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Medication Development in Alcoholism: Apremilast versus Placebo

IRB Informed Consent Form Date: 03/13/2020

SCRIPPS IRB

CONSENT TO PARTICIPATE IN RESEARCH

Apremilast for Protracted Abstinence in Alcoholism

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Before you start reading about this research, please read the California Experimental Subjects' Bill of Rights, which is page 10 of this form.

Why is this research being done?
This research is being done to find out if apremilast will help reduce the urge to drink in people with alcohol use disorder. Apremilast may be a possible treatment to prevent relapse following withdrawal from alcohol.

You have been asked to participate because you may meet criteria for alcohol use disorder and are not currently seeking treatment. Investigators at The Scripps Research Institute hope to learn how well apremilast (a medication used to treat psoriasis) works in comparison to a placebo pill for reducing craving for alcohol. This study involves two laboratory sessions. During the first laboratory session you will be asked how much you want to drink, and during the second laboratory session you will be asked how much you want to drink while your body responses are being recorded. The second laboratory session will be conducted after you have taken a drug that may change your response to alcohol. The drugs to be used in this study are apremilast or placebo. A "placebo" looks like study drug but does not contain real drug.

Apremilast is a drug that has not been approved by the US Food and Drug Administration (FDA) to treat alcohol use disorder (but is approved for a different purpose, treatment of psoriasis). You will be on the study drug for 14 days. The dose of apremilast to be used in this study will start at 10 mg per day, and will be increased up to 90 mg over the 14 day dosing period. The investigators hope that apremilast will reduce craving for alcohol in people with alcohol use disorder by helping to normalize their brain activity, thereby reducing craving.

Up to 70 people will be admitted to the study, all of them treated here at The Scripps Research Institute. To date, forty-eight subjects have been enrolled in this study.

How long is the study?
If the study suits you and you agree to join, you will be in it for about 5 weeks.

What will happen to me?
You will first come to The Scripps Research Institute for a screening visit. During that visit, which will last about 2 hours, you will be asked questions regarding your alcohol use and health. Blood and urine samples will be collected.

At the next visit, a doctor will examine you. This examination and the medical care you will receive in the study is not the same as seeing your regular doctor. You will also fill out some questionnaires.

Some procedures and tests would be done to determine your eligibility, even if you did not join the study. They are:

- Your medical history
- Your history of alcohol use
- Electrocardiogram (ECG) to measure your heart rate and rhythm
- Urine sample for kidney function and drug screen
- Blood sample

These procedures and tests will be repeated at some visits (see schedule below):

Blood sample: The medical assistant will draw a blood sample (1-2.5 Tablespoons) from your vein for lab tests of your body functions, and factors related to your disorder or response to study procedures, such as the amount of study drug in your blood. If you are female, you will also be tested to be sure that you are not pregnant.

Urine sample: You will be asked to give a urine sample to screen for drugs of abuse (Visits 1, 2, and 4) and to verify abstinence from alcohol on Visit 4. If your urine shows you have used any disallowed drugs you will not be able to proceed with the study and you will not be paid for the visit. THC is not a disallowed drug but you must refrain from using marijuana for at least 3 days prior to the lab session at Visit 4. If you are female, you will also be asked to provide a urine sample at Visits 2 and 4 for a pregnancy test.

Vital Signs: Your blood pressure, heart rate, temperature and weight (vital signs) will be measured.

Breath Samples: Samples of your breath will be collected at each study visit. You will be asked to blow into two small tubes for up to 15 seconds. This is done to measure alcohol and carbon monoxide levels in your body.

Salivary Samples: Saliva samples will be taken during Visits 2-5. This is done to measure cortisol levels in your body.

ECG: Self-stick pads will be placed on your chest, arms and legs. Wires will be attached to the pads and to a machine that will record the electrical activity of your heart. An electrocardiogram (ECG) is a tracing of your heart's activity. The ECG will be performed Visits 2 and 5.

Medication/Study Drug: If you join the study you will be assigned, by chance, to receive either apremilast or placebo. **You have a 1-in-2 chance of getting real drug**. You won't know which you get and neither will the study physician or staff. The study doctor could find out in an emergency. Study drugs will be dispensed in a container with sections for each day. You will be asked to take the drug as directed and return the container and any unused drug at the next study visit.

Laboratory Session: During the laboratory session you will be asked to rate your craving for alcohol following exposure to pictures that may cause different emotions and after viewing and smelling a glass of water and/or your preferred alcoholic beverage (that you are not to drink). In addition to craving, we will also be measuring your heart rate; facial movements and skin responses during that time. **You must also not drink alcohol or use marijuana for at least 3 days before your laboratory session at Visit #4.** A urine sample will be collected to measure ethyl glucuronide and ethyl sulfate (EtG/EtS), which can reliably detect alcohol metabolites in urine 80 hours after alcohol consumption. You will be asked to blow into a small tube for up to 15 seconds to measure breath alcohol on the day of the visit. If you have drunk alcohol, you will have to wait until it has cleared your system. You will not be paid for that visit, and the visit will have to be rescheduled.

Follow Up: A follow-up visit will be scheduled 1 week after you have finished taking the study drug to make sure you are as healthy as you were at the start of the study. The researcher will tell you about treatment options and offer referral choices, if you want treatment.

Visit Schedule

Scheduled Visit / **Procedures**	**1**	**2**	**3**	**4**	**5**
Informed consent; demographics; medical and alcohol history; Illicit Drug Use Index; MINI	X				
Columbia Suicide Severity Rating Scale (CSSRS)	X		X	X	
Fagerstrom Test for Nicotine Dependence; Alcohol Use Disorder Scale	X				
BAC, vital signs, concomitant treatments	X	X	X	X	X
Pregnancy test[1]	X	X		X	
Salivary cortisol		X	X	X	X
ECG		X			X
Urinalysis, CBC w/diff, blood chemistry	X			X	
Urine Drug Screen (UDS)	X	X		X	
Blood draw for cytokine and endotoxin analysis		X		X	
Mini cue session- in vivo beverage presentation	X				

Timeline Follow Back Interview- TLFB Alcohol Craving Questionnaire- ACQ Pittsburg Sleep Quality Index-PSQI Beck Depression Inventory-BDI-II State-Trait Anxiety Inventory-STAI	X	X	X*	X	X
Physical Exam[2],		X			X
Adverse Events (AE's), Concurrent Drug Therapy	X	X	X	X	X
Dispense study medication[3]		X			
Collect study medication			X	X	
Human lab session				X	
CIWA, Addiction Research Center Inventory-ARCI Post-Drug Questionnaire				X	
Motivational Interviewing					X

1 – Females only. Blood sample at Visit 1 and urine sample at Visits 2 and 4.
2 – Physical exam will be repeated as needed in the case of significant adverse events.
3 – Phone call scheduled a few days after starting the medication to see how you're doing.

Could I experience any side effects or discomforts?
All drugs can cause reactions or side effects. The most commonly occurring side effects reported in clinical trials using apremilast up to 60 mg per day are:

	Apremilast	Placebo
Diarrhea	17%	6%
Nausea	17%	7%
Upper respiratory tract infections	9%	6%
Headache	6%	4%

Less commonly, depression and suicidal thoughts may occur. If you experience signs of depression, suicidal thoughts or other mood changes, contact the researchers and your doctor immediately.

There could be other side effects that we just don't know about yet and we do not know if the same side effects will occur, or if new side effects will emerge in persons who have a problem with alcohol.

You should be cautious about operating machinery, including automobiles, until you are certain that taking apremilast does not affect your ability to drive or work with machinery.

The placebo pill will be a pill that looks like real drug, but contains no active drug. Study drugs may contain lactose. People who are unable to digest lactose properly are called lactose intolerant. If you are lactose intolerant you might experience side effects such as nausea, abdominal cramping, bloating or gas, after taking study drugs. These side effects are usually not dangerous and will stop when the medication is stopped. Please let the study coordinator know if you are lactose intolerant.

Alcohol Withdrawal
You must not drink alcohol for at least 3 days before the laboratory session at Visit 4. This could put you at risk for alcohol withdrawal symptoms. If you do have alcohol withdrawal symptoms, you will be referred to a local detoxification center. The costs of detoxification will be your responsibility.

Laboratory Session Testing Procedures
Testing procedures could cause unpleasant reactions. You might feel:

- Fatigued (tired) or distressed (anxious or uncomfortable) by the rating scales,
- You will be tempted by your favorite alcoholic beverage and this may give you the urge to drink.
- Depressed or anxious after cue exposure

Is there anything else I should know?

- If you are female, you will have a pregnancy test at screening, randomization and at the end of medication. You can't be in the study if you are pregnant or plan to get pregnant. Therefore, to participate in the study you must agree to use an effective form of birth control for the study duration.
- If you have been in another research study in the last month, you should tell the study doctor.
- You can't use any drugs or supplements without asking the study doctor.
- You can't give the drug to anyone else and you should keep it away from children.
- We may use information you give us to help find you in case you move. Any information (like your address or phone numbers) will be used only to help find you for follow-up studies.

Blood Sampling: You may feel pain or discomfort when the needle pokes your 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. If you have ever felt dizzy or fainted while having blood drawn, you should tell the person drawing your blood. You might not get dizzy if you lie down. If these problems occur, you will be given proper treatment until you recover.

Abnormal Medical Test Results: Medical testing performed during your participation may increase the possibility of receiving an abnormal test result, for example, high blood sugar or elevated liver enzymes. Medical tests performed within the protocol are for research purposes and are not intended to, and may not be suitable for, diagnosing a medical problem. Your medical results will be reviewed by a study physician. Abnormal results will be communicated to you by a research team member. If you decide to pursue medical follow-up, we will release the results to your physician with your written permission. In order for the Certificate of Confidentiality to protect sensitive information, the identity of the study will not be released to your physician along with the abnormal test results. If you do not have medical insurance, we will supply you with a list of medical service providers in the San Diego area that can be accessed for free or at little cost to you.

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

Since this is an investigational drug for alcohol use disorder there may be some unknown risks that are currently unforeseeable. You will be informed of any significant new findings.

If you choose to join the study, you must agree to take study medication as prescribed and abstain from alcohol for three days in a row before your laboratory session at Visit #4.

If you are under the influence of alcohol at your appointment, which will be checked by an intoximeter, you will have to either stay in our office until your blood alcohol level goes down to .000, call someone to pick you up, or call a taxi to take you home at your own expense. If you are found to be impaired by alcohol at your study visit, the visit will have to be rescheduled for another time, and you will not be paid for that visit. Because your blood alcohol level may remain elevated for a period of time after drinking, it is recommended you do not drink the night before your appointment in order to attain a reading of .000.

www.ClinicalTrials.gov
A description of this study is available on http://www.ClinicalTrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

What's in it for me?
You will not benefit personally, but your participation may help identify drugs to help others stop drinking.

Will I get paid?
Yes, you will be paid $50 for completing the screening Visit 1, $75 for completing randomization Visit 2, $10 for the phone call that takes place in the period between when you start taking the medication and when you come into the office for Visit 3, $50 for completing medication follow up Visit 3, $150 for completing the laboratory session at Visit 4, and $50 for completing the Visit 5 follow-up. If you complete the study, you will receive a total of $385. If for any reason you leave the study early, you will be paid only for those study visits that you have completed. As part of our referral bonus system, you will be given 3 unique referral cards with your research ID number on them. Every individual you refer to this study that is successfully randomized into this study, will result in you earning a $50 bonus. All the person you refer has to do is bring in that unique referral card you gave them to their first in-person visit so that we can link their entry into this study to your referral. If you make 3 successful referrals, you will earn $150 in bonus money. It is important to know that these referral cards cannot be replaced if you happen to lose them or if you refer an individual who decides to not follow through with study participation. For this reason, it will be important for you to be careful with your cards and to refer people who you think are appropriate and interested in study participation. This referral system is completely voluntary and you do not have to participate in it.

Will it cost anything to be in the study?
Everything in the study is provided at no cost to you. If you choose to pursue medical follow-up for abnormal medical test results, the financial costs will not be paid by The Scripps Research Institute, they will be your responsibility.

What if I end the study early?
If you quit the study or are taken out early, you will not be paid for follow-up visits you have not completed. You may be asked to return for tests to be sure your health has not changed during the study. The investigator can take you out of the study if you fail to follow study procedures or for other reasons

What other treatments could I take?
This is not a treatment study. The alternative is not to participate in this study.

What about confidentiality?
We have several ways to protect electronic data, in both technical ways, as well as by rules and physical security, just as we control access to your paper medical record. Using technology, we hide our computers on the network so that unauthorized viewers can't see them, and the computers that can be seen can only be accessed with unique passwords and authorization using "security certifications," data encryption in some instances and passwords. We also keep track of who opens what computer files. We give access to members of our research staff on a case-by-case basis for the specific purposes of having them enter data or to help us with your care and our research. We grant this access according to the same level staff would have to look at your medical and research paper files. Thus, we impose a set of standards to protect your information as it resides in our computers.

There also may be other privacy risks that we have not foreseen.

The study doctor, the research staff, and the funding institution will keep your personal information confidential. Your research records could be reviewed by agencies within the Department of Health and Human Services who evaluate and monitor research studies for their accuracy of findings as well as your safety and welfare. These agencies included the Office of Human Research Protection, the Food and Drug Administration (FDA) and National Institutes of Health (NIH). Your research records will also be reviewed by an Independent Safety Monitor throughout the study.

To help us protect your privacy, we have applied for a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local, civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under the following circumstances: disclosure that a child is being abused, or an indication of intent to hurt yourself or others.

With our referral bonus system, we have taken every step to preserve your confidentiality. Referral cards will only have your research ID number on them, so if they are ever lost by you or the person you referred, there is no direct way of linking you to this card. Additionally, study staff will not discuss the relationship of participants in any way, and will not confirm the participation of an individual in this study. Finally, referral links will be tracked by study staff for reimbursement purposes using only a participant's research ID number to preserve confidentiality and anonymity. Even with these safeguards in place, if you chose to participate in this referral system, you are disclosing your knowledge of this study to the individuals you chose to speak to about it or refer to this study. In this way, we are not able to assure your confidentiality will be preserved by the individuals to whom you chose to disclose your connection to this study.

What are my rights?

- You can call the staff to ask any questions about this study. The telephone number is listed at the top of this form.
- You can decide not to be in this study or you can quit after starting. Whatever you do, your medical care at Scripps will not be affected.
- If you have any questions about your rights, call the Scripps Office for the Protection of Research Subjects at (858) 678-6402. You should also read the *Experimental Subject's Bill of Rights,* which is the last page of this form.
- You do not have to be in this study. You still have all your legal rights whether you join the study or not.

What are my responsibilities if I join?

If you are in this study, you are expected to:

- Follow the instructions of the research staff
- Report any serious or unusual side effects to the study doctor
- Take study drugs as directed
- Keep your study appointments

What if I get hurt in the study?

You may call Dr. Shadan at (858) 752-2913, Monday through Friday, 8:00 a.m. to 5:00 p.m., if you get sick or injured while on this study, or have any questions about the medication (apremilast). If you get sick or injured or have questions about the medication at night or on a weekend, you should call Dr. Shadan at (858) 752-2913 or seek treatment at an Urgent Care or Emergency Room facility. If you feel you need immediate attention, you should call 9-1-1.

If you need either medical care or urgent medical treatment as a result of your participation in the study, TSRI general liability insurance will cover these costs.

No money is available to pay you for time off from work. You are not giving up any of your legal rights by being in this study.

What's in it for the institution and the researchers?

The Scripps Research Institute and the study doctor are being paid to do this study by the National Institute on Alcohol Abuse and Alcoholism.

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I agree to participate.

I have read the explanation of the study and understand it. The study has also been explained to me by Dr. Mason or a member of her research staff. I have had a chance to ask questions and have them answered to my satisfaction. I agree to take part in this study. I have not been forced or made to feel obligated to take part.

*I have read the attached **Experimental Subject's Bill of Rights**, which contains some important information about research studies. I must sign this consent form, the **Experimental Subject's Bill of Rights** and will be given a signed copy of each to keep.*

Printed Name of Subject	*Signature of Subject*	*Date*

Signature of person conducting the informed consent discussion	*Date*

Role of person named above in the research project

*EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

If I am asked to consent to be a subject in a research study involving a medical experiment, or if I am asked to consent for someone else, I have the right to:

Learn the nature and purpose of the experiment (also called "study" or "clinical trial").

Receive an explanation of the procedures to be followed in the study, and any drug or device to be used.

Receive a description of any discomforts and risks that I could experience from the study.

Receive an explanation of any benefits I might expect from the study.

Learn about the risks and benefits of any other available procedures, drugs or devices that might be helpful to me.

Learn what medical treatment will be made available to me if I should be injured as a result of the study.

Ask any questions about the study or the procedures involved.

Quit the study at any time, and my decision will not be used as an excuse to withhold necessary medical treatment.

Receive a copy of the signed and dated consent form.

Decide to consent or not to consent to a study without feeling forced or obligated.

If I have questions about a research study, I can call the contact person listed on the consent form. If I have concerns about the research staff, or need more information about my rights as a subject, I can contact the Scripps Office for the Protection of Research Subjects, which protects volunteers in research studies. I may telephone the Office at (858) 678-6402, 8:00 a.m. to 4:00 p.m. weekdays, or I may write to the Scripps Office for the Protection of Research Subjects, Mail Stop CPB200, 4275 Campus Point Court, San Diego, CA 92121.

By signing this document, I agree that I have read and received a copy of this Bill of Rights.

_____ _____

Signature of Subject or Legal Representative Date

*California Health & Safety Code, Section 24172