NCT03175549

Medication Development in Alcoholism: Apremilast versus Placebo

IRB Study Protocol Document Date: 06/14/2016

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: Apremilast 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 purpose of this study is to evaluate apremilast, a new selective PDE4 and TNF-a inhibitor that acts selectively on immune system targets. A recent review of pre-clinical studies indicate PDE4 and TNF-a inhibitors may be promising new medications for the treatment of alcohol and drug addiction. INIA-N investigators and others have found that nonspecific PDE4 inhibitors like rolipram and ibudilast reduce alcohol consumption in rats and mice, but these drugs have side effects, particularly nausea and vomiting, that significantly reduce patient acceptability. Apremilast is a new selective PDE4 and TNF-α inhibitor that shows less of the PDE4 adverse reactions; it has lower affinity for the PDE4D isozyme which is thought to be associated with the emetic effects of PDE inhibition. The Crabbe INIA-N group found apremilast (20 mg/kg)

significantly reduced g/kg of EtOH intake in 12 male and 12 female HDID-1 mice, with no interaction with sex; similar findings were obtained for rolipram using the same model (see Crabbe component for data). Furthermore, INIA-N investigators reported apremilast (15-50 mg /kg) reduced alcohol intake in C57Bl/6J male mice in both 24 h 2-bottle choice (2BC) and 2BC with intermittent EtOH exposure, with some anti stress-like effects noted. Effects of apremilast on reducing EtOH intake were replicated by the INIA-N Bell group in male P rats, with effects increasing in relationship to dose in a 24 h 3-bottle choice experiment.

The primary hypotheses under test are that alcohol dependent subjects treated with apremilast will report significantly decreased craving for alcohol following alcohol cue- and stress 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.

1.4 Include any appropriate comments for the submission.

The study procedures and research methods are the same for all of Dr. Mason's Medication Development for Protracted ABstinence in Alcoholism studies. The only change is the medication under investigation. An example is HSC#11-5841-Mifepristone for Protracted Abstineence. All questionnaires associated with this study have been submitted with prior applications.
After this submission has received approval from the Scripps Office for the Protection of Research Subjects, Dr. Mason will apply for an IND or IND exemption from the FDA (IRB approval of the protocol is required for IND submission). As required by the FDA, Dr. Mason will not initiate the study until 30 days after the date the FDA recevied the IND application, unless she receives early notification from the FDA that the study may begin. The Scripps IRB will be provided with the FDA notification prior to study initiation.

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: Apremilast 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
1.4	Consent dated 7/26 /16 *Clean	null	English	07/07 /2017	Void		402.74 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		Email response from PI /Coord. RE: statistical power	Correspondence				9.27 KB
1.0		FDA Waiver of IND letter dated 1/10 /2017 IND# 133604	FDA Letter				86.08 KB
1.0		1/9/17 Email from BGB allowing final IRB approval to be released with condition. see email	Correspondence				36.92 KB
1.0		Subject Drinking /Smoking Diary (undated)	Patient Diary				44.54 KB
1.0		Alcoholic Beverage Preference (undated)	Questionnaire				26.11 KB
1.0		Columbia-Suicide Severity Rating Scale (C-SSRS) Ver. 1/14/09	Questionnaire				91.14 KB
1.0		Clinical Institute Withdrawal Assessment for Alcohol Revised	Questionnaire				38.40 KB

		(CIWA-AR) (undated)				
1.0		Addiction Research Center inventory (ARCI) (undated)	Questionnaire			64.51 KB
1.0		Alcohol History and Illicit Drug Use Index (undated)	Questionnaire			53.76 KB
1.0		Fagerstrom Test for Nicotine Dependence (FTND) (undated)	Questionnaire			39.42 KB
1.0		Alcohol Dependence Scale (ADS) (undated)	Questionnaire			43.52 KB
1.0		State-Trait Anxiety Inventory (STAI) Dated: 1983	Questionnaire			43.52 KB
1.0		Pittsburgh Sleep Quality Index (PSQI) (undated)	Questionnaire			47.10 KB
1.0		Beck Depression Inventory-II (BDI-II) (undated)	Questionnaire			54.78 KB
1.0		Alcohol Craving Questionnaire-Short Form (ACQ-SF) (undated)	Questionnaire			35.33 KB
1.0		Apremilast (OTEZLA) Package Insert dated December 2014.	Investigator brochure			183.49 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: Apremilast versus Placebo

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

Apremilast 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
Kyle, Mark C, M.D.	**Sub-Investigator**	View Training Record
Quello, Susan B., B.A., B.S.	**Sub-Investigator**	View Training Record
Shadan, Farhad, M.D.	**Sub-Investigator**	View Training Record

B) Research Support Staff

Name	Role	Training Record
No Research Support Staff have been added		

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?**

Committee on the Neurobiology of Addictive Disorders

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: 858-652-5500] 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:

We are not associated with Scripps Health

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 ***Will the research involve obtaining individual patient authorization (via patient consent) to use and/or disclose Protected Health Information? *(If No, you must apply for a Waiver of Authorization from the IRB.) (Important: If you plan to use Protected Health Information, you must either obtain written authorization from the individual/patient/subject OR request a Waiver of Authorization from the IRB. If you apply for a Waiver, you will also need to provide a description of the data you plan to use. This description can be provided by using the Confidential Data Request form, available 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 - 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

If Other, enter site name.

14.6 Non Scripps and other collaborative research sites.

Please identify additional locations or facilities not listed above.

LabCorp will analyze urine and blood samples for general bodily functioning.
Redwood Toxicology Laboratory will analyze urine for ETG/ETS levels.

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.***

☐ 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.

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 study detail in Section 28.1

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

○ Yes ◉ No

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

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:** Otezla **Generic Drug Name:** Apremilast **Investigational Drug Name:**	Yes	Yes	Requires initial IRB approval.

Trade Drug Name:	Otezla
Generic Drug Name:	Apremilast
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:	The PI will obtain and hold the IND through the entirety of the study.
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	
Dose Range:	5-60 mg
Frequency:	1 tablet, twice a day (AM/PM)
Route of administration:	Oral
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:	Medication will be purchased from a retail pharmacy, over-encapsulated by San Diego Compounding Pharmacy, and dispensed in blister cards by the lab pharmacy technician.
Indication(s) under Investigation:	Alcohol Use Disorder
Where will the drug be stored	The drug will be stored in a locked cabinet which is located in a locked room accessible by study staff.
Drug Storage Restrictions (including temperature, etc.):	The drug will be stored in its initial packaging in a temperature controlled, locked room until it is placed into study-specific blister cards for dispensation to the research subject.
Administration Instructions:	Administration and dosing instructions will be provided by the Study Coordinator to the subject. Subjects will be instructed to take 2 tablets (1 in the AM, 1 in the PM) a day, for every day leading up to their Cue reactivity session. They will be instructed to return any unused study medication upon their return to the laboratory. Safety information (such as not taking any supplemental or over-the-counter medications, not sharing the study medication with others, etc.) will also be provided, along with the study physician's emergency contact information in case of adverse events or side effects.
Possible Untoward Effects, Their Symptoms & Treatment:	Common adverse reactions (5% or greater) are diarrhea, nausea, headache and upper respiratory tract infections, which will be managed, if necessary, by interventions recommended by study physicians. Less commonly, depression and suicidal thoughts may occur. Subjects will be screened with the MINI diagnostic interview, Columbia Suicide Scale and Beck Depression Inventory-II to exclude at risk subjects from study participation, and mood will be systematically monitored through study completion.
Contraindications and Interactions, If Known:	Contraindications are known hypersensitivity to apremilast or any excipients in formulation. Use with strong cytochrome P450 enzyme inducers may result in loss of efficacy and are disallowed by the study protocol.

⊟	**Trade Drug Name:** Otezla **Generic Drug Name:** Apremilast **Investigational Drug Name:**	Yes	Yes	Requires initial IRB approval.

Trade Drug Name:	Otezla
Generic Drug Name:	Apremilast
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:	The PI will obtain and hold the IND through the entirety of the study.
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	
Dose Range:	5-60 mg
Frequency:	1 tablet, twice a day (AM/PM)
Route of administration:	Oral
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:	Medication will be purchased from a retail pharmacy, over-encapsulated by San Diego Compounding Pharmacy, and dispensed in blister cards by the lab pharmacy technician.
Indication(s) under Investigation:	Alcohol Use Disorder
Where will the drug be stored	The drug will be stored in a locked cabinet which is located in a locked room accessible by study staff.
Drug Storage Restrictions (including temperature, etc.):	The drug will be stored in its initial packaging in a temperature controlled, locked room until it is placed into study-specific blister cards for dispensation to the research subject.
Administration Instructions:	Administration and dosing instructions will be provided by the Study Coordinator to the subject. Subjects will be instructed to take 2 tablets (1 in the AM, 1 in the PM) a day, for every day leading up to their Cue reactivity session. They will be instructed to return any unused study medication upon their return to the laboratory. Safety information (such as not taking any supplemental or over-the-counter medications, not sharing the study medication with others, etc.) will also be provided, along with the study physician's emergency contact information in case of adverse events or side effects.
Possible Untoward Effects, Their Symptoms & Treatment:	Common adverse reactions (5% or greater) are diarrhea, nausea, headache and upper respiratory tract infections, which will be managed, if necessary, by interventions recommended by study physicians. Less commonly, depression and suicidal thoughts may occur. Subjects will be screened with the MINI diagnostic interview, Columbia Suicide Scale and Beck Depression Inventory-II to exclude at risk subjects from study participation, and mood will be systematically monitored through study completion.

Contraindications and Interactions, If Known:	Contraindications are known hypersensitivity to apremilast or any excipients in formulation. Use with strong cytochrome P450 enzyme inducers may result in loss of efficacy and are disallowed by the study protocol.

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 blistercard packages of medication (apremilast and placebo) for the study. They will also keeps the randomization code and maintains record of study medications dispensed and returned throughout the study. The Study Coordinator will monitor medication compliance by recording the number of pills dispensed at randomization Visit 2 and returned at lab sessions Visit 3 (using returned blistercards) 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
Study Coordinator

20.5 *Has the investigational pharmacy been notified?

- ○ Yes
- ◉ No

If Not, please explain:

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:

Apremilast (15-50 mg/kg) has been associated with reduced alcohol intake in C57Bl/6J male mice in both 24 h 2-bottle choice (2BC) and 2BC with intermittent EtOH exposure, with some anti stress-like effects noted. Effects of apremilast on reducing EtOH intake were replicated in male P rats, with effects increasing in relationship to dose in a 24 h 3-bottle choice experiment. The results from genomic computational analyses and converging results in mice and rat models provide novel evidence for a selective role for PDE4 in regulating ethanol drinking in mice and suggest that PDE4 inhibition may be an unexplored target for medication development to reduce excessive alcohol consumption.

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:

Apremilast is currently marketed for treatment of moderate to severe plaque psoriasis.

23.0 Data and Safety Monitoring

23.1 ***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 for participants, 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., suicidal ideation, 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 2 weeks 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.
• 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 visit including the following:
• Participants will be asked about adverse events and concomitant medications at each study visit and vital signs will be obtained before administering the study medication.
• 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 at the end of treatment and 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 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 applied for 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 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 a decade 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 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 IRB, NIAAA and the FDA.

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

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 with differential (CBC w/diff) for general bodily functioning. In addition, blood will be drawn for drug concentration and to assess the HPA-axis function (plasma cortisol and ACTH).

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?

Melissa St. John, 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 unidentified?**

◉ Yes ○ No

25.10 ***Will leftover unidentified 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), $150 for cue reactivity procedures (Visit 3), $50 for the 1-week follow-up visit (Visit 4), and $50 for the 1-month follow-up visit (Visit 5). Total compensation for completion of all 5 study visits is $375.00.

We provide taxi transportation for subjects who would otherwise be unable to participate in the study, to and from our laboratory at TSRI. We have a voucher system arranged with Yellow Cab specifically for this purpose. Estimates from our current human laboratory study indicate this will apply to 20% of the 50 randomized subjects.

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?

See above

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.

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 participation 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)*

Overview of Study Design.

A total of 50 subjects per study will be randomly assigned to double-blind, subchronic dosing with active drug (n = 25) or matched placebo (n = 25). 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 during the last 3 days of the dosing period in order to test the effect of study drug when motivational symptoms of early abstinence are manifest. Human lab testing occurs on the last day of dosing/third day of abstinence.

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 drug relative to placebo on responsivity to in vivo alcohol cue exposure in the lab, as well as on naturalistic measures of drinking, affect, and craving through 1-month posttreatment.

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 proof-of-concept study. Self-reported drinking data are collected as a secondary outcome variable, as the 3-day abstinent interval constrains complete evaluation of this variable, and drinking data are collected under less

controlled conditions than craving in response to in vivo alcohol cue exposure in the lab.

Subjects return 1 week and 1-month after drug discontinuation to assess any persisting effects on naturalistic measures of drinking, craving 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 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 blistercard containing the double-blind study drug. A phone call is scheduled for Day 3 (and Day 7 in studies having 8-10 days of drug exposure) to address any questions or concerns and assess compliance.

Visit 3-Human Lab Testing: The human lab session is conducted in the afternoon on the last day of dosing and will last for approximately 2 hours. Subjects are instructed to take their last dose of drug at 8 AM. Medication compliance will be assessed on the day of testing using returned pill count and confirmed retrospectively with drug plasma determinations. 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. A 3 (positive, neutral, negative affect) × 2 (alcohol, water) within-subjects, block-factorial design (6 repeated measures) will be employed for the cue reactivity manipulation. All six mood-beverage combinations will be presented to each subject. Order of affect-beverage combinations will be determined by computer-generated randomization code to control for potential order effects. Time-locked subjective and physiological data will be collected by computer in response to each affect-beverage pair. Upon completion of the study, subjects relax, are debriefed, and complete measures of craving and mood to verify a return to baseline.

Visits 4 and 5 – Follow-Up: Subjects return 1 week and 1 month 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 at Visit 5.

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.**

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.)

Apremilast is a selective PDE4 and TNF-alpha inhibitor that acts on immune system targets. A recent review of pre-clinical studies indicate PDE4 and TNF-alpha inhibitors may be promising new medications for the treatment of alcohol and drug addiction. INIA-N investigators and others have found that nonspecific PDE4 inhibitors like rolipram and ibudilast reduce alcohol consumption in rats and mice, but these drugs have side effects, particularly nausea and vomiting, that significantly reduce patient acceptability. Apremilast shows less of the PDE4 adverse reactions. Importantly, it has lower affinity for the PDE4D isozyme which is thought to be associated with the emetic effects of PDE inhibition. Apremilast (20 mg/kg) has been found to significantly reduce g/kg of EtOH intake in 12 male and 12 female HDID-1 mice, with no interaction with sex; similar findings were obtained for rolipram using the same model. Furthermore, INIA-N investigators reported apremilast (15-50 mg/kg) reduced alcohol intake in C57Bl/6J male mice in both 24 h 2-bottle choice (2BC) and 2BC with intermittent EtOH exposure, with some anti stress-like effects noted. Effects of aprernilast on reducing EtOH intake were replicated by the INIA-N Bell group in male P rats, with effects increasing in relationship to dose in a 24 h 3-bottle choice experiment. The results from genomic computational analyses and converging results in mice and rat models provide novel evidence for a selective role for PDE4 in regulating ethanol drinking in mice and suggest that PDE4 inhibition may be an unexplored target for medication development to reduce excessive alcohol consumption.

***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 advertise in the San Diego Reader magazine. We also use our website, flyers, and Craig's List.

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)
- [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

☐ Social Media
☐ Other

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

We use the San Diego Reader magazine, which comes out bi-weekly. We also use our own website wwww.tsriaddiction.com to recruit potential subjects.

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
☑ 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?

N/A

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 form 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.)

Susan Quello, B.A., B.S.

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

Susan Quello has been working in Dr. Mason's lab as a Study Coordinator 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 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.

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

Documentation of ICFs will be by written signature on the Informed Consent Form 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.

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 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 faiting 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:

Common side effects (5% or greater) are diarrhea, nausea, headache and upper respiratory tract infections, which will be managed, if necessary, by interventions recommended by study physicians.

Less commonly, depression and suicidal ideation may occur. Subjects will be screened with the MINI diagnostic interview, Columbia Suicide Scale and Beck Depression Inventory-II to exclude at-risk subjects from study participation, and mood will be systematically monitored through study completion.

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 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.

Recruitment and Informed Consent
Recruitment is by IRB-approved print, television, internet advertisements and public service announcements. Initial screening to determine interest and potential study eligibility will be done over the telephone. Interested individuals who meet initial inclusion criteria will be scheduled for a face-to-face interview to further determine eligibility. A verbal and written consent procedure will be provided. An explanation will be given covering the procedures involved, expected duration of the study, benefits and risks, and their right to refuse or discontinue the protocol without any penalty. Consent will be documented by the signature of the subject. The contents of the consent forms fulfill the requirements of The Scripps Research Institute Human Subjects Committee.

Protections Against Risk
Apremilast 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 be advised to avoid driving or performing hazardous tasks until they know how they will react to the medication, and to not take any herbal, over-the-counter or prescribed drugs unless approved by the study physician. Daily doses are within the currently approved dose ranges for fenofibrate. 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. Apremilast 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., 10 days. Subjects with any conditions which would represent increased risk, e. g. significant medical or psychiatric disorders, pregnancy, or suicidal ideation, will not be admitted to the study. The most common reactions are typically more unpleasant than dangerous. 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 fenofibrate 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 2 weeks thereafter; 5.) close medical supervision, and if significant adverse drug events occur the study physician will evaluate the subject's condition and may discontinue the medication. 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 physician at the screening and lab study visits 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 at the beginning and end of study to verify medical health 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 applied for 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 clinical 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.

Subject may benefit directly from evaluation of their medical status, and study participation compensation.

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 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 apremilast 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 apremilast as a potential treatment option for alcohol dependence, 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 outweighted 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, alcohol-dependent but otherwise healthy male and female volunteers between the ages of 18 and 65.

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

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

65

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.)***

0

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	***Inclusion Criteria:*** • Male or female volunteers, 18-65 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 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. • Females with childbearing potential must have a negative pregnancy test on the screening, randomization, and lab session 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 daily oral medication.
1	***Inclusion Criteria:*** • Male or female volunteers, 18-65 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 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. • Females with childbearing potential must have a negative pregnancy test on the screening, randomization, and lab session 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 daily oral medication.

37.11 Exclusion Criteria

*Use the link below to add exclusion criteria.

Order Number	Criteria
1	***Exclusion Criteria:*** • Active suicidal ideation, as systematically assessed with the Columbia Suicide Severity Rating Scale. • Meets DSM-5 criteria for a major psychiatric disorder, including mood or anxiety disorders or substance use disorders other than alcohol or nicotine. • Has a urine drug screen (UDS) positive for substances of abuse other than alcohol. • 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. • 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], anticonvulsants, or antidepressants). • 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.
1	***Exclusion Criteria:*** • Active suicidal ideation, as systematically assessed with the Columbia Suicide Severity Rating Scale. • Meets DSM-5 criteria for a major psychiatric disorder, including mood or anxiety disorders or substance use disorders other than alcohol or nicotine. • Has a urine drug screen (UDS) positive for substances of abuse other than alcohol. • 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. • 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], anticonvulsants, or antidepressants). • 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.

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 stress and 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 all follow-up visits, 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.

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)
- ☑ 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
- [x] 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-listed 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?

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.

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:**

41.5 **Grant Number:**

GRANT12116859

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	National Institute on Alcohol Abuse and Alcoholism	■	□	□	□	□	□
Private							
CRO							
Department funds							

41.7 **Proposed Funding Date - BEGIN**

02/01/2017

41.8 **Proposed Funding Date - END**

01/31/2022

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

○ Yes ◉ No

NCT03175549

Medication Development in Alcoholism: Apremilast versus Placebo

IRB Summary of Amendments-06/01/2017-05/08/2020

Summary of Amendments for NCT03175549

2017 Continuing Review Application-Prior to Study Initiation

Submitted on 06/01/2017/Approved on 06/19/2017

In the current application, we propose amending the final fixed dose of apremilast from 60 mg (30 mg/bid) for 5 days to a final fixed dose of 100 mg (50 mg/bid) for 5 days based on the pre-clinical data.

Animal data showed apremilast in dose of 10 mg/kg (human equivalent of 56 mg per day) was ineffective for reducing alcohol consumption and achieved efficacy in dose of 20 mg/kg which equivalents to human dose of 112 mg per day. This information was communicated to Dr. Mason in a personal email correspondence dated 05/26/17 from Dr. Yuri Blednov, an INIA collaborator at the University of Texas-Austin.

We searched the Clinical Pharmacology and Biopharmaceutical Review for apremilast and noted doses up to 100 mg per day have been studied. A series of studies showed any side effects (primarily diarrhea) are successfully reduced through dose titration and dosing on a twice a day schedule. Therefore, we are requesting IRB approval to treat 25 subjects on 5 days of a final fixed dose of 100 mg (50 mg BID) per day after a 7-day titration starting at 10 mg per day and increasing in 10 mg doses and 25 subjects on placebo. The titration to 100 mg per day will be according to the following schedule:
Day 1: 10 mg in morning
Day 2: 10 mg in morning and 10 mg in evening
Day 3: 10 mg in morning and 20 mg in evening
Day 4: 20 mg in morning and 20 mg in evening
Day 5: 20 mg in morning and 30 mg in evening
Day 6: 30 mg in morning and 30 mg in evening
Day 7: 30 mg in morning and 40 mg in evening
Day 8: 40 mg in morning and 40 mg in evening
Day 9: 40 mg in morning and 50 mg in evening
Day 10: 50 mg in morning and 50 mg in evening
Day 11: 50 mg in morning and 50 mg in evening
Day 12: 50 mg in morning and 50 mg in evening
Day 13: 50 mg in morning and 50 mg in evening
Day 14: 50 mg in morning and 50 mg in evening

Based on this titration schedule, we request modifying the duration of study drug administration from 10 days to 14 days.

Amendment-Prior to Study Initiation

Submitted on 07/20201/Approved on 08/11/2017

-Added Jessica Bess as the Sub Investigator and Study Contact Person.
-Changed the visit schedule.
-Removed the Structured Clinical Interview for the DSM-IV (SCID) and replaced it with the Mini International Neuropsychiatric Interview (MINI) for DSM-V criteria.
-Added the Columbia Suicide Severity Rating Scale (CSSRS) to the screening visit.
-Removed the Profile of Mood States (POMS) from the self-report battery.
-Added that subjects will be stratified by sex and by High-sensitivity C-reactive Protein (hs-CRP).
-Added obtaining blood to visits two and four.
-Added Cytokine analysis that will be performed at the end of the study by Dr. Toby Eisenstein at Temple University's School of Medicine.
-Added medication over-encapsulation by Austin Compounding Pharmacy in Austin, TX.
-Eliminated the need for women of child bearing age to use an effective form of birth control for 2 weeks following study duration. Revised to through study duration.
-Removed "History of Seizure Disorder" from exclusion criteria.
-Changed recruitment website from www.pearsoncenter.org to www.tsriaddiction.com.

-Clinicaltrials.gov number obtained NCT03175549
-Added a urine drug screen (UDS) at visit two.
-Added the Columbia Suicide Severity Rating Scale (CSSRS) at visit four.

Amendment-Prior to Study Initiation

Submitted on 09/28/2017/Approved on 10/13/2017

-Changed the dose range from 10 mg to 100mg/day to 10 mg to 90 mg/day and revised the dosing schedule.

Amendment

Submitted on 05/17/2018/Approved on 06/08/2018

Revised upper age limit to include subjects above the age of 65.

Revised the exclusionary criteria regarding positive urine drug screens to allow subjects who test positive for THC to participate in the study as long as they do not meet DSM-V criteria for cannabis use disorder at a moderate level or greater, and that these subjects agree to maintain three days of abstinence from cannabis prior to the laboratory session at the fourth visit of the study.

Amendment

Submitted on 08/30/2018/Approved on 10/12/2018

Obtained permission to collect serum at Visit 2 and Visit 4 to assay endotoxins to rule out a factor other than alcohol as a source of abnormal cytokine activity.

Amendment

Submitted on 05/15/2019/Approved on 07/12/2019

Expanded the inclusion criteria to enroll subjects who do not meet current criteria for depression who have been on a stable dose of anti-depressant medication for at least 3 months.

Amendment

Submitted on 04/15/2020/Approved on 05/08/2020

Modified exclusionary criteria to exclude subjects with a total score of less than or equal to 30 on the Alcohol Craving Questionnaire (ACQ) at their screening visit (Visit 1).

We had 16 other IRB amendments/approvals for recruitment advertisements and administrative issues such as staff changes.