Official Title: A Pilot Placebo-controlled Human Laboratory Feasibility Study of Lacosamide Effects in Alcohol Use Disorder

NCT number: NCT03897348

Document date: 03/13/2019

Department of Veterans Affairs	**INFORMED CONSENT FORM**
Subject Name:	**Date:**
Title of Study: A PILOT PLACEBO-CONTROLLED HUMAN LABORATORY FEASIBILITY STUDY OF LACOSAMIDE EFFECTS IN ALCOHOL USE DISORDER	
Principal Investigator: STEVEN L. BATKI, MD	**SAN FRANCISCO VAMC**

This is a medical research study funded by UCSF's Alcohol Center for Genes and Translation (ACGT). The principal investigator (PI) is Steven L. Batki, MD from the San Francisco VA Medical Center and the UCSF Department of Psychiatry. One of the study staff, supervised by the PI, will explain the study to you.

You are being invited to take part in this study because you have indicated that you are drinking alcohol at levels or in a manner that may harmful to your health (you meet diagnostic criteria for alcohol use disorder) and you have indicated that *you are not interested in seeking treatment to reduce your alcohol use*.

The purpose of this form is to give you information about the study. This form describes the purpose, procedures, benefits, risks, discomforts and precautions of the study. You should take part in the study only if you want to. Signing this form will give your permission to take part in the study. You may decide not to join the study. It is important to know that if you start the study, you may leave at any time. There is no penalty for leaving and you will not lose any benefits to which you are otherwise entitled. Some risks of this study are known; not all possible risks are known.

1. Why is this study being done?
The purpose of this study is to discover how the medication **lacosamide** affects a person's use of alcohol and other alcohol related behavioral measures. Lacosamide, marketed under the brand name Vimpat®, is an FDA approved medication for treating epilepsy. There is some preliminary evidence from research using animals that a single dose of lacosamide might reduce alcohol craving and/or consumption.

Lacosamide has not been proven safe or helpful by the US Food and Drug Administration (FDA) for the treatment of alcoholism.

The PI and other study staff in this study do not have a financial interest in the company that manufactures lacosamide.

2. How many people will take part in this study?
About 4-6 men will be enrolled in this study.

3. Are there some people who should not be in this study?
The study doctor or a member of the study staff will talk with you about the requirements to be in this study. It is important that you are truthful with them about your history. You should not be in this study if you do not meet all the qualifications.

You should not be in this study if:

- You are currently receiving lacosamide or other medication for alcoholism, including disulfiram (Antabuse), naltrexone (Depade, Revia or Vivitrol), or acamprosate (Campral).
- You are younger than 18 years old or older than 50 years of age.
- You are seeking treatment for alcoholism, or if you would like to receive treatment to help reduce alcohol use.
- You are currently receiving treatment for alcoholism, or have received treatment for alcoholism in the past 6 months.
- You are already in another alcohol treatment study or study involving medication as a treatment for alcohol use.
- You have liver disease, heart disease, pancreas problems, diabetes, neurological problems, or if you have gastrointestinal problems that are worsened by drinking alcohol.
- You are taking medications that may have bad interactions with the study medication, lacosamide (the study doctor will ask check this).
- You regularly used in the past 30 days opioids, cocaine, benzodiazepines, or barbiturates.
- You regularly used in the past 30 days medications that can affect your brain and nervous system such as medicines used to treat psychiatric conditions like psychosis, anxiety, depression, or medications to treat epilepsy (seizures).

4. How long will I be in the study?
In total, you would be asked to commit approximately 40 hours of your time over the course of 7 weeks.

5. What will happen if I take part in this research study?
All study procedures will take place at the San Francisco VA Medical Center. The study can be divided into the 3 parts:

a. **Screening**: 1-3 visits over approximately 1 week
b. **Main part**: 3 visits over 5 weeks to complete 3 all-day Alcohol Drinking Paradigm (ADP) sessions

These 3 all-day ADP sessions will be at the San Francisco VA Medical Center. At each of these 3 all-day study visits, you will participate in an alcohol drinking session under observed conditions. We refer to each of these all-day sessions as an Alcohol Drinking Paradigm (ADP).

At each of these 3 ADP sessions, you will be asked to take study medication and then you will be offered alcoholic beverages, mixed with fruit juice, and allowed to drink them within a certain period of time, under observed conditions. Study staff will be measuring how much alcohol you consume at each of these 3 ADP sessions. Each ADP session starts at 8am and finishes around 8pm, for a total of 12 hours.

c. **Follow-up**: 1 visit 7 days after the last ADP

5a. During the screening part of the study
To see if you are eligible to participate in the study, we will ask that you take part in the following exams, tests and procedures. Information will be kept confidential (as detailed later in this Consent Form).

Breath alcohol test + informed consent:
The study will be discussed with you, and you will be asked to sign this consent form after you blow a 0.00 on your breath alcohol test. If you have ANY alcohol on your breath, as measured by the breathalyzer, you will be asked to wait until you have no alcohol on your breath or to complete your visit at another time.

- You can also ask to be referred to other treatment if you wish.
- If you are legally intoxicated, you will be offered transportation home.

Contact information:
You will be asked to provide the names and phone numbers of people we may contact in case you miss a study appointment. Research staff will confirm your personal contact information, as well as that of your alternate contact, before you can continue in the study.

Medical history and physical exam:
The study doctor will take your medical history and review the medication you use. You will also have a brief physical examination. The history and physical exam are similar to those done for regular medical care.

Vital signs:
A study staff member will measure your blood pressure, heart rate, height and weight.

Concomitant medication:
A study doctor will review all the other medications you are currently taking to make sure it is safe for you to take the study medication, lacosamide.

Electrocardiogram (ECG):
A study nurse will conduct an electrocardiogram (ECG or EKG) to check the health of your heart to make sure it is safe for you to participate in the research study.

Blood drawing (venipuncture):
You will be asked to give a blood sample for routine laboratory tests to check your health. Approximately 2 teaspoons of blood (8 ml) will be drawn by inserting a needle into a vein in your arm for these tests. Blood will be taken for routine medical tests.

Urine sample:
You will be asked to give a urine sample to test for drug use, including recreational and illegal drugs and alcohol.

Medical and psychiatric diagnoses:
You will be evaluated for current and previous diagnoses.

Substance use assessments: You will be asked to report your use of alcohol and other substances (cigarettes, marijuana, cocaine, etc.)

Questionnaires: You will be asked to complete questionnaires about your education, work, and other aspects of life. Some of the questionnaires ask that you answer detailed questions about your alcohol use, alcohol craving and family history of alcohol use.

Cognitive testing:
Your cognition (ability to think) will be measured through a serious of tests. We will continue to administer these tests throughout the study so that we can try to understand how alcohol use and/or the study medication, lacosamide, affects your thinking.

5b. During the main part of the study
After the screening tests have been reviewed by the study doctor, and you continue to meet eligibility requirements, you will begin the main part of the study.

Overview:
You will be asked to attend 3 all-day study visits at the San Francisco VA Medical Center for the main part of the study. At each of these 3 all-day study visits, you will participate in an alcohol drinking session under observed conditions. We refer to each of these all-day sessions as an Alcohol Drinking Paradigm (ADP).

At each of these 3 ADP sessions, you will be asked to take study medication and then you will be offered alcoholic beverages, mixed with fruit juice, and allowed to drink them within a certain period of time, under observed conditions. Study staff will be measuring how much alcohol you consume at each of these 3 ADP sessions. Each ADP session starts at 8am and finishes around 8pm, for a total of 12 hours.

Details:
We ask that you not consume alcohol after 5 pm on the evening prior to each ADP session. When you arrive at the San Francisco VA Medical Center (SFVAMC), we will monitor your breath alcohol level by asking you to blow into the breathalyzer. If you arrive with a positive breath alcohol level and your breath alcohol level is above 0.05 and/or is increasing, indicating recent alcohol consumption, then the session will have to be rescheduled. If your breath alcohol level is less than 0.05 and is decreasing, we will have to wait until it comes down to 0 before conducting any assessments. If your breath alcohol level is above 0.05 and the session has to be rescheduled, we will have to keep you at the SFVAMC and advise you not to drive until it comes down to 0.02. Alternatively, we could provide you with transportation.

We will also collect a urine sample to screen for the use of drugs (e.g. cocaine, opiates, benzodiazepines). This test will have to be negative, except for marijuana, for you to continue in the study.

Once you are settled in the room where the study visit will be conducted, you will be asked to take study capsules. At each ADP session, you will receive different study capsules, either 100 mg of lacosamide, 200 mg of lacosamide or placebo. Neither you nor the study staff will not know which capsules you are being asked to take. The only person who knows is the San Francisco VA Research Pharmacist.

After medication, we measure your height and weight, your heart rate and blood pressure, and ask you to complete some assessments and computer tasks. You will be given a light breakfast around 9:00 am,

and a late lunch/early dinner around 3:30pm. If you are a smoker, you will be provided with 2 "smoke-breaks" during which you will be escorted out and allowed to smoke up to 2 cigarettes. Non-smokers will also be given the option of taking 'breaks' at certain intervals. When you are not completing assessments, you will be able to relax, read a book or be on your cell phone.

Later that same day, you will participate in the ADP. A video camera will be recording this session to monitor your drinking behavior. Prior to the start of this session, you will be asked to complete some questionnaires and rating scales. We will test your breath alcohol level over the course of the ADP and we will test your blood alcohol level once during the ADP. To test your blood alcohol level, approximately 1/2 a teaspoon of blood (3 ml) will be drawn by inserting a needle into a vein in your arm for these tests.

At 12 noon, you will be provided with your first alcohol drink. The alcohol content of this drink will vary according to your weight and will be equivalent to one typical mixed drink. You will be asked to drink it in 5 minutes. You must consume this drink in order to remain in the study. If you do not wish to consume the drink, you will be discharged from the study. You will then be monitored for the next 55 minutes and asked to complete assessments.

At 1:00 pm you will be presented with 4 drinks, each of which we consider to be worth $3, for a total of $12. During the next 50 minutes, you can either choose to drink or keep the money value of the drinks ($3 per each drink that you do not drink). If you choose the money, it will be given to you after the session is completed.

At 1:50 pm, the old drinks will be removed.

At 2:00 pm you will be presented with 4 fresh, new drinks, each worth $3. These will be available to you for the next 50 minutes. Again, you can choose to drink them or keep the money. The drinks will be removed at 2:50 pm at which time the ADP session is over. Your breath alcohol level, blood pressure and heart rate will be monitored until your breath alcohol level returns to 0.02. You will also be asked to complete various assessments during the remainder of your stay.

At 8:00 pm you will be discharged and paid in return for your time and effort. If your breath alcohol level is above 0.02 at 8:00 pm, then a study doctor will conduct a brief examination to make sure it is safe for you to go home. If in the judgment of the study physician you are too intoxicated to safely go home, you will be taken to SF VA Emergency Department by the study physician for further evaluation and treatment, if needed.

The following day, a member of the study team will check in with you by phone to assess for any side effects.

You will repeat the ADP sessions on 2 more days, for a total of 3 ADP sessions. There will be 7 days between the 1st and 2nd ADP session and 7 days between the 2nd and 3rd ADP session. All ADP sessions are identical in nature, except for the study medication given to you when you arrive.

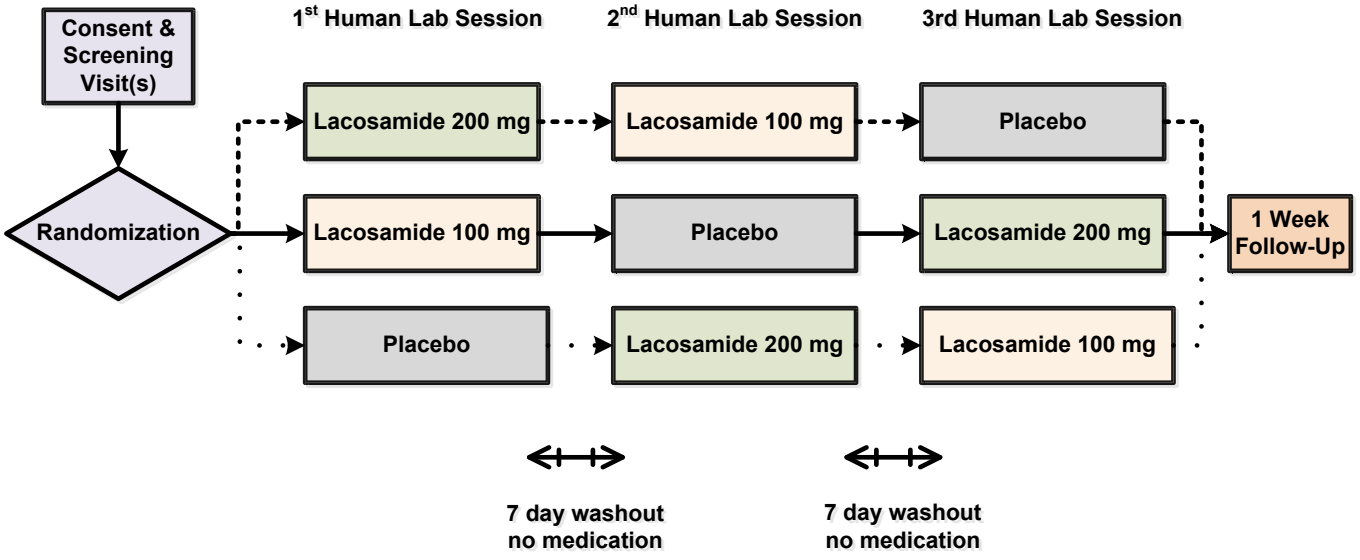
It is important to note that during the ADP sessions phone use, watching TV, and sleep will be restricted as follows:

TIME	PHONE USE	TV	SLEEP
8:30 AM – 9:30 AM	NO	NO	NO
9:30 AM – 10:00 AM	YES	NO	NO
10:00 AM – 11:00 AM	NO	NO	NO
11:00 AM – 11:30 AM	YES	NO	NO
11:30 AM – 3:00 PM	NO	NO	NO
3:00 PM – 8:00 PM	YES	YES	NO

5c. During the follow-up part of the study
There is 1 follow-up visit – 1 week after you 3rd and final ADP session.

Follow-up visit at 1 week:
You will be asked to describe any emotional side effects you may have experienced since the last study visit. A psychiatrist or psychologist will talk to you about your drinking behavior, and if you are interested, will provide you with treatment referrals. This appointment will be conducted with all participants, even those who do not complete the entire study, and will take approximately 1 hour.

5d. Study Plan
Another way to find out what will happen to you during the study is to read the chart below. Start reading on the left side of the paper, and following the lines and arrows.



6. How long will I be in the study?
The study is 7 weeks in total. There are only 5 visits over the course of 7 weeks. Please refer to the Study Visit Schedule below.

Study Visit Schedule

WEEK	STUDY VISIT	AMOUNT OF TIME PER VISIT (approximate)
Week 1	Screening visit	3 hours*
Week 2	ADP session #1	12 hours
	Follow-up phone visit #1	10 minutes
Week 3	No visits	
Week 4	ADP session #2	12 hours
	Follow-up phone visit #2	10 minutes
Week 5	No visits	
Week 6	ADP session #3	12 hours
	Follow-up phone visit #3	10 minutes
Week 7	Follow-up visit @ 1 week	1 hour*
TOTAL	5 (in-person) STUDY VISITS	APPROXIMATELY 40 HOURS AND 30 MINUTES

*The amount of time is an approximation

7. Can I stop being in the study?
Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop your participation safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the lacosamide can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

8. What side effects or risks can I expect from being in the study?
The study visits and procedures are designed to limit risks to your health and limit your discomfort as much as possible. These procedures closely monitor your safety throughout the study.

You may have side effects while in the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the lacosamide. In some cases, side effects can be serious, long lasting, or may never go away. You should talk to your study doctor about any side effects you experience while taking part in the study.

Below, we have listed side effects that have been known to occur when lacosamide is administered up to 200 mg as treatment for epilepsy. The maximum dose you would receive in this study is 200 mg:

Less Likely (less than or equal to 20% of patients)

- Dizziness (16%)
- Headache (11%)
- Nausea (7%)
- Fatigue (7%)
- Vomiting (6%)
- Double vision (6%)
- Sensation of spinning (vertigo) (5%)
- Sleepiness (5%)
- Tremor (4%)
- Loss of coordination of muscle movements (ataxia) (4%)

Rare but serious

- Suicidality: Like other epilepsy treatment medicines, lacosamide may very rarely cause suicidal thoughts or actions in a very small number of people, about 1 in 500.
- Abnormal heartbeat: In less than 1% of patients lacosamide could cause abnormal heart rhythm.

Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse or worry you: thoughts about suicide or dying, attempts to commit suicide, new or worse depression, new or worse anxiety, feeling agitated or restless, panic attacks, trouble sleeping (insomnia), new or worse irritability, acting aggressive, being angry, or violent, acting on dangerous impulses, an extreme increase in activity and talking (mania), other unusual changes in behavior or mood.

Risks associated with lacosamide and alcohol:
There are no published reports about combining lacosamide and alcohol. There may be added effects from combining lacosamide with alcohol. Possible risks include sedation and trouble with thinking or coordination that could persist for several hours after last alcohol drinking (3:00 pm – 4:00 pm). It is expected that alcohol effects will wear off in the ensuing 4 hours before discharge from the CRC at 8:00 pm.

Risks associated with lacosamide and other medications:
Lacosamide may cause a change (increase or decrease) in the effect of some other medications. If you are taking other medications during your participation in this study, immediately inform study staff. The study doctor will review any medications that you are talking and make the determination as to whether continued study participation is safe for you.

Risks associated with alcohol:
A number of medical conditions could potentially be worsened by acute alcohol administration, such as liver disease, heart disease, pancreas problems, diabetes, neurological problems, or gastrointestinal problems. If you have any of these medical problems, you should not participate in this study. Alcohol may also cause nausea in high doses; however, nausea is not expected at the dose being used in this study. In order to ensure that you do not fall and hurt yourself after consuming alcohol, we will ask you to stay at the SF VA Medical Center until your breath alcohol level returns to 0.02 or less. Alcohol can be

addictive. We do not recommend that you continue drinking alcohol in the quantities that will be used in this research study.

Risks associated with alcohol withdrawal:
We are not going to ask you to change your drinking behavior while you are participating in this study. However, you should know that some individuals who suddenly reduce or stop their drinking can experience alcohol withdrawal symptoms such as nervousness, shaking, loss of appetite, difficulty sleeping or more severe symptoms like extreme restlessness, confusion, hallucinations (hearing and seeing things that are not there) and seizures -- but these are extremely rare. We will monitor you very closely for withdrawal symptoms during your daily visits to our clinic. If you experience worsening of withdrawal symptoms, you may have to be hospitalized and will be given the standard medications that are used to treat and manage withdrawal.

Blood drawing (venipuncture) risks: Drawing blood may cause temporary discomfort from the needle stick, bruising, infection and fainting. We expect to draw 17 mL amount of blood (about 3.5 teaspoons) over the course of the study.

STUDY VISIT	**AMOUNT OF BLOOD**
Screening	8 mL or 2 tsp
1st ADP session	3 mL or ½ tsp
2nd ADP session	3 mL or ½ tsp
3rd ADP session	3 mL or ½ tsp
TOTAL	17 mL or 3.5 tsp

Risk of distress/fatigue due to psychiatric and other assessments:
Risks related to answering questions about your medical/psychiatric history, reporting of drug use, taking part in assessments of your thinking may include fatigue and distress. You are free to decline to answer any questions or to stop assessments at any time. Assessments and interviews will include breaks. If you are uncomfortable, let us know and the session will be immediately discontinued.

Reproductive risks:
You should not father a baby while on this study because the drugs in this study can affect an unborn baby. It is important to understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

Unknown risks:
The study medicine may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

For more information about risks and side effects, ask your study doctor.

9. Are there benefits to taking part in the study?
There will be no direct benefit to you from participating in this study. However, this study will help doctors learn more about lacosamide and whether it can help treat alcoholism, and it is hoped that this information will help in the treatment of future patients with a desire to reduce alcohol use.

10. What other choices do I have if I do not take part in this study?
You do not have to be in this study.

You may choose to seek treatment services.

You can obtain FDA-approved medications for alcoholism through your general medical care provider. You are free to seek treatment through your general care providers.

You may also choose not to seek treatment for your use of alcohol.

11. How will information about me be kept confidential?
Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total privacy. Some information from your medical records will be collected and used for this study. If you do not have a San Francisco VA Medical Center medical record already, one will be created for you by the study staff.

The information that will be collected includes demographic information (for example: name, address, age, date of birth, social security number) and health information (psychiatric information, alcohol and drug use, and medical information). By signing this form, you are giving the study staff permission to use the information collected about your health (medical, mental health, alcohol and other substance use). This authorization to access and use the information will not expire. You have the right, at any time, to take back your authorization and end the study staff's access to your personal information.

Every effort will be made to protect the confidential nature of your identifying information by assigning you a unique identification code during the study. All information and data collected by the study staff during this study will contain this identification code instead of any identifying personal information. This identification code will be stored in an electronic database on a password-protected, secure web server managed through the SFVAMC. The data manager will download study data from the server that will be needed for analysis and store it in a password-protected database, stored on a VA server behind a secure VA firewall at the SFAVMC. The written log that connects your identification code to the demographic information you give us will be kept in a file separate from the collected data. This log will have restricted access and will be stored in locked cabinets when not in use. Any data sent via email messages or delivery service will be encrypted and password-protected.

Video recordings will be stored on a password-protected, secure web server managed through the SFVAMC and will not be deleted in accordance with VA research rules.

To ensure your safety and the safety of others, information may be shared between research staff and your clinical team only under the following circumstances: 1) If in the judgment of the study physician, you have a psychiatric or medical condition that requires urgent attention to protect your safety and that of others; and 2) If you have missed several study appointments, and research staff needs to verify your whereabouts and/or verify your safety.

Progress notes will be added to your medical record, which indicate your participation in the study and that you will be taking the study medication and consuming alcohol in the laboratory setting, and the name and contact information for the investigator conducting the study. Details like urine drug test results, the study name or number will <u>not</u> be included in the progress notes.

Study tests that are performed by non-VA research labs and information gathered directly from you by the study staff will be part of your research study records but will not be added to your medical record. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are several regulatory organizations that may look at and/or copy your research and medical records for research, quality assurance, and data analysis. These organizations include:

- Members of the study's Data and Safety and Monitoring Board
- Alcohol Center for Genes and Translation (ACGT)
- University of California, San Francisco Institutional Review Board (UCSF IRB)
- The Food and Drug Administration (FDA)
- Department of Veterans Affairs
- Office for Human Research Protections (OHRP)

In this study, you will be asked questions about illegal drug use and your urine will be tested for illegal drugs. The researchers will keep information about you as confidential as possible, but complete confidentiality cannot be guaranteed. On rare occasions, research records have been subpoenaed by a court.

12. Will any research-related procedures be billed to me?

No. There will be no direct costs to you if you take part in this study. The study will pay for the medication and study procedures (for example: blood tests). Study participation will be free to you. You may need to pay an indirect cost of transportation to the San Francisco VA Medical Center in order to complete study visits.

13. Will I be paid for taking part in this study?

You will be paid in cash for all screening measures completed, with the potential to earn up to $85.

For ADP Sessions 1, 2 and 3, you have the potential to earn up to $224 per visit. You will be paid **$200** by check for each of the 3 completed ADP Sessions. The check will be issued by UCSF and mailed to the address you provide, and should be received within **2 weeks** after your visit.

Depending on how many drinks you consume per session, you could **receive up to $24** in cash per ADP session**. This cash payment will be issued at the end of each drinking session.

You will also receive $25 in cash for attending the follow-up visit 1 week after the 3rd and final ADP session.

If you attend all 3 ADP sessions, plus the final follow-up visit, then you will receive an additional $50 in cash at the follow-up visit.

In summary:

WEEK	ATTEND STUDY VISIT	ATTEND ALL SESSIONS	TOTAL PER VISIT
Screening	$85*		$85
ADP Session #1	$200 (+ up to $24)**		$224
ADP Session #2	$200 (+up to $24)**		$224
ADP Session #3	$200 (+up to $24)**		$224
Follow-up @ 1 Week	$25	$50 if attend 3 ADP sessions***	$75
POTENTIAL TOTAL AMOUNT PAID			$832

*Payment for screening visits depends on the completion of tasks at each visit. You will earn up to $85 total if you complete all screening measures.

**Please note that you could earn up to $24 per ADP session, depending on how many drinks you consume per session. At each session, you will be offered 8 drinks, each worth $3. You will receive $3 for each drink not consumed.

***If you attend all possible study visits, you will receive an extra $50 at the last study visit.

Because this study offers participants total payments equal or greater than $600 in a calendar year period, then the payments are considered tax reportable income. This means that we will share your home address and Social Security Number with the Accounts Payable Manager, using a secured file via email. You will also be asked to fill out a W-9 form.

14. What happens if I am injured because I took part in this study?
It is important that you tell your study doctor, Steven L. Batki, MD, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him at 415-221-4810 x 23671.

Treatment and Compensation for Injury: If you are experiencing a medical emergency, please call 9-1-1. If you incur an injury or illness as a result of being in this study, the Department of Veterans Affairs (VA) will ensure that treatment is made available at a VA medical facility or non-VA facility, as appropriate. If you were following study instructions, the costs of such treatment will be covered by the VA or the study sponsor (if applicable). If you were NOT following study instructions, the costs of such treatment may be covered by the VA or the study sponsor (if applicable), or may be billed to you or your insurer just like any other medical costs,

depending on a number of factors. The VA and a study sponsor do not normally provide any other form of compensation for injury or illness. For further information about this, call the study team at the number(s) provided.

15. What are my rights if I take part in this study?
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

16. What are my responsibilities as a study participant?
- As a participant in this study, your responsibilities are as follows:
  Following the instructions given to you by the study staff and study doctor.
- Attending all study visits as scheduled.
- Communicating with study staff if you will not be able to attend a study visit as scheduled.
- Reporting any side effects, injuries, or other changes in your health to the study doctor.
- Reporting all medicines, vitamins, recreational drugs, herbal products, supplements, or over-the-counter products you use during the study.
- Speaking with the study doctor if you would like to stop participation in the study.

IMPORTANT: We request that you abstain from driving to the VA Medical Center for study visits if you have been drinking. If you do drive and your breath alcohol level is above a 0.08, then a clinician will assess your safety before you will be allowed to leave. This is a VA protocol established to ensure your safety.

NEW INFORMATION ABOUT THE STUDY DRUG: If important or new information about the study drug (good or bad) is learned while you are in the study, you will be told. You will be asked for your consent to continue in the study with the new information. You are free to leave the study at any time without penalty.

17. Clinical Trial Registry Data Bank
A description of this clinical trial will be 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.

18. Who can answer my questions about the study?
You can talk to your study doctor about any questions or concerns you have about this study. At the San Francisco VA, please contact you study doctor, Steven L. Batki, M.D. at 415-221-4810 x 23671 or page him at 415-313-6537.

For questions about your rights while taking part in this study, call the office of the **Committee on Human Research**, UCSF's Institutional Review Board (a group of people who review the research to protect your rights) at 415-476-1814.

CONSENT OF RESEARCH PARTICIPANT

You have been given copies of this consent form and the Experimental Participant's Bill of Rights to keep.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

Optional Procedures: Please indicate if you agree to participate in the following optional procedure by placing your initials on one of the lines below

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_____ I agree to be contacted after this study is done and/or to be asked to be in other studies.

_____ I do not agree to be contacted after this study is done or to be asked to be in other studies.

If you wish to participate in this study, you should sign below.

Signature of Participant Date

Printed Name of Participant

Signature of Person Obtaining Consent Date

Printed Name of Person Obtaining Consent

PROTOCOL VERSION	3/08-1-18
FILE NAME	ACGT Protocol
STUDY TITLE	A Pilot Placebo-Controlled Human Laboratory Feasibility Study of Lacosamide Effects in Alcohol Use Disorder
STUDY NUMBER	17-22190
CLINICAL PHASE	Phase 2

1. INTRODUCTION

This document is a protocol for a human research study. The purpose of this protocol is to ensure that this study is to be conducted according to ICH GCP guidelines (CRF 21 Part 312), applicable government regulations and Institutional research policies and procedures.

2. BACKGROUND

2.1 Background Prevalence of Research Topic

AUD is difficult to treat, and currently available medications are underutilized, due at least in part to their limited effectiveness [1-3]. There is a critical need for more efficacious medications for AUD. Preclinical rodent work from ACGT investigator Dr. Dorit Ron has identified a specific molecular target that promotes excessive alcohol intake. Dr. Ron discovered that *collapsin response mediator protein-2 (CRMP-2)* [4], a downstream mediator of *mammalian target of rapamycin complex 1 (mTORC1)* signaling [4-8], is critical for promoting excessive alcohol intake [4].

The central goal of this pilot project is to lay down the groundwork necessary for the later conduct of more definitive studies designed to translate the ACTG's basic science discoveries into human trials of novel pharmacotherapies for AUD. The FDA-approved anticonvulsant, lacosamide [13,38-40] inhibits CRMP-2 [4,12,13]. We will conduct the first pilot laboratory clinical trial of lacosamide in humans with AUD. The ultimate goal of this proposal is that this medication can be repurposed for the treatment of AUD if it is safe and feasible to use in future larger studies that will test its ability to reduce alcohol drinking and behavioral biases for alcohol in heavy drinkers with AUD.

2.2 Prior Experience

2.2.1 Preclinical Experience

CRMP-2 as a novel molecular target for AUD treatment**:** Studies from Dr. Ron's groups established that alcohol exposure activates mTORC1 in specific brain regions in rodent, and that mTORC1-related signaling is centrally important for promoting excessive alcohol drinking [4-8]. mTORC1 acts by increasing translation of synaptic plasticity proteins [48], and recent work by Dr. Ron's group identified one of these proteins, CRMP-2, as critical for promoting excessive alcohol intake [4]. CRMP-2 is a microtubule-binding protein that regulates synaptic structure [4,12,13], and alcohol drinking increases CRMP-2 and microtubule assembly [4]. Importantly, inhibition of CRMP-2 with systemic administration of **lacosamide**, an FDA-approved small molecule inhibitor of CRMP-2 [4,12,13], significantly reduces excessive alcohol intake without altering sucrose intake, open field locomotion or anxiety [4], suggesting that lacosamide does not have more general motor or motivational effects. These exciting findings implicate lacosamide, which is available as the FDA-approved anticonvulsant Vimpat®, as a novel treatment for AUD.

2.2.2 Clinical Experience

Assessing lacosamide effects on alcohol drinking, impulsivity, craving, and approach bias: We will conduct the first human tests of the efficacy of lacosamide to reduce alcohol drinking in non-treatment-seeking heavy drinkers with AUD, using the Yale Alcohol Drinking Paradigm (ADP). The ADP is also referred to as the "O'Malley Choice Against Money Paradigm" in a recent review by Bujarski and Ray [100], who state that the ADP is the more widely used of the two main categories of current oral alcohol-self administration methods. Dr. Krishnan-Sarin at Yale University helped to develop the ADP, which has been adopted by a number of investigators [16-27], since it has proven highly reliable in measuring medication effects on intake. In addition to alcohol intake, we will also assess whether the test medications are able to *reduce neurobehavioral vulnerabilities* such as *craving, impulsivity, and alcohol approach bias*, that are known to promote heavy alcohol drinking [1,28-34]. We propose to employ measures that are widely used and well-validated. Significant effects by the test medications would indicate that CRMP-2 and/or OXR are also critical to promoting the neurobehavioral vulnerabilities that promote drinking.

3. RATIONAL SIGNIFICANCE

3.1 Problem Statement

Based on findings discussed above, the premise of this work is that (1) molecular mechanisms that drive excessive alcohol intake in rodents can also promote heavy drinking in humans with AUD, that (2) the use of lacosamide, to inhibit CRMP-2 [4,12,13], for reducing human drinking is supported by rodent studies from ACGT researchers and that (3) the Alcohol Drinking Paradigm and the proposed measures of neurobehavioral contributors to alcohol drinking are well-validated and are drivers of alcohol use by heavy drinkers with AUD in human laboratory studies; and that (4) lacosamide may represent a novel and potent pharmacotherapy to treat AUD, which is our overall goal.

3.2 Purpose of Study/Potential Impact

The proposed project will help fulfil the ACGT's goal of translating preclinical findings into clinical trials leading to new pharmacologic approaches to the treatment of alcohol use disorder (AUD).

The goal of the proposed Pilot project is to translate basic science findings from Alcohol Center for Genes and Translation (ACGT) preclinical investigators into clinical research to improve the treatment of alcohol use disorder (AUD). AUD is difficult to treat, and currently available medications are underutilized, due at least in part to their limited effectiveness [1-3]. There is a critical need for more efficacious medications for AUD.

Using preclinical rodent models, ACGT investigator Ron identified the mammalian target of rapamycin complex 1 (mTORC1) [4-8] as a potential drug target for AUD. Lacosamide targets collapsin response mediator protein-2 (CRMP-2) [4,12,13], a downstream mediator of mTORC1 [4]. *We will conduct the first controlled pilot human laboratory study to assess the effects of two doses of lacosamide, versus placebo, on alcohol craving, drinking, and psychomotor effects.*

Based on findings discussed above, the premise of this work is that (1) molecular mechanisms that drive excessive alcohol intake in rodents can also promote heavy drinking in humans with AUD, that (2) the use of lacosamide, to inhibit CRMP-2 [4,12,13], for reducing human drinking is supported by rodent studies from ACGT researchers and that (3) the Alcohol Drinking Paradigm and the proposed measures of neurobehavioral contributors to alcohol drinking are well-validated and are drivers of alcohol use by heavy drinkers with AUD in human laboratory studies; and that (4) lacosamide may represent a novel pharmacotherapy to treat AUD, which is our overall goal. If successful, our experiment will facilitate the development of a new pharmacological strategy for treating human AUD -- inhibition of CRMP-2. In addition, it will provide important scientific information about the salience of CRMP-2 to human heavy drinking and to human behavioral antecedents to drinking.

3.3 Potential Risks and Benefits

3.3.1 Potential Benefits

There is no direct benefit to these participants besides referral to treatment, which will be provided at the end of the study. They will be able to withdraw from the study at any time. The direct benefit is not great for participants, but given the potential benefit to developing effective treatments for alcoholism, the risk-benefit ratio appears favorable.

Participants may benefit somewhat from the extra physical examination, laboratory tests, and attention. In the informed consent form, participants are instructed: "Taking part in this study may not make your health better. If you are in this study, you may benefit from the physical examinations, blood tests, and review of your symptoms. Others may benefit from the overall conclusions drawn from the results of this study."

AUD is major public health problem that contributes prominently to the global burden of disease [58]. While there are several approved medications for the treatment of AUD, the available pharmacotherapies are hampered by small effect sizes, adverse effects, and limited adoption into practice. Currently available FDA-approved pharmacological agents have major limitations and there is a critical need to identify novel medication strategies for AUD treatment. Despite the large numbers of patients who suffer from AUD, medications are greatly underutilized and only a small minority of adults in the United States who have AUD are treated with medications. *This low utilization is thought to be in part due to a perception of AUD medication ineffectiveness*. The potential knowledge to be gained in this study is judged to be highly significant. This research seeks to expand the knowledge base regarding the treatment of alcohol use disorder. Because of the known low to moderate risk profile of the study medications and the close monitoring afforded by the study design, the level of risk for prospective participants is judged to be modest, and therefore, is considered to be reasonable, in comparison with the potential knowledge to be gained.

The results of this laboratory-based drinking paradigm will provide an important initial signal regarding the potential efficacy of lacosamide in reducing alcohol drinking. There is a great need for the development of new agents and combination of agents to treat alcohol use disorder. This laboratory paradigm will also provide information regarding the mechanism of action of these agents and thus significantly contribute to the literature**.**

3.3.2 Potential Risks and Procedures to Minimize Risks

The major potential risks in this study are related to administration of alcohol, lacosamide, and blood drawing during the physical exam and the alcohol drinking period, and risks to privacy.

Alcohol

A number of medical conditions could potentially be worsened by acute alcohol administration (e.g., liver disease, cardiac abnormality, pancreatitis, diabetes, neurological problems, diabetes, and gastrointestinal disorders). During screening, the study physician will conduct a medical history and physical exam and review laboratory findings. As a result, participants with medical problems that are judged by the study physician/PI (Dr. Batki) will be excluded from the study.

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

Another area of potential risk to participants under the influence of alcohol involves their safety during the experimental procedures. Although impairment of gross motor coordination in heavy drinkers is rare at the alcohol dose used in this study, all participants will be under the supervision of the experimenters to prevent possible accidents such as falls. Participants will not leave the laboratory during the self-administration procedure,

Alcohol is a reinforcing agent, which may cause changes in behavior including repetitive or excessive alcohol consumption. Because of this, the administration of alcohol to alcoholics in treatment could potentially impede the progress of their recovery. In addition, the administration of alcohol to sober alcoholics living in the community presents a possible risk of relapse. As a result, we will be recruiting non-abstinent non-treatment-seeking alcoholics in keeping with the National Advisory Council on Alcohol Abuse and Alcoholism's recent update of its 1989[41] recommended guidelines on ethyl alcohol administration. At completion of the study, we will make a serious and concerted effort to link the participant with treatment for their alcohol problems. This will be done by giving the participant objective feedback about the fact that their drinking exceeds standards for avoiding hazardous drinking, providing a brief one-session motivational intervention for their drinking, and by arranging for alcohol treatment services if they are interested. In our previous and ongoing work, several participants quit drinking and many others reduced their drinking in the three months following this intervention.

****Protection against risks of alcohol challenges****

The alcohol challenges will be conducted by Dr. Batki and research staff, using methodology adopted from the Yale group, and trained by our Yale colleague, Dr. Suchitra Krishnan-Sarin.

We provide a number of safeguards to reduce the risk of physical injury by supervising all sessions and having participants stay in the CRC until they are alert and do not show signs of psychomotor impairment. We also exclude participants for whom physical or psychological problems contraindicate alcohol consumption. By selecting non-treatment-seeking participants who are currently drinking heavily on a regular basis, we are not exposing participants to alcohol consumption levels that differ from their normal drinking context. Although this has not happened in the Yale group's experience, should a participant insist on leaving the research setting prematurely, we will provide transportation back to their residence. This contingency will be explicitly addressed in the consent form.

Clearly, participants are free to discontinue the experiment at any time, although we would strongly encourage them to remain in the research setting until their blood alcohol level is below .02 and alertness and psychomotor status are judged to be safe.

Because participants are not in treatment, participation in an alcohol challenge study will not interfere with efforts to achieve abstinence. At the end of the study, however, a potential benefit is that participants will be provided with a professional evaluation and treatment will be arranged if they express interest.

****Protection against the risk of heavier alcohol use, suicidality, or other medical or psychiatric problems that may arise over the course of the study****

To protect against this risk, we will do the following:

-We will closely monitor alcohol use at each visit.

-Participants will be withdrawn from the study if, in the opinion of the PI or the DSMB, there is: sustained clinically significant increase in alcohol use between ADP sessions 1, 2 and 3, suicidal ideation consisting of suicidal intent or plan, unacceptable

adverse events judged by the study physician (the PI, Dr. Batki) to be related to study interventions, or any other clinically significant medical, psychiatric, or substance use related poor outcome that makes continued study participation unsafe.

Blood and Urine Collections

Screening blood and urine collections are performed primarily as safeguards to participants and should add no risks other than those normally associated with these procedures. Participants will have approximately 40 cc of blood drawn at the intake appointment to determine liver and kidney functioning, and during the self-administration portions of the study we will draw approximately 20 cc of blood at each of the 3 visits. Therefore, the total amount of blood drawn during the study (100 ml) poses minimal risk in healthy participants. We will advise participants against donating blood for six weeks following study participation.

Risk of Study Medication - Lacosamide

Adverse effects

The 10 most common adverse effects associated with lacosamide 200 mg/day (100 mg twice per day) when used as *adjunctive therapy* in patients with partial-onset seizures (placebo comparison in parentheses) were: dizziness 16% (8%); headache 11% (9%); nausea 7% (4%); fatigue 7% (6%); vomiting 6% (3%); diplopia 6% (2%); vomiting 6% (3%); vertigo 5% (1%); somnolence 5% (5%); tremor 4% (4%); ataxia 4% (2%)[13].

Relevant Warnings/ Precautions in FDA-approved Package Insert for Lacosamide (Vimpat®)

Suicidality associated with anticonvulsants

Even though participants will be exposed to only a single dose of lacosamide, it has been noted that "all antiepileptic drugs including lacosamide increase the risk of these thoughts or behaviors in patients taking these drugs for any indication"[13]. An FDA Alert, updated 12/16/2008, (US Food and Drug Administration 2008) 11 antiepileptic or anticonvulsant drugs associated with: "reports of suicidality (suicidal behavior or ideation [thoughts])…FDA is requiring … that all manufacturers of drugs in this class include a Warning in their labeling.... FDA's pooled analyses of 199 clinical trials of eleven antiepileptic drugs… showed that patients who received one of the antiepileptic drugs had almost twice the risk of suicidal behavior or ideation (0.43%) compared to patients who received placebo (0.24%). This… represents the occurrence of approximately one additional case of suicidal thinking or behavior for every 530 patients treated with an antiepileptic drug… The increased risk was observed as early as one week after starting treatment and throughout the observed duration of treatment. The increased risk of suicidal thoughts or behavior was generally consistent among the eleven drugs with varying mechanisms of action and across a range of indications. This observation suggests that the risk applies to all antiepileptic drugs used for any indication…."

Dizziness and ataxia

The package insert notes this as a warning/precaution[13]. See above for incidence of these adverse effects. At the doses that we will be using, dizziness and ataxia could be expected to occur in 16% and 4% of participants, respectively, and may be increased by combining lacosamide with alcohol.

Cardiac rhythm and conduction abnormalities

The package insert notes this as a warning/precaution[13]. It is recommended that an ECG be obtained before starting lacosamide and that other medications that could prolong PR interval be avoided.

Syncope

Although listed as a warning/precaution[13], the package insert notes that there was no increase in syncope compared to placebo in epilepsy patients with no significant system illnesses.

Controlled substance

Lacosamide is schedule V controlled substance, indicating a potential for human abuse that is the lowest among the 5 schedules of controlled substances. In a human abuse potential study, single doses of 200 mg and 800 mg of Lacosamide produced euphoria-type subjective responses[13]. At therapeutic doses, the rate of euphoria reported as an adverse effect was less than 1%[13]. No withdrawal syndromes have been reported.

Interactions of Lacosamide and Alcohol

There are no published reports of lacosamide-alcohol pharmacokinetic (PK) or pharmacodynamics interactions. It is reasonable to assume that there may be additive effects of the combination of lacosamide 100mg with alcohol. Possible risks may include added sedation and added psychomotor impairment that could persist for several hours after last alcohol self-administration (2:00-3:00 PM). It is expected that alcohol effects will wear off in the ensuing 5 hours before discharge from the CRC at 8:00 PM. Tests of alertness and gait/body sway will be administered throughout the testing day to monitor these effects.

****Protection against risks of medications****
Effective screening will exclude participants who would be at greater risk for complications because of medical, neurological or psychiatric illnesses. Individuals currently dependent on other drugs will be screened out. Participants will be carefully monitored during each human laboratory session and will be given only single, observed doses of study medications. Participants will be educated of the risks attendant to study participation through the informed consent process.

Protection Against Risks of Lacosamide
Participants will take lacosamide only in an observed single dose administration by research staff. They will then be monitored closely from the time of medication administration at 8:30 until leaving the CRC at 8:00 PM.

Protection Against Effects of Lacosamide on Other Medications
To protect against this risk, we will do the following:
-The study physician will review all concomitant medications and determine whether there are potential drug interactions that need to be avoided.
-In the informed consent form, participants are instructed, "Lacosamide may cause a change (increase or decrease) in the effect of some other medications. If you are taking other medications during your participation in this study, immediately inform study staff. The study doctor will review any medications that you are talking and make the determination as to whether continued study participation is safe for you."

Blood Drawing (Venipuncture) Risks
Participation in the study requires participants to have their blood drawn 4 different times over the course of study (screening and human laboratory ADP sessions 1, 2, and 3). Having blood drawn may cause pain (common), fainting/passing out (not very often), a bruise where the needle goes in (not very often), and infection at the same place (rare).

****Protection against blood drawing (venipuncture) risks****
To protect against this risk, we will do the following:
1) Professionally trained phlebotomists at the CTSI Clinical laboratory will perform all phlebotomies.

Risk of Privacy/Confidentiality
Participation in the study presents a risk to the participant of loss of privacy and confidentiality regarding research material, particularly with respect to potentially embarrassing or harmful personal health information, particularly related to mental health and alcohol and substance use. This includes detailed and sensitive information regarding alcohol and drug use, and psychiatric symptoms. For example, urine drug testing will be conducted. Potential release of information regarding drug use, in particular, could have serious implications if made known, for example legal ramifications, jeopardizing insurability or employability.

In order to ensure the safety of the participant and others, information may be shared between research staff and the clinical team only under the following circumstances: 1) If in the judgment of the study physician, the participant has a psychiatric or medical condition that requires urgent attention to protect the safety of the participant or others; and 2) If a participant has missed several study appointments, and research staff needs to verify the participant's whereabouts and/or verify the participant's safety. These above circumstances will be clearly outlined in the informed consent form, and be discussed and clarified with prospective participants at the start of the study.

****Protection against risks to privacy/confidentiality****
To protect against this risk, we will do the following:
- In the informed consent form, participants are instructed: "Participation in research may involve a loss of privacy, but information about you will be handled as confidentially as possible. If you do not already have a medical record at the VA Medical Center, San Francisco, one will be created because of your participation in this study."
- *HIPAA regulations will be followed throughout this study.* Several methods will be used to decrease the risk *of loss* of confidentiality to participants.
  - First, all study forms will be labeled with a unique, identifying code number, and maintained in a locked cabinet. Those that contain the names of participants or other identifying information will be stored in a locked cabinet, separate from other study forms.
  - Second, research material will not be shared between the research team and clinical staff - with the exception of information to be shared only to ensure the safety of the participant and others.

- Third, no names will be used in any published reports about this study.
- Fourth, most of the questionnaire data will be collected using an online survey instrument called Qualtrics:

All collected research data will be referenced by unique study identification codes only, stored in an electronic database (SQL server) on a password-protected secure VA server behind a secure VA firewall at SFVAMC available to study staff only. After receiving CHR and R&D approval, we will be collecting most of our questionnaire measures in digital format, so that this questionnaire data can be collected using an online survey instrument called Qualtrics, which meets strict IRB and HIPAA data security requirements. Data will be entered into SQL Server tables using MS Access as a front-end or batch load from an external file. At a point of entry, form values are subjected to consistency edit checks (e.g. range and type verification, missing data). Scoring algorithms are applied where appropriate. Once data is entered into the database, edit checks are run for accuracy.

Unknown Risks

Participants may experience side effects that are not known yet.

****Protection against unknown risks****

To protect against this risk, we will do the following:

-During the informed consent process, participants will be notified about the possibility of unknown risks associated with taking lacosamide or their combination with alcohol.

-During the informed consent process, the possibility of unknown risks are explained and that researchers will let participants know if new information about risks and side effects becomes available over the course of the study.

-Adverse effects will be carefully monitored during each ADP lab session.

4. STUDY OBJECTIVES

4.1 Hypothesis

Include a clearly defined hypothesis, if relevant, and list the key questions the study is expected to answer. Be detailed, clear and as specific as possible.

4.2 Primary Objective

As this is a small pilot study, the Primary Aims are *process*- rather than *outcome*-oriented:

1. To establish the feasibility and safety of giving lacosamide to human participants in a laboratory alcohol self-administration procedure; and

2. To allow our research team to gain experience with these procedures and fine-tune them.

4.3 Secondary Objectives

The Secondary Aim is to obtain a preliminary assessment of the effects of lacosamide on alcohol consumption and related behaviors in individuals with AUD.

5. STUDY DESIGN

5.1 General Design

We will conduct a double-blind, placebo-controlled, within-subjects pilot laboratory trial. Four heavy-drinking, non-treatment seeking community volunteers with AUD will each undergo 3 ADP human laboratory sessions. They will be randomly assigned to receive a single dose of either 1) lacosamide 100 mg, 2) lacosamide 200 mg, or 3) placebo, in a balanced crossover design, in each of 3 human laboratory sessions, with 1 week between sessions. In each session, 2 hours after medication administration, participants will undergo a series of tests (impulsivity, craving, alcohol approach-avoidance task, and as a control measure, a reaction time task (the *Digit Vigilance Test*), followed by a priming drink and two alcohol self-administration periods, using the ADP.

5.1.1 Study Duration

The study begins with a screening visit that is expected to last approximately 3 hours. If it is deemed safe for the participant to enroll in the study and they meet all eligibility criteria, then the participant will be scheduled for 3 human lab sessions, each 12 hours long. The human lab sessions will take place on separate weeks with at least 7 days, or a washout period, before the next human lab session can commence. A follow-up visit will be scheduled at least 7 days after the 3rd and final human lab session.

5.2 Outcome Variables
This section describes the primary and secondary outcome variables, which are the endpoints that will be used to assess the study.

5.2.1 Primary Outcome Variables
The primary outcome variables are measures of feasibility:

1. Time needed to recruit, screen, and run the study procedures for 4 participants.
2. Retention rates at the various in the study process (screening, Human Lab ADP session 1,2,3, and follow-up).
3. Adverse effects of study medication (lacosamide at 2 doses and placebo), before and after alcohol self-administration.

5.2.2 Secondary Outcome Variables
Secondary outcomes:

1. Alcohol craving
2. Alcohol consumption during each of the 3 Human Lab ADP sessions.
3. Alcohol – medication interaction effects on BAES, DVT, MD gait and body sway check, Alertness VAS and computer tasks (AAT, BART, and DD)

5.3 Study Population
A total of 4 male non-treatment seeking healthy community volunteers will be enrolled.

5.3.1 Number of Participants
The study will enroll 4 men participants. We anticipate needing to start up to 6 participants to get 4 to complete all 3 human lab sessions.

5.3.2 Eligibility Criteria

Inclusion Criteria:

1. Men, ages 21-50;
2. Able to read English and to complete study evaluations;
3. Meet DSM-V criteria for current alcohol use disorder (AUD);
4. Average weekly alcohol use of 25-70 standard drinks for men over the past 30 days;
5. No more than an average of 3 days/week of alcohol abstinence in the past 30 days, to maximize likelihood that participants will choose to drink during the laboratory sessions.

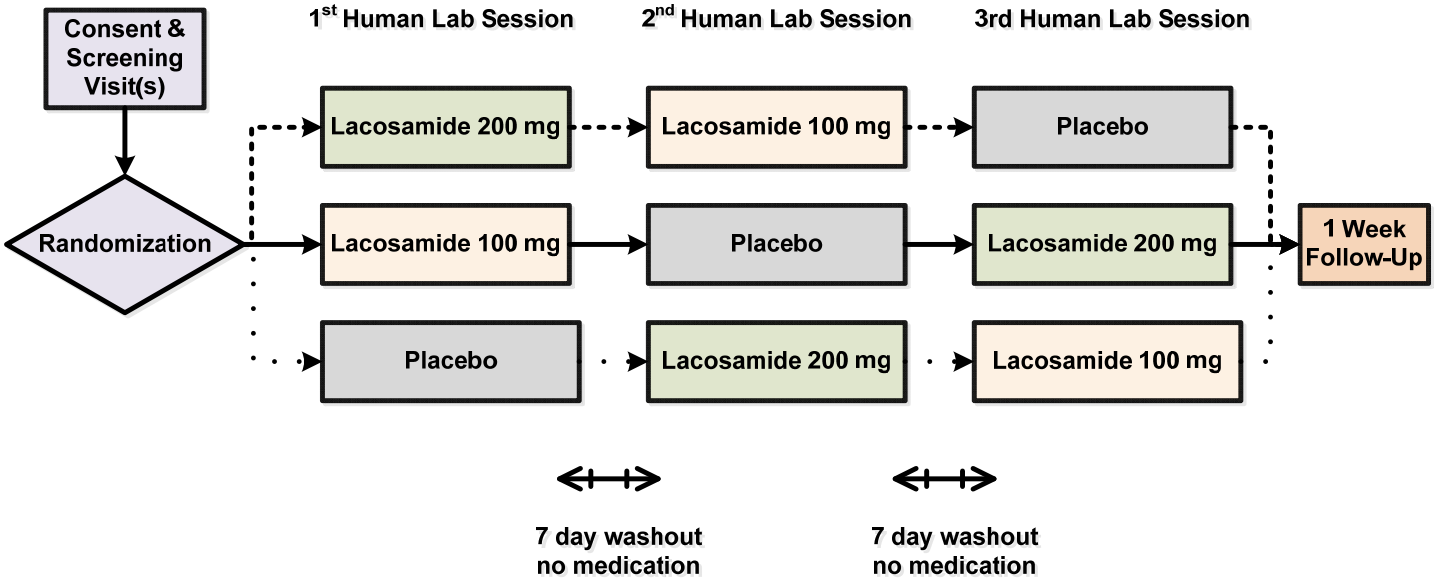
Exclusion Criteria:

1. Individuals who are seeking AUD treatment or have been in treatment within the past 6 months;
2. Current DSM-V non-alcohol substance use disorders other than tobacco and cannabis;
3. Positive urine drug test results at more than one screening appointment for opioids, cocaine, benzodiazepines, or barbiturates;
4. Regular use of psychoactive drugs including antipsychotics, anxiolytics and antidepressants during the 30 days prior to entry, as well as regular use of anticonvulsants, beta blockers, central nervous system stimulants or depressants, or other drugs that cause excessive sedation;
5. Taking medications that may interact with lacosamide, e.g. medications that prolong the ECG PR interval, or medications with strong CYP3A4 and CYP2C9 inhibition;
6. Psychosis or any other serious mental illness as judged by SCID and study physician assessment;
7. Medical conditions that in the judgment of the study physician contraindicate the consumption of alcohol;
8. Medical conditions that in the judgment of the study physician contraindicate LAC (no contraindications listed in the FDA-approved Prescribing Information for LAC);
9. Any other medical conditions that in the opinion of the study physician would make study participation hazardous;
10. History of serious alcohol withdrawal (e.g. seizures, DTs, hospitalization) or a Clinical Institute Withdrawal Assessment Scale (CIWA-AD) score $\geq$ 8;
11. Participants who report disliking spirits will be excluded because 80 proof liquor will be provided during the alcohol self-administration periods;
12. Participants who have taken any investigational drug within 4 weeks preceding study entry.

13. Participants with first-degree atrioventricular block (AV block), PR interval lengthened beyond 0.20 seconds, or greater.

6. METHODS

The study will consist of the following steps, replicating the Yale ADP methods:
(1) Recruitment;
(2) Pre-screening: Brief telephone or in-person to determine eligibility for full screening beginning with establishing non-treatment seeking status;
(3) Full Screening/baseline visit: 1-2 in-person visits to obtain consent and to evaluate eligibility (e.g. to reject participants with medical conditions): a *diagnosis of AUD* and *heavy drinking criteria*, and by confirming that the individual is *non-treatment seeking*. If these criteria are met, physical examination and laboratory testing will be conducted. Eligible participants then proceed to
(4) Human Lab ADP Sessions 1, 2, and 3, in which participants will receive a single dose of lacosamide 100 mg, lacosamide 200 mg, or placebo. The order of medications will be randomly assigned and counterbalanced across participants. Between each session, there is a 7-day washout period when no study medication is given.
(5) The day following each ADP Session, a study staff member will call the participant to ask about well-being, assess for adverse effects and collect drinking data.
(6) Participants then undergo a 1-week Follow-up visit, where adverse events and alcohol use will be assessed and a research clinician will provide a motivational enhancement session to encourage these non-treatment seeking participants to consider treatment and provided with referral materials.



6.1 Treatment – Drug

6.1.1 Identity of Investigational Product

Lacosamide (LAC) is a functionalized amino acid analogue of D-serine, and is FDA-approved as an anticonvulsant for the treatment of partial-onset seizures. The pharmacokinetic profile of LAC indicates it is rapidly and completely absorbed after oral administration with negligible first-pass effect and a high absolute bioavailability of approximately 100%, minimal CYP450 interaction, low (<15%) protein binding. Food does not affect rate and extent of absorption. The maximum LAC plasma concentrations occur approximately 1-4 hours post dose after oral dosing and elimination half-life is approximately 13 hours [91]. There is no published data in humans on LAC-alcohol interactions.

6.1.2 Dosage, Admin, Schedule

The manufacturer for lacosamide (LAC) (Vimpat®) has no involvement with the study. The Wellspring Compounding Pharmacy (WCP) in Oakland, CA is selected by the SFVAMC Research Pharmacy to compound placebo-controlled medications. WCP will obtain LAC from the manufacturer, and prepare 100 mg of LAC, 200mg capsules of LAC, and matching placebo. The SFVAMC Research Pharmacist will directly receive all study medications from WCP and store

appropriately. A single dose of either LAC 100 mg, LAC 200 mg or matching placebo will be given in each of the 3 Human Lab Sessions.

6.1.3 Method of Assignment/Randomization
Participants will be randomly assigned to one of 3 sequences for the 3 Human Lab ADP sessions, in a balanced within-subjects crossover design.

6.1.4 Blinding and Procedures for Unblinding
Matching study medications will be prepared by Wellspring Pharmacy and stored and dispensed by the SFVAMC Research Pharmacist. The Research Pharmacist will keep the randomization list. The investigators and participants will be blinded to the particular sequence of medication assignments.

6.1.5 Packaging/Labelling
The SFVAMC Research Pharmacist will manage these procedures: The Wellspring Compounding Pharmacy (WCP) in Oakland, CA is selected by the SFVAMC Research Pharmacy to compound placebo-controlled medications. WCP will obtain LAC from the manufacturer, and prepare 100 mg of LAC, 200mg capsules of LAC, and matching placebo. The SFVAMC Research Pharmacist will directly receive all study medications from WCP and store appropriately. A single dose of either LAC 100 mg, LAC 200 mg or matching placebo will be given in each of the 3 Human Lab Sessions.

6.1.6 Concomitant Therapy
Participants will be informed that they cannot use psychoactive drugs including antipsychotics, anxiolytics and antidepressants during the 30 days prior to entry, as well as anticonvulsants, beta blockers, central nervous system stimulants or depressants, or other drugs that cause excessive sedation in the judgment of the study physician/PI.

6.1.7 Restrictions
As per Exclusion Criteria, above.

6.2 Assessments
Please see the list of study measures below, Sec. 6.3.5

6.2.1 Efficacy
This is a pilot feasibility study, not an efficacy study. The primary outcome variables are measures of feasibility:

1. Time needed to recruit, screen, and run the study procedures for 4 participants.
2. Retention rates at the various in the study process (screening, Human Lab ADP session 1,2,3, and follow-up).
3. Adverse effects of study medication (lacosamide at 2 doses and placebo), before and after alcohol self-administration.

6.2.2 Safety
Please see the study procedures, below, Sec. 6.3.5, and steps to minimize risks, above, in Sec.3.3.5.

6.2.2.1 Adverse Events Definition and Reporting

Adverse Events
During the study, site personnel will note any change in the condition(s) and the occurrence and nature of any adverse events. For 7 days after the last dose of study supplement/placebo (post-discontinuation evaluation) participants will be closely followed for study drug-related adverse events in order to detect delayed toxicity. If drug-related toxicity is present beyond 7 days post last dose, participants will be followed every 7 days until the toxicity resolves, another therapy is initiated, or death. Important clinical information that comes to light during study participation will be communicated by research coordinators to the study physician in real time.

The study physician (either the PI, Dr. Batki, or, in his absence, the study sub-I, Dr. Ellen Herbst) will review each participant's safety at each study visit.
-Lab results will be reviewed on the same day that the results are received.
-Adverse effects reported by participants will be reviewed on the same day as they are reported by the study participant.
-Adverse effect assessment will be done by the research coordinators and discussed with the study physician on a daily basis, immediately after these adverse effects are reported by the participant to the study coordinator.

As with our current, CHR-approved clinical trials, the study physician, if not immediately present at the time of adverse effect data collection, will be contacted in real time by the study coordinator by phone, pager, or text message, so that adverse effects can be discussed with the study physician. The study physician, based on examination of the participant and/or review of the participant's data, will make a clinical judgment at each visit regarding whether it is safe to proceed with study medications.

The PI will report to the IRB, DSMB and study sponsor his assessment of the potential relatedness of each AE to protocol procedure, studied disease state, study drug via the CRF. For each adverse event recorded on the Adverse Event CRF, the PI will make an assessment of seriousness, severity, and causality.

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition).
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug. If a participant's dosage is reduced or treatment is discontinued as a result of an AE, the PI will report to the study sponsor via CRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

Events leading to the clinical outcome of death from progressive disease will not be recorded as adverse events unless the PI believes that the event may have been caused by the study drug.

Serious adverse event (SAE) collection begins after the participant has signed informed consent and has received study drug. If a participant experiences an SAE after signing informed consent, but prior to receiving study drug, the event will NOT be collected unless the PI feels the event may have been caused by a protocol procedure.

The PI will alert the study sponsor of any SAE within 24 hours of the PI's awareness of the event. Alerts issued via telephone will be immediately followed with official notification on study-specific SAE forms.

An SAE is any adverse event from this study that results in one of the following outcomes:

- death (excluding death due to progression of study disease, unless related to study drug);
- initial or prolonged inpatient hospitalization;
- a life-threatening experience (that is, immediate risk of dying);
- persistent or significant disability/incapacity;
- congenital anomaly/birth defect;
- considered significant by the PI for any other reason.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse events (SAEs) occurring after a participant has taken the last dose of study drug will be collected for 7 days after the last dose of study drug, regardless of the PI's opinion of causation. Thereafter, SAEs will not be reported unless the PI feels the events were related to either study drug, or drug delivery system, or a protocol procedure. Any SAE occurring prior to enrollment that the PI believes may have been caused by a protocol procedure will be reported to the study sponsor within 24 hours of the PI's awareness of the event and recorded on the CRF.

Study-specific clinical outcomes of death from progressive disease will be reported as SAEs only if the PI deems them related to use of the study drug.

Immediate Reporting Requirements From

PI to Sponsor:
Certain events will be immediately reported to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The PI will report such events to the Sponsor immediately; under no circumstances will be reporting take place more than 24 hours after the PI learns of the event. The following is a list of events that the PI will report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:
Serious adverse events
Non-serious adverse events of special interest
Pregnancies

The PI will report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis;
- Significant new diagnostic test results;
- Change in causality based on new information;
- Change in the event's outcome, including recovery;
- Additional narrative information on the clinical course of the event.

Emergency Medical Contracts

Medical Monitor Contact Information:
Any life-threatening (i.e., imminent risk of death) or fatal AE that is attributed by the PI to the investigational product will be telephoned to the Medical Monitor immediately, followed by submission of written case details on an CRF within 24 hours.

The following is the contact information that will be utilized by the PI:
MEDICAL MONITOR
Anne Richards, MD, MPH
SFVAMC/UCSF
4150 Clement Street
San Francisco, CA 94121
Telephone:415/221-4810 x 23312
Email: anne.richards@va.gov

Follow-up of Participants after Adverse Events

PI Follow-Up:
The PI will follow all unresolved treatment-related adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the PI, new therapy is initiated, the participant is lost to follow-up, or the participant withdraws consent.

Every effort will be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported. During the study period, resolution of adverse events (with dates) will be documented on the Adverse Event CRF and in the participant's medical record to facilitate source data verification (SDV). If, after follow- up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event CRF.

Data Review - For Phase II or III Sponsor Studies
PIs will conduct continuous review of data regarding participant safety at weekly study group meetings where the results of each participant's treatment are discussed, as is currently done for the PI's other UCSF CHR approved clinical trials. The discussion will include the number of participants, significant toxicities as described in the protocol, doses adjustments, and observed responses.

6.3 Study Procedures
Identify all procedures considered experimental, those performed exclusively for research purposes and those that would occur regardless of the research (i.e. standard of care). Include all observations that will take place during the study, and

Study Schedule listing study procedures (visit by visit) with timing intervals to provide a summary for study team and reviewers.]

6.3.1 Study Schedule

STUDY VISIT	WEEK	TYPE OF VISIT	AMOUNT OF TIME
1	1	Baseline/screening	3 hours
2	2	Human lab session 1	12 hours
		Phone visit 1	10 minutes
	3	WASHOUT	
3	4	Human lab session 2	12 hours
		Phone visit 2	10 minutes
	5	WASHOUT	
4	6	Human lab session 3	12 hours
		Phone visit 3	10 minutes
5	7	Follow-up visit	1 hour
TOTAL		5 visits	40 hours and 30 minutes

6.3.2 Informed Consent

The process of informed consent will minimize undue influence or coercion and offer sufficient time for review. Typically study coordinators will receive thorough training on the correct way to conduct informed consent. On a rare occasion, a study physician or project manager will conduct informed consent. All staff conducting informed consents have at least a Bachelor of Arts or Science in a health-related field and/or have 2 years of research-related experience. Training for the administration of informed consent teaches study staff how to move through the consent, assessing participant's comprehension along the way. A staff member in training will (1) shadow a trained staff member conducting informed consent 2 times, then (2) practices informed consent with other lab members, and finally (3) conducts informed consent with a participant while another trained lab member watches. Once the staff member-in-training satisfactorily conducts informed consent under the supervision of another trained staff member, the staff-in-training becomes authorized to conduct informed consent.

6.3.3 Screening

After consent, participants will be scheduled for screening assessments. The screening phase is accomplished over a total of 1 to 2 visits.

6.3.4 Enrollment

[Identify who will enroll the subjects in the study and how this process will take place (for instance, after they have been consented, screened and meet eligibility criteria).]

6.3.5 On study visits

Baseline/screening visit 3 hours	Patient Locator form Demographics Eligibility form Electrocardiogram (ECG) Medical History Physical Exam Lab tests Height/weight Concomitant Medications Concomitant Treatment Log Columbian Suicide Severity Rating Scale AE Checklist Breath alcohol test Structured Clinical Interview for DSM-5 (SCID) Timeline Followback (TLFB) Clinical Institute Withdrawal Assessment (CIWA-AD)

	Urine Drug Screen (UDS) Family Tree Questionnaire (FTQ) Barratt Impulsiveness Scale (BIS-11) Alcohol Use Disorders Identification Test (AUDIT) Vitals Balloon Analogue Risk Task (BART) Delay Discounting (DD)
Human Lab Sessions 1, 2 and 3 12 hours each human lab	Weight AE Checklist Concomitant Medications Approach Avoidance Task (AAT) Breath alcohol test Timeline Followback (TLFB) Clinical Institute Withdrawal Assessment (CIWA-AD) Urine Drug Screen (UDS) Blood alcohol level Vitals Alcohol Urge Questionnaire (AUQ) MD gait and body sway check Concomitant Treatment Digit Vigilance Test (DVT) Biphasic Alcohol Effects Scale (BAES) Yale Craving Scale – Short (YCS) Balloon Analogue Risk Task (BART) Delay Discounting (DD) Ratings of Drinking Behavior During the Alcohol Self-Administration Period
Phone visits 1, 2, and 3 10 minutes each phone call	AE Checklist Timeline Followback (TLFB)
Follow-up Visit 1 hour	Participant End of Study Questionnaire AE Checklist Breath alcohol test Timeline Followback (TLFB) Alcohol Urge Questionnaire (AUQ) Medical Management (MM)

Assessments at Study Entry and During and After Human Lab Sessions

At Entry:

These are adapted from previous/ current clinical studies at the UCSF/SFVAMC Addiction Research Program.

▪ Demographic data, will be assessed with data on age, race, socioeconomic status, marital status, educational and occupational levels, and significant medical history.

►A number of safety evaluations are included: Medical history and physical examination; Suicide Risk Assessment: The Columbia Suicide Severity Rating Scale [101]. It is a standard, thorough, frequently used method to screen for suicidal ideation, used by our group in alcohol use disorder clinical trials;

- Clinical Laboratory Tests for Health/Safety Monitoring: Blood samples will be collected for chemistry, liver panel, renal panel and complete blood count (CBC); urine will be collected for urinalysis and urine pregnancy tests on women of childbearing potential;
- ECG**:** an electrocardiogram will be performed to check cardiac conduction, in particular for PR interval prolongations, as this is of relevance to LAC, which can cause small, dose-related increases in mean PR interval

▪ Structured Clinical Interview for DSM-5, (SCID) [96]**:** the SCID will be used to determine DSM-V diagnosis of current (current year) Alcohol Use Disorder, and the DSM-V current psychiatric diagnoses for anxiety, mood, psychotic, and non-alcohol substance use disorders in order to determine study eligibility.

▪ Alcohol Use Disorders Identification Test (AUDIT): The AUDIT [97] is valid and reliable self-report measure of alcohol-related problem severity.

▪ Barratt Impulsiveness Scale (version 11) (BIS-11) [98]: This provides a trait measure of impulsiveness and will be used to characterize the study cohort at study entry.

▪ Study Physician Review: All health measures, medical history/exams and labs will be reviewed by a study physician to ensure that the subject meets all the eligibility criteria and are ready for randomization

At Entry and at various times throughout the study:

▪ Clinical Institute Withdrawal Assessment for Alcohol, DSM-IV Version (CIWA-AD): at entry and before each Human Lab Session and at each Follow-up;

▪ Urine Drug Screen: For opioids, benzodiazepines, cocaine, amphetamines, barbiturates: at entry and before each Human Lab Session;

▪ Breath alcohol concentration (BrAlc); at entry and before each Human Lab Session; and during each Human lab Session

▪ Vital Signs**:** Temperature, heart rate, and blood pressure will be measured at study entry and multiple times during each Human Lab Session.

▪ Concomitant Medications Review: at entry and before each Human Lab session: thorough review of all concomitant medications (prescription or over-the-counter) in the past 30 days, as well as those started during the study.

▪ AE Checklist: At Entry and at Human Lab Session 1, 2 and 3; Phone visits 1, 2, 3; 1-wk FU; The most commonly experienced side effects listed in the FDA package insert will be reviewed. Participants will be asked how many times they have experienced each side effect since the last study visit and severity.

▪ Timeline Followback (TLFB): at study entry, then Human Lab Session 1, 2 and 3; phone visits 1, 2 and 3. TLFB will be used to calculate standard drinks consumed per week in the past 30 days prior to consent and at the two Human Lab Sessions, and the 1-week follow-up. The TLFB will be used to determine whether subjects meet minimum alcohol consumption criteria at entry. Other substance use will also be collected by TLFB.

▪ Balloon Analogue Risk Task (BART): at each Human Lab session after medication

▪ Delay Discounting: at each Human Lab session after medication

At Follow-up visit:

▪ Medical Management: at the follow-up visit, research clinician will provide a motivational enhancement session to encourage the non-treatment seeking participants to consider treatment.

Measures of Alcohol Effects:

▪ Breath alcohol concentration (BrAlc) [99] *at each visit, and multiple times in ADP Sessions 1 and 2*. BrAlc will be measured at each session to detect recent alcohol use with the *Intoximeters Alco-Sensor IV* instrument.

▪ Blood Alcohol Levels**:** Human Lab Sessions 1 and 2 (Table 1)**:** Blood samples will be drawn to measure plasma levels of blood alcohol (BAC) during the priming dose and during the alcohol self-administration paradigm. Blood samples will be stored at -4°C and will be analyzed at the San Francisco VA.

▪ Biphasic Alcohol Effects Scale (BAES) [81]: Human Lab Sessions 1 and 2 (Table 1). This 14-item self-report rating scale measures alcohol stimulant/ sedative effects and is used regularly in the Yale ADP.

▪ Alcohol Urge Questionnaire (AUQ): At study entry; multiple times in Human Lab Sessions 1 and 2 (Table 1); 1-wk FU; 1-mo FU: The AUQ is an 8-item questionnaire assessing *desire, expectation of positive effect,* and *inability to avoid drinking if alcohol is available.* The AUQ is a reliable and valid scale for the measurement of self-reported alcohol urges. Its brevity and time frame for ratings (i.e. right now) makes it suitable for the ADP.

▪ Yale Craving Scale -Short (YCS): Multiple times in Human Lab Sessions 1 and 2; visual analog scale that measures craving for alcohol

▪ Ratings of Drinking Behavior During the Alcohol Self-Administration Period: multiple times in in Human Lab Sessions 1 and 2. Subjects will be videotaped during the alcohol self-administration portion of ADP 1 and ADP 2. Videotapes will be rated by two independent for the onset and offset of each sip of alcohol. Dependent measures will be constructed including time until the first sip and average time to consume each drink.

▪ Vital Signs: Human Lab Sessions 1 and 2 (Table 1). These will include heart rate, blood pressure, and skin. The blood pressure cuff will be on subject's dominant arm while the probe of will be attached to the middle finger of the subject's non-dominant arm. These data will be further used to examine the safety of using the study medications during alcohol self-administration.

Participant Incentives

STUDY VISIT	REIMBURSEMENT AMOUNT
Screening/baseline	$85*
ADP Lab Session 1	$224**
ADP Lab Session 2	$224**
ADP Lab Session 3	$224**

Follow-up visit	$25
Bonus for completing ADP Sessions 1 + 2 + 3	$50
Total	$832

*At the screening/baseline visit, participants are paid per task they complete. At the end of screening, they will earn $85.

**Participants will receive $200 for each ADP Lab Session they complete. They could earn an additional $24 per ADP Lab Session, depending on how many drinks they consume per session. At each session, participants are offered 8 drinks, each worth $3. They will receive $3 per drink for every drink that is not consumed.

6.3.6 Removal of participants

Stopping Rules

Discontinuation of participants:
Participants for whom there has been at least 2 weeks without participant contact will be discontinued from the study. Exceptions may be made after discussions with the PIs, approval by the Medical Monitor, and consistency with the regulations of the Institutional Review Board/Ethics Committee (IRB/EC).

Discontinuation of study:
The study will be stopped if, in the judgment of the DSMB or the PI, there are sufficient safety concerns that arise during the conduct of the study that would indicate that participants are being harmed by the study interventions. Examples of such safety concerns would be:
-Other events that pose unacceptable risks to participants, e.g., multiple SAEs that are judged to be related to study interventions.

Withdrawal Rules

Discontinuation of Participants:
If a participant who does not meet enrollment criteria is enrolled, the study sponsor will be contacted. In such cases, the PI will provide information on the participant´s anticipated benefit or current benefit from being enrolled in the study or continuing to receive study drug respectively. In addition, the PI will discontinue participants from the study drug or the study or both in the following circumstances:

- Participant has evidence of progressive disease.
- The participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.
- The PI decides that the participant should be withdrawn from the study. If a SAE or a clinically significant laboratory value is the basis for this decision, the PI will discontinue the study therapy and take appropriate measures. The PI will immediately notify the study sponsor or its designee.
- The participant or attending physician requests withdrawal of the participant from the study.
- The investigator or the study sponsor stops the study or stops the participant's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).
- The study therapies have shown unacceptable toxicity.
- The participant is noncompliant with study procedures.
- In the clinical judgment of the investigator, the participant requires acute detoxification from the alcohol.
- In the clinical judgment of the investigator, the participant's clinical condition worsens substantially (for example, if weekly alcohol use increases 25% or more over baseline) and it is felt to be in the participant's best interest to obtain alternative treatment including, but not limited to, additionally psychotherapy, pharmacotherapy, hospitalization, etc.

When a participant withdraws before completing the study, the reason for withdrawal will be documented in the CRF and in the source document.

6.4 Statistical Method
Descriptive statistics will be used to summarize the data set. Measures of central tendency and measures of variability will be reported for the chief variables of interest as noted below in 6.4.3.

6.4.1 Statistical Design
As this is a pilot feasibility study, no inferential statistics will be used.

6.4.2 Sample Size Considerations
Not applicable.

6.4.3 Planned Analyses
Descriptive statistics will be used to describe the data set. Measures of central tendency and measures of variability will be reported. Chief variables of interest are listed below in 6.4.3.1, 6.4.3.2, and 6.4.3.3.

6.4.3.1 Primary Analyses
Primary analyses will consist of descriptive statistics. These measures of feasibility are:
1. Time needed to recruit, screen, and run the study procedures for 4 participants
2. Retention rates at the various timepoints in the study process (screening, Human Lab ADP session 1,2,3, and follow-up).
3. Adverse effects of study medication (lacosamide at 2 doses and placebo), before and after alcohol self-administration.

6.4.3.2 Secondary Objectives Analyses
Descriptive statistics will be used to summarize the data set. The variables analyzed will include:
1. Alcohol craving
2. Alcohol consumption during each of the 3 Human Lab ADP sessions.
3. Alcohol – medication interaction effects on BAES, DVT, MD gait and body sway check, Alertness VAS and computer tasks (AAT, BART, and DD)

6.4.3.3 Safety
Descriptive statistics will be used to summarize the data. The AE checklist will be used to assess adverse effects. Descriptive statistics will be used.

7. TRIAL ADMINISTRATION

7.1 Institutional Review Board (IRB) Review
[Include a statement about IRB oversight and review throughout the study. This may be institution or sponsor specific.]

7.2 Unanticipated Problems
[Explain how unanticipated problems that may occur during the study will be handled, communicated to the IRB, sponsor, and FDA, if applicable.]

7.3 Study Monitoring
[Specify who will monitor the study (third party, sponsor, internal team, etc.), where monitoring will occur and frequency. Describe any related responsibilities and identify anyone who will review the study for accuracy and how often.]
Study monitoring will be conducted by the DSMB.

7.4 Data Safety Monitoring Plan

Plan to monitor study progress and safety: The Data and Safety Monitoring Plan (DSMB)
The DSMP for this project consists of:
- a Data and Safety Monitoring Board (DSMB)
- a schedule of DSMB meetings to review study data and events
- a list of study data and event items to be reviewed by the DSMB
- procedures for communicating DSMB findings to the CHR, the study sponsor (Department of Defense) and other appropriate entities

- a plan for conducting and reporting interim analysis
- stopping rules
- rules for withdrawing study participants from the study interventions

These elements of the DSMP are described below:

The Data and Safety Monitoring Board (DSMB)
The Data and Safety Monitoring Board (DSMB) is a group of 3 physicians who are not study investigators and who are experts in the area of clinical research and substance use disorders. The current composition of the PI's DSMB is: William Wolfe, M.D., a clinical investigator and Medical Director, PTSD Clinic, SFVAMC; Anne Richards, M.D. [medical Monitor], an experienced human clinical investigator, Assistant Professor of Psychiatry at University of California, San Francisco and Steven Lieske, M.D., Ph.D., an experienced basic neuroscience investigator and attending psychiatrist, SFVAMC.

The DSMB will meet biannually to review data reports prepared by the PI regarding the progress of the study and will monitor patient enrollment, retention, outcomes, adverse events, and other issues related to patient safety. The DSMB will make recommendations to the PI as to whether the study should continue or be modified or terminated. The DSMB can consider patient safety or other circumstances as grounds for early termination. Any member of the DSMB can ask for a meeting of the group if he/she feels that it is necessary, based upon the data.

During the course of the study, reports will be prepared and distributed to the Data and Safety Monitoring Board on a biannual basis. In order for the Data and Safety Monitoring Board to discharge their duties for overseeing the study and the rights of the patients, they will receive analyses of the primary outcome measures and the important secondary measures on a quarterly basis. The DSMB will receive reports of serious adverse events (SAEs) within 72 hours of their occurrence.

DSMB Minutes will be prepared by the Study Coordinator within 5 working days after each biannual DSMB meeting.

Medical Monitor
Anne Richards, M.D., Medical Director of the PTSD Clinic at San Francisco VA Medical Center will serve as the Medical Monitor. As Medical Monitor, Dr. Richards will review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the medical monitor will comment on the outcomes of the event of problem and in case of a serious adverse event or death, comment on the relationship to participation in the study. The Medical Monitor will also indicate whether she concurs with the details of the report provided by the principal investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation and reports of events resulting in death will be promptly forwarded to the IRB and other governing authorities.

7.5 Study Discontinuation
[explain the circumstances under which the study may be discontinued]
If a serious adverse effect occurs and is considered by the PI and DSMB to be study-related, the study will be stopped until study procedures can be reassessed and modified as needed, with concurrence by the DSMB.

7.6 Study Completion
We will conduct the following procedures to close-out the study:
Submit a close-out report to the UCSF CHR
Submit a notification to the Biosafety Committee to close-out the Biological Use Authorization (BUA).
Submit notification to the SF VA R&D Committee to close-out the project, BATS-XXXX
Once all close-out reports have been processed, we will submit a notification to the study sponsor (ACGT) with all other close-out reports.

7.7 Funding Source
The study is funded by the University of California Alcohol Center for Genes and Translation.

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