days) after their Visit 3. Due to prior COVID restrictions, we scheduled this visit off campus. Now that Scripps Research has eliminated visitor COVID restrictions, scheduling subjects at our lab will allow us more control in obtaining this blood collection in the time period (7-11 days after Visit 3) window. We added this as a Visit 4 in the schedule of procedures and will also obtain Vitals as we do for all subject visits. The virtual follow up visit with the study physician is now changed to Visit 5.

Updated enrolled subjects and minor editorial changes (spacing) were also made to the informed consent.

We had 13 other IRB amendments/approvals for recruitment advertisements and administrative issues such as staff changes.