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INTEGREVIEW IRB
MAY 26, 2020
NOT TO BE USED FOR SUBJECT ENROLLMENT

INFORMED CONSENT DOCUMENT
AGREEMENT TO BE IN A RESEARCH STUDY

NAME OF SPONSOR COMPANY:	National Institute on Alcohol Abuse and Alcoholism (NIAAA)
PROTOCOL NUMBER AND TITLE OF STUDY:	HLAB-002; "Human Laboratory Study of ANS-6637 for Alcohol Use Disorder"
NAME OF PERSON IN CHARGE OF THE RESEARCH STUDY (STUDY DOCTOR/INVESTIGATOR):	$$Name of Investigator$$
TELEPHONE NUMBER(S), DAYTIME:	$$Day Number$$
AFTER HOURS:	$$After Hours$$

KEY INFORMATION

1. This is a research study and your participation is voluntary.
2. This research study is to look at the effects of two different doses of ANS-6637 (the study drug) compared with placebo (like a sugar pill) on how much you crave alcohol and should take up to 10 weeks of your time.
3. You will be asked to visit the clinic weekly for 6 weeks and have a telephone call one week after the last study visit. You will be given a breathalyzer test to ensure you are able to provide consent and participate in the study assessments. You will be asked to give blood for testing how your liver, kidney and body are functioning and for checking to see if you have a genetic marker. You will be asked about your cravings for alcohol and about your drinking. This study uses a smartphone to check to make sure you took your study medication. The study drug is "investigational". This means that it has not been approved by the United States Food and Drug Administration (FDA).
4. If you drink alcohol, you may feel flushing or heat sensation, heart fluttering, nausea, breathlessness, rash, and headache while taking this study drug. The complete list of risks / discomforts is listed later in this informed consent.
5. The main benefit to you (or others) for taking part in this study is your drinking habits may change.
6. There are several alternative treatments that may be effective for treating alcohol problems, including other medications and/or counseling. These other treatments are not offered to you as part of this research study, but if you decide not to participate, or are not eligible, study personnel will give you contact information for existing treatment programs in your area.

INTRODUCTION

You are deciding if you would like to volunteer for a medical research study. You must read this form before you agree to take part in this study. If you agree, you must sign this form to show you would like to participate. This form will give you more information about this study. Please ask as many questions as you need to before you decide if you want to be in the study. Do not sign this form if you have any questions that have not been answered.

The investigator is being paid by the sponsor (NIAAA) to conduct this research study. Amygdala Neuroscience is the pharmaceutical company that manufactures ANS 6637 and placebo for this study.

THIS IS AN IMPORTANT DOCUMENT - KEEP FOR FUTURE REFERENCE

VERSION CONTROL
jnb/master: 6-3-19 snb/master: 8-7-19 kmj/master: 12-30-19 bgb/master: 4-6-20 ar/master: 5-26-20

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You must be honest with the investigator about your health history or you may harm yourself by participating in this study.

PURPOSE OF THE STUDY

The purpose of this study is to determine if the study drug decreases craving for alcohol and reductions in alcohol drinking while taking the study drug. The purpose is also to test the safety of this drug in persons who drink alcohol. The study drug being tested in this clinical trial is ANS-6637. It is a class of drug called an aldehyde dehydrogenase 2 (ALDH – 2) inhibitor that may lower the dopamine surge in the brain and stop alcohol craving. It is considered "investigational" as the FDA has not approved this drug.

In this document, you may see the terms "medication", "treatment", and "treatment period"; these are terms used in research studies as mentioned above and does not mean that you will be receiving medical treatment for any condition. These terms apply to the study drug and parts of the study where you will receive the study drug or placebo.

If you qualify for the study, you will receive tablets to take orally with a glass of water containing: Placebo OR 200 mg ANS-6637 OR 600 mg ANS-6637 once a day for 5 weeks. Placebo tablets contain no active ingredient.

This is a double-blind study, which means that neither you nor the investigator will know which drug you are taking. The study staff can get this information if needed for an emergency.

The drug you receive will be assigned by chance, like the flip of a coin. An approximately equal number of people will be assigned to receive placebo, 200 mg ANS-6637, or 600 mg ANS-6637.

HOW LONG THE STUDY WILL LAST AND HOW MANY PEOPLE WILL BE IN THE STUDY

The study will last about 10 weeks and involve up to 7 visits to the clinic. About 81 men and women, ages 21 and over with moderate to severe alcohol use disorder, are expected to be in this study.

TO BE IN THIS STUDY

You cannot be in this study if you are taking any drugs of abuse (illegal). A urine test will be performed to check for the use of these drugs. If you are female able to become pregnant you will be given a pregnancy test that must be negative. Both men and women must use an acceptable method of birth control during the study or will not be allowed to participate.

<u>Subject Responsibilities:</u>

While participating in this research study, you must agree to:

- Not give the study drug to other people and keep it out of the reach of children
- Be willing and able to follow the study directions and procedures
- Tell the study staff about any side effects or problems
- Ask questions as you think of them
- Tell the investigator or the study staff if you change your mind about staying in the study.

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- Provide a valid form of identification (ID). Acceptable forms of ID are as follows: Driver's License, Passport, Military ID, State or National ID, Cedula Government Issued ID, or Medicare or Medicaid card.
- Undergo a physical exam to assess your overall health and wellness and have an electrocardiogram (ECG) to measure the electrical activity of your heart.
- Have vital signs taken (blood pressure and heart rate).
- Provide a blood sample to assess how your liver, kidneys, thyroid gland, and immune system are working.
- Provide a urine sample to test for drug use and alcohol consumption.
- Give your medical history and have your weight measured.
- Provide your age, gender, occupation, and income.
- Provide the names of any prescription and "over-the-counter" drugs you may be taking now or in the recent past.
- Answer questions about your mental health, and any withdrawal symptoms from alcohol.
- Provide your daily alcohol use
- If you are a female, provide a urine sample to test for pregnancy and agree to use an acceptable method of birth control.
- If you are male, agree to use acceptable birth control with your female partner (if applicable).
- Agree to use a smart phone (either your own or one provided to you) that has an application to remind you to take your study drug and record when you have taken your study drug.

WHAT WILL HAPPEN DURING THE STUDY

Study Procedures:

Visit #1: Screening: (up to 14 days)

The screening phase will be completed within 14 days and will involve one clinic visit. Additional visits may be requested if laboratory tests need to be repeated.

If you decide to volunteer for this study, your first visit will take approximately 2 1/2 to 3 hours to complete. This involves a number of tests to make sure that you meet all of the requirements for participation and that you can safely take the study drug. You will not be given study drug during this first screening visit.

At the beginning of Screening Visit #1, your blood alcohol level will be measured using a breathalyzer. If your blood alcohol is greater than 0.000, you may not be able to complete your visit as scheduled. If your blood alcohol level is very slightly higher than 0.000, study staff may give you the option of waiting until it reaches 0.000 to continue with your first visit. If you blood alcohol level is 0.080 or higher and you drove to your visit, study staff will ask you to remain in the clinic until you are capable of leaving without risking your (or others) safety.

During this visit you will be asked to:

- Provide a valid form of identification (ID). Acceptable forms of ID are as follows: Driver's License, Passport, Military ID, State or National ID, Cedula Government Issued ID, or Medicare or Medicaid card.
- Provide your age, gender, occupation, and income.

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- Provide a urine sample to test for drug use.
- Undergo a physical exam to assess your overall health and wellness and have an electrocardiogram (ECG) to measure the electrical activity of your heart.
- Give your medical history and have your weight measured.
- Have vital signs taken (blood pressure, heart rate, and temperature).
- Answer questions about your mental health.
- Provide a blood sample to assess how your liver, kidneys, thyroid gland and immune system are working.
- If you are a female, provide a urine sample to test for pregnancy and answer questions about your birth control method(s).
- If you are a male, you will be asked about birth control method(s).
- Provide your daily alcohol use for the past 28 days.
- Provide the names of any prescription and "over-the-counter" drugs you may be taking now or in the recent past.
- Answer questions about any withdrawal symptoms from alcohol.
- Participate in an exercise (called a cue session) where you will be shown beverages (including your favorite alcoholic beverage) and complete computerized questions about your craving for the beverages.

You will also be asked to provide addresses and telephone numbers for yourself and other people, such as family members or friends who will know how to contact you if you fail to show up for clinic visits, or if study personnel have problems getting in touch with you. In doing so, you give study personnel permission to contact these people to find out how to contact you. Please be aware that telling others you are in this study could jeopardize your privacy.

At the end of this visit, you will be told if you are still eligible to participate in the study and have a second visit scheduled to complete the final screening tests and start study participation.

Visit #2: Completion of Screening and Start of Study Treatments (Week 1)

If you are still eligible for the study, a second screening and study start visit will be scheduled. At the beginning of this visit your blood alcohol level will be measured using a breathalyzer. If your blood alcohol is greater than 0.02, the same rules apply that were described above.

At this visit you will be asked to:

- Provide a urine sample to test for drug use.
- Update your medical history.
- Undergo a physical exam if new problems have occurred.
- Have vital signs and weight taken.
- Answer questions about thoughts or attempts of harming yourself, and alcohol withdrawal symptoms.
- Provide a urine sample for a pregnancy test if you are female.
- Review of acceptable birth control methods (men and women).
- Provide the names of any prescription and "over-the-counter" drugs or herbal remedies you may be taking.
- Provide your daily alcohol use since your last visit and your drinking goal at the end of the study.

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If you are still eligible, you will be asked to:

- Provide blood samples for DNA marker testing for ALDH2 (a specific genetic marker that does not affect your ability to participate in the study). If you have a certain type of this gene, you are likely to have a flushing reaction to alcohol. This is a heat sensation with redness of the face, neck, or chest.
- Fill out questionnaires or answer questions about your mood, desire to quit drinking, sleep, drinking urges, smoking cigarettes, and use of other nicotine products.

At this visit if you are eligible, you will start an alcohol education program called Take Control which is designed to help people cut back or stop drinking and will be given a bottle containing tablets of the study drug.

During this Study, you will monitor yourself taking your study drug on a smartphone application. This application is provided by a company named AiCure that will collect and store your data during the conduct of the study. You will be able to download the application with help by the study site staff. If you do not have a smartphone or do not want to use your own device, you have an option to use a device provided by the study site. If you download the application, you will be reimbursed $10.00 per month to account for the cost of data transmission. You will be required to use the application to monitor each time you take the study drug while you are enrolled in the study.

The application will be used only for the purpose of making sure you are taking your dose. If you are provided with a device, you will not be able to make general phone calls, respond to text messages, or use the device to access the Internet. This application uses artificial intelligence to confirm that the same person uses the device, and that the study drug is correct and taken properly. The application's interactive software will send a message to a secure server, confirming that you took the study drug. The application will record the date and time that you took the drug so that the study site can confirm it was taken for that day.

To protect your identity at all times, all of your video recordings and data are encrypted by the application and will be automatically forwarded to a secure server. The cloud-based server is compliant with the Health Insurance Portability and Accountability Act (HIPAA), which protects the privacy and security of healthcare information. The data are securely stored and only accessible to healthcare providers and other authorized personnel through two-way authentication. The study site staff can tell you more about this application and how it will be used.

Before starting use of the smartphone application, the study site staff will assist you in setting up the application so that the application can confirm your identity and register your preferred settings. Through prompts, the application will assist you to practice monitoring yourself taking the study drug. During the practice training session, you will be asked to take something called a "dummy" tablet (Smarties candy). The practice "dummy" tablet will be used only for the training session. You will not take the "dummy" tablet home with you. The "dummy" tablet does not contain any active drug, and will be digested just like food.

You will practice several times to learn how to use the application and how to take the study drug. The study staff will help you set the application so that it will remind you to take the study drug in the morning. It is important that you remember to use the application on the smartphone device every time you take your drug. If you are not using the device or not taking your drug correctly, you may be discontinued from the Study.

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Treatment (Weeks #1 to #5)

During the first week (Week #1), you will be contacted two times by study staff by phone to see how you are feeling. Also at the second phone contact, you will be reminded about things to do before your next visit. You will be reminded on this phone call to take the study drug as usual in the morning and to not drink caffeine after arriving for this visit until study tests are completed and that you must refrain from smoking about 1-1.5 hours before the testing and during the testing.

During the Weeks 2 to 5 visits, the following information will be collected and tests will be performed:

- Your blood alcohol level will be measured using a breathalyzer. If your blood alcohol is greater than 0.020, you may not be able to complete your visit as scheduled. If your blood alcohol level is very slightly higher than 0.020, study staff may give you the option of waiting until it reaches 0.000 to continue with your visit. If you blood alcohol level is 0.080 or higher and you drove to your visit, study staff will ask you to remain in the clinic until you are capable of leaving without risking your (or others) safety.
- A urine sample to test for drug use.
- A blood sample to measure drug levels in your blood (Week 2 and 4 only)
- A blood sample to check your liver, kidney and thyroid gland functions (at Weeks 2 and 4 blood will also be collected to check your immune system)
- Update your contact information.
- Questions about thoughts or attempts of harming yourself, and alcohol withdrawal symptoms.
- Vital signs and weight measured.
- Questions about any medications you are taking (or have taken since the last visit).
- Your study drug bottle collected and a new bottle(s) provided.
- Asked about your cravings for alcohol and alcohol withdrawal symptoms.
- View an alcohol education program called Take Control.
- Fill out questionnaires or answer questions about your mood, desire to quit drinking, sleep, drinking urges, smoking cigarettes, and use of other nicotine products.
- Your daily alcohol use since your last visit.
- Week #2 only - Participate in a second cue session (like the one done at the screening visit) where you will be shown beverages (including your favorite alcoholic beverage) and complete computerized questions about your craving for the beverages.

End of Study Visit – Week #6

At Week 6, the last clinic visit, the following information will be collected and tests will be performed:

- Your blood alcohol level will be measured using a breathalyzer. If your blood alcohol is greater than 0.020, you may not be able to complete your visit as scheduled. If your blood alcohol level is very slightly higher than 0.020, study staff may give you the option of waiting until it reaches 0.000 to continue with your visit. If you blood alcohol level is 0.080 or higher and you drove to your visit, study staff will ask you to remain in the clinic until you are capable of leaving without risking your (or others) safety.
- A urine sample to test for drug use.
- A blood sample to check your liver, kidney, thyroid gland, and immune system functions
- Questions about thoughts or attempts of harming yourself, and alcohol withdrawal symptoms.
- Vital signs and weight measured.

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- Questions about any medications you are taking (or have taken since the last visit).
- An ECG will be performed.
- Questions about your cravings for alcohol and alcohol withdrawal symptoms.
- Fill out questionnaires or answer questions about your mood, desire to quit drinking, sleep, drinking urges, smoking cigarettes, and use of other nicotine products.
- Your daily alcohol use since your last visit.
- Questions about your experience with the study drug.

You will also be provided with information about your options for continued treatment of your alcohol use disorder.

You will be required to bring your used and unused bottles with you every time you attend a clinic visit.

For your own safety and to ensure our study results are valid, we ask that you provide truthful and honest information when answering any of the study related questions. Not telling study staff about parts of your previous medical history, medications you are taking, or symptoms you are having, could put your health at risk and ruin the study findings. Please provide staff with complete and honest answers throughout the study.

If you experience a side effect, you may have unscheduled visit(s) to make sure you are well at the discretion of the investigator.

Follow-up Contact: (2 weeks after last in-clinic visit)

Two weeks after you complete the study, a study staff member will contact you by telephone to ask you questions about your alcohol use and any side effects you may have had since you stopped taking the study drug. If study staff is not able to reach you by telephone, they may contact friends or family members you provided at screening to get your new contact information. Please be aware that if you tell others that you are in this study, this could be a risk your confidentiality. In order to maintain your confidentiality when attempting to contact you or a contact person by telephone, the research staff will not say that you are a participant in this research study. Once we have contacted you and/or the contacts you gave us, your participation in the study will end.

Blood Samples:

Blood samples will be taken by single needle-sticks or by a tube that is left in your arm during the blood collection. You cannot choose how the blood is taken.

There will be about 7 blood draws during the course of the study. The total amount of blood drawn will be about 86 mL or 1/3 cup. For comparison, the standard blood donation is about 480 mL (two cups).

POSSIBLE SIDE EFFECTS AND RISKS

If you do not understand what any of these side effects mean, please ask the investigator or study staff to explain these terms to you.

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Because this drug is investigational, all of its side effects or reactions may not be known. There may be rare and unknown side effects. Some of these may be life threatening.

You must tell the investigator or study staff about all side effects that you have. If you are not honest about your side effects, you may harm yourself by staying in this study.

There have been 5 studies in humans to look at the safety of ANS-6637. The first study included 111 healthy subjects, both smokers and non-smokers. This trial studied the safety, tolerability and effect of food on ANS-6637. A total of 23 of 84 subjects experienced side effects when given ANS-6637. Side effects reported include runny nose, dizziness, itchiness, rash, abdominal pain, dry mouth, fatigue and nausea. One subject was withdrawn from the study after developing an itchy rash and one was withdrawn due to heart rhythm changes.

In the second study, 12 healthy adults were given a drink of alcohol (in an amount equal to about 6 ounces of beer). Side effects from just drinking alcohol without ANS-6637 were mild reports of feeling hot (2 subjects) and mild headache (3 subjects). Itching, redness, and a papule (small bump) on the chest were reported by one subject for each of these events. Four days later, one female subject received one 200 mg dose of ANS-6637 with the same amount of alcohol. Side effects that were mild in this subject included feeling cold (abdomen), feeling hot (back and arm), chest pain (not in the heart), throat pain, tingling in the hands, decrease appetite, and lack of energy. Moderate effects were face and neck flushing, feeling hot, feeling heart beating strongly and rapidly, anxiety, dizziness, nausea, and headache. The most severe effect was dizziness when standing up and fainting. All of these effects resolved.

In the third study, healthy adults were given 25 mg or 50 mg of ANS-6637 with different amounts of alcohol at the same time. Two of 15 people who took 25 mg of ANS-6637 with a drink of alcohol equivalent to about one or two 6 ounce beers had a mild heat sensation. One person who took 50 mg of ANS-6637 with alcohol at the same time had an increased heart rate (increase of 28 beats per minute) within an hour that was accompanied by flushing (skin redness). The other person who took 50 mg of ANS-6637 with alcohol also had increased heart rate (from 50 beats per minute before to 113 beats per minute about 1 hour after dosing) with a decrease in blood pressure and flushing.

The fourth study examined the safety and tolerability of 6 dose levels (25 mg to 600 mg) of ANS-6637 with up to 5 drinks of vodka containing 40% every 30 minutes in healthy, male alcohol drinkers as compared to healthy males who received a placebo (sugar pill). Of the 48 people who received ANS-6637 in combination with alcohol more were likely to report experiencing a heat sensation, heart fluttering, breathlessness and headache than the 12 people who received the placebo pill. These effects were mostly mild. They were also more likely to experience flushing (skin/face becomes red and hot). Fewer people taking ANS-6637 reported feeling drunk than those who took placebo.

One study subject experienced evidence of liver damage and other side effects that were considered serious and possibly related to the study drug. Some study subjects have had laboratory value changes indicating a temporary mild change in their thyroid hormone levels. These changes were not associated with symptoms of overactive or underactive thyroid function. These laboratory changes returned to normal after the study medication was stopped.

In a fifth study of 12 healthy subjects, slight reversible increases in serum creatinine, some within normal limits, and presumed mildly reduced kidney function have been noted in several participants receiving multiple 600 mg daily doses. Creatinine levels returned to normal limits 7 days after the last dose in a participant who had creatinine levels above the normal range.

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Animal studies have shown there may be a risk to a developing baby during pregnancy.

There may be risks associated with the use of the study drug and other medications that are not known at this time. Before starting any new drug while you are in the study, you must get your study doctor's permission.

ADDITIONAL RISKS OR DISCOMFORTS

Common discomforts of participating in a research study:

- Some of the questions about your personal habits, lifestyle, and drug and alcohol use may embarrass you. If any question makes you feel uncomfortable you may discuss its importance and the need to answer it with the specially trained interviewer. You may refuse to answer a question if it is upsetting to you.
- You may become bored with answering questionnaires.

Physical discomforts of participating in this study:

- The drawing of blood may cause pain, redness, bruising bleeding, lightheadedness, nerve damage, blood clots, which may cause inflammation, swelling and pain, and on rare occasions, infection. You may briefly feel the prick of the needle when it is inserted into your vein. You may feel dizzy or faint when your blood is drawn. Precautions will be taken to minimize these risks. If you feel faint tell the study staff right away.
- ECGs may cause discomfort and/or irritation of the skin (redness and itching) from the adhesive electrodes. Hair on your chest may need to be removed in order to obtain the best electrical contact between the adhesive electrodes and your skin. Irritation from hair removal (shaving) also could occur.

Risks to Providing a DNA Sample:

- The results of genetic testing provide a similar amount of information as many non-genetic tests that are part of ordinary medical practice. The results do not present a social risk that is meaningfully different than other test results from this study. Your test results are confidential. However, if your test results go into the wrong hands, the confidentiality of your health information may be lost. The sponsor, NIAAA, will make every effort to make sure no one gets your test results except people or companies you read about in this form. In addition, the Genetic Information Nondiscrimination Act of 2008 prohibits the use of genetic information in health insurance and employment decisions.

  Be aware that this Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long term-care insurance, nor does it prohibit discrimination on the basis of a genetic disease or disorder that you already know about.

RISKS FROM ALCOHOL WITHDRAWAL

Some people may experience symptoms of alcohol withdrawal if they stop drinking suddenly. At your screening visit, you will be given information to help you recognize the symptoms of withdrawal. You will be monitored carefully throughout the study in case you begin to have symptoms of alcohol withdrawal. If you experience any of these symptoms, you will be instructed to call the clinical site using the 24-hour phone number provided to you. When you contact the clinical site, a staff member will ask

you questions to determine if you are having serious withdrawal symptoms. If you have serious withdrawal, staff may advise that you go to the nearest emergency room. During your in-person clinic visits and telephone interviews throughout the study, you will be assessed for withdrawal symptoms you might be experiencing. You will be asked about changes in your health and drinking status. If you experience significant withdrawal symptoms, you should go to your local emergency room for evaluation.

BIRTH CONTROL, DANGERS OF PREGNANCY AND BREASTFEEDING

Animal studies have shown there may be a risk to a developing baby in pregnancy. For that reason it is very important that you not become pregnant or father a child while you are in this study.

If you are a female, you must not get pregnant while in this study or for 1 week after stopping the study drug. The only certain way to not get pregnant is to not have sex. If you are a female and choose to have sex, you must use a type of birth control listed below, unless you are surgically sterile, your partner is surgically sterile or you are postmenopausal for one year:

- oral contraceptives;
- contraceptive sponge;
- patch;
- double barrier (diaphragm/spermicidal or condom/spermicidal);
- intrauterine contraceptive system;
- etonogestrel implant;
- medroxyprogesterone acetate contraceptive injection;
- complete abstinence from sexual intercourse, and/or
- hormonal vaginal contraceptive ring.

If you are a man, you must use birth control if you choose to have sex with women while in this study. You must also not donate sperm during the study and for at least 1 week after stopping the Study drug.

Methods of birth control for males include:

- surgical sterilization (vasectomy with documentation of azoospermia);
- your participant's female partner uses oral contraceptives (combination estrogen/progesterone pills), injectable progesterone or sub dermal implants (commenced at least 14 days before study drug dosing)
- your female partner uses a medically prescribed topically applied transdermal contraceptive patch (commenced at least 14 days before study drug dosing);
- your female partner has undergone documented tubal ligation (female sterilization) or is postmenopausal (one year);
- your female partner has undergone documented placement of an intrauterine device or intrauterine system; and/or
- true abstinence: when this is in line with your preferred and usual lifestyle.

Even if you use birth control during the study, there is a chance you or your partner could become pregnant. If you or your partner are pregnant or become pregnant during the study, the study drug or procedure may involve unforeseeable risks to the unborn baby. A pregnancy test is not always right, especially in the early stages of pregnancy.

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You cannot be in the study if you are breastfeeding. It is not known whether the study drug can be given to breast fed babies. Therefore, if you are breastfeeding a child you cannot participate in the study.

POSSIBLE BENEFITS OF THE STUDY

There is no known benefit of ANS-6637 in the treatment of alcohol use disorder and there are other known drug treatments for this disease. ANS-6637 is thought to decrease your consumption of alcohol; however, we cannot guarantee that you will receive this benefit. Viewing the *Take Control* alcohol education modules may help you become aware of how much you drink and the risks associated with drinking in excess. Participation in this study may or may not help you cut back or quit drinking. However, by participating in this study you will receive information and advice about reducing your drinking, as well as close medical attention and monitoring of your overall well-being. Your participation in this study will also contribute to knowledge about ways to help others reduce or stop drinking alcohol.

There is no promise that your condition will get better. It might stay the same or it might get worse, especially if you get the placebo.

ALTERNATIVES TO PARTICIPATING IN THE STUDY

There are several alternative treatments that may be effective for treating alcohol problems, including other medications and/or counseling. These other treatments are not offered to you as part of this research study, but if you decide not to participate, or are not eligible, study personnel will give you contact information for existing treatment programs in your area.

SHARING OF YOUR PROTECTED HEALTH INFORMATION (CONFIDENTIALITY)

Your records of being in this study will be kept private except when ordered by law. The following people will have access to your study records:

- The investigator
- Sponsor company or research institution [including monitor(s) and auditor(s)]
- NIAAA research collaborators from Amygdala Inc. (the company that provides the investigational product(s))
- Fast-Track Drugs & Biologics, LLC (a company hired by NIAAA to monitor your study information and health and welfare during the study)
- AiCure (the company that provides the smart phone application)
- The study site's financial analyst for clinical research (if applicable)
- The United States Food and Drug Administration (FDA)
- The Office of Human Research Protections in the U.S. Department of Health and Human Services
- Other state or federal regulatory agencies
- IntegReview IRB

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.

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The Institutional Review Board (IRB), IntegReview, and accrediting agencies may inspect and copy your records, which may have your name on them. Therefore, total confidentiality cannot be guaranteed. If the study results are presented at meetings or printed in publications, your name will not be used.

ADDITIONAL REQUIRED PRIVACY LANGUAGE

By submitting my personal telephone number(s), I grant the Study site and AiCure permission to contact me at this number by SMS (text) messaging or by phone if:

- study medication is not taken or not taken correctly; or
- the Study smartphone or app requires updates or alterations.

Additionally, I grant the Study site and AiCure permission to contact me on the smartphone-like device if my personal telephone number(s) cannot be reached.

CERTIFICATE OF CONFIDENTIALITY

This study is covered by a Certificate of Confidentiality (CoC) from the National Institutes of Health. All studies funded by the National Institutes of Health that involve identifiable information or biological samples are covered by a CoC.

The CoC is issued to protect the investigators on this study from being forced to tell people that are not connected with this study about your participation in this study, even under a subpoena. This protection, however, is not absolute. The protection offered by the CoC does not stop us from voluntarily reporting information about suspected or known sexual, physical, or other abuse of a child or older person, or a subject's threats of violence to self or others.

If any member of the research team is given such information, he or she will make a report to the appropriate authorities. Individuals who participate as research subjects in the specified research project are protected permanently during any time the Certificate is in effect - even if the subject gave the researcher data before the Certificate is issued. Also, because this research is sponsored by NIAAA, staff from NIAAA and other DHHS agencies may review records that identify you but only for the purposes of audit for quality and accuracy or program evaluation.

Even when a CoC is in place, you must still continue to actively protect your own privacy. If you voluntarily give your written consent to anyone to receive information about your participation in the research or freely volunteer information to anyone other than the study staff that you are a research participant in this study, then we may not use the CoC to withhold this information.

IN CASE OF STUDY RELATED INJURY

No medical care, evaluations or financial compensation for research-related injuries or illness will be provided. The costs of such additional treatment will be paid by you or by your health insurance carrier. You also have the right to pursue legal remedy if you believe that your injuries justify such action. Compensation for injury/illness may be payable under the Federal Tort Claims Act. The availability of this compensation may vary depending upon the circumstances involved and there are certain limitations.

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Please be aware that some insurance plans may not pay for research-related injuries. You should contact your insurance company for more information.

EMERGENCY CARE

If you are experiencing a life-threatening medical emergency call 911 or go to your nearest emergency room.

If you experience any medical problems or psychological symptoms at any time during your participation, please contact your study doctor.

You will be given and encouraged to carry a wallet card that identifies the research study by number, states that you are taking either study drug or placebo, and indicates that you are participating in a double-blind clinical trial; This card does not identify the purpose of this study. This card provides the name and phone number of the main study doctor who can provide information to other doctors in the event of an emergency. The card also instructs the emergency room, or other doctor treating you to provide information to the study doctor about your care.

LEGAL RIGHTS

You will not lose any of your legal rights by signing this consent form.

CONTACT INFORMATION

If you have questions, concerns, or complaints about this study or to report a study related injury, contact:

$$Name of Investigator$$
$$Day Number$$ daytime telephone number
$$After Hours$$ after hours number

If you are unable to reach anyone at the number(s) listed above and you require immediate (life threatening) medical attention, please go to the nearest emergency room.

If you do not want to talk to the investigator or study staff, if you have concerns or complaints about the research, or to ask questions about your rights as a study subject you may contact IntegReview. IntegReview is a group of people that has reviewed this research study. The main goal of this review is to protect the rights and well-being of the human subjects participating in research studies. IntegReview's policy indicates that all concerns/complaints are to be submitted in writing for review at a convened IRB meeting to:

Mailing Address:	**OR**	**Email Address:**
Chairperson IntegReview IRB 3815 S. Capital of Texas Highway Suite 320 Austin, Texas 78704		integreview@integreview.com

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If you are unable to provide your concerns/complaints in writing or if this is an emergency situation regarding subject safety, contact our office at:

512-326-3001 or
toll free at 1-877-562-1589
between 8 a.m. and 5 p.m. Central Time

IntegReview has approved the information in this consent form and has given approval for the investigator to do the study. This does not mean IntegReview has approved your being in the study. You must consider the information in this consent form for yourself and decide if you want to be in this study.

COSTS

Although there will be no cost to you for any treatment or testing that is done as part of this research study, you may be responsible for care related to injury or complications that could arise from participation in the study.

PAYMENT FOR BEING IN THE STUDY

You may receive up to $595.00 for being in the study. You will be paid per completed visit as follows:

Visit	Compensation
Visit 1 Screening	$30.00
Visit 2 Week 1 - Study Start	$50.00
Visit 3 Week 2 - Cue Session	$100.00
Visit 4 Week 3	$75.00
Visit 5 Week 4	$75.00
Visit 6 Week 5	$75.00
Visit 7 Week 6	$90.00
Telephone checkup Week 8	$100.00

If you must have additional unscheduled study visits during or after study for safety follow-up, you will be paid in gift cards for these visits. For each additional visit you attend, you will receive a gift card valued at $50.00. If you choose to leave or are withdrawn from the study for any reason before finishing all visits you will be paid only for each completed visit. You will receive payment within 2 weeks after your last study visit.

You may be required to report the payment received for this study to the Internal Revenue Service as taxable income.

VOLUNTEERING TO BE IN THE STUDY

It is your choice if you want to be in the study. No one can force you to be in the study. You may not want to be in this study or you may leave the study at any time without penalty or loss of benefits to which you are otherwise entitled. You can still get healthcare in the future.

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Employees of the investigator or sponsor are not allowed to participate in this study. Students at any site University are also not allowed to participate.

OR

Students of this institution are allowed to participate in this study. If you are a student:

- The decision to participate or not will not affect your grade, recommendations, employment or the like.
- For mandatory participation or for extra credit, you will be given other options for fulfilling the research requirement, such as writing short papers or book reports, special projects, and brief quizzes on additional reading.
- Failure to participate will not have a negative effect on your relationship with the investigator or the faculty.

The investigator, the sponsor company, IntegReview, or the FDA, if applicable, may take you out of the study without your permission, at any time, for the following reasons:

- If you do not follow the investigator's instructions
- If we find out you should not be in the study
- If the study is stopped
- If it becomes harmful to your health
- You become pregnant
- You have a physical illness that prevents you from taking the study drug
- You start to drink more alcohol
- Confinement in a controlled environment (like a hospital or jail)
- Psychiatric Crisis

If you leave the study or if you are taken out of the study, you may be asked to return for a final visit to have some end of study evaluations or tests. If information generated from this study is published or presented, your identity will not be revealed. If you leave the study, no more information about you will be collected for this study. However, all of the information you gave us before you left the study will still be used.

NEW FINDINGS

If there is new information or any significant new findings that could relate to your willingness to continue participation we will tell you. You can then decide if you still want to be in the study.

REQUIRED FOR CALIFORNIA SITES ONLY
SUBJECT'S BILL OF RIGHTS

You will be given a separate copy of the California Experimental Research Subject's Bill of Rights. If you have not received a copy of this document, please notify study staff.

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RESEARCH RESULTS

Researchers are required to publish the results of this study. These results will be based on outcomes for the entire group of participants and will not identify you as a participant. No individual information about you or your participation in this research will be made public without your express written permission. You will not be told the results of this research; however, after the end of the study, you may request and be provided with the name of the study drug that you received, ANS-6637 or placebo.

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AGREEMENT TO BE IN THE STUDY

This consent form contains important information to help you decide if you want to be in the study. If you have any questions that are not answered in this consent form, ask one of the study staff.

Please answer **YES** or **NO** to the following questions:

A. Is this document in a language you understand? _____

B. Do you understand the information in this consent form? _____

C. Have you been given enough time to ask questions and talk about the study? _____

D. Have all of your questions been answered to your satisfaction? _____

E. Do you think you received enough information about the study? _____

F. Do you volunteer to be in this study of your own free will and without being pressured by the investigator or study staff? _____

G. Do you know that you can leave the study at any time without giving a reason and without affecting your health care? _____

H. Do you know that your health records from this study may be reviewed by the study sponsor and by government authorities? _____

I. Do you know that you cannot be in another study while you are in this study? _____

IF YOU ANSWERED "NO" TO ANY OF THE ABOVE QUESTIONS,
OR YOU ARE UNABLE TO ANSWER ANY OF THE ABOVE QUESTIONS,
YOU SHOULD NOT SIGN THIS CONSENT FORM.

_____
Printed Name of Adult Study Subject

_____
Signature of Adult Study Subject Date/Time

_____
Printed Name of Person Explaining Consent Form

_____
Signature of Person Explaining Consent Form Date/Time

You will receive a signed and dated copy of this consent form to keep.

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Attachment #1
CONSENT FORM QUESTIONS

ANS-6637 for Alcohol Use Disorder

Check the appropriate response:	**TRUE**	**FALSE**
1) If a study participant becomes pregnant while participating in this study, she will be taken off the study drug.		
2) ANS-6637 has already been approved by the Food and Drug Administration (FDA) as a treatment for alcohol use disorder.		
3) You will take two pills per day of ANS-6637 or placebo.		
4) You are expected to give truthful answers about your drinking.		
5) You will be told whether you are receiving ANS-6637 or placebo.		
6) You will have to give blood and urine samples during the course of the study.		
7) The study staff may end your participation in this study if they feel that it is in your best interest.		
8) You will be compensated for your time and travel.		
9) You must bring your drug bottles to every visit.		
10) You will never be contacted by telephone during the study.		
11) You must inform the study staff of starting any new medications that you take during the study.		
12) The research data I provide in this study may be made available to the general research community, but will be de-identified so that any personally identifiable data will removed.		

The correct answers to the questions above have been discussed with me.

_____
Participant Signature

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CHANGE TO 14 PT FONT FOR CA SITES:

PROTECTED HEALTH INFORMATION COLLECTED DURING THIS STUDY

Health information about you will be collected if you choose to be part of this research study. Health information is protected by law as explained in the study site's Privacy Notice. If you have not received this notice, please request a copy from the investigator. At the study site, your information will only be used or shared as explained and authorized in this consent form or when required by law. The government Privacy Act (Systems of Record Notice #09-25-0200) applies to the information to be collected from you. The authority to collect study information is under 42 USC 285n as it applies to NIAAA.

The investigator and staff involved with the study will keep your protected health information collected for the study strictly confidential. Protected health information covered by the Health Insurance Portability and Accountability Act of 1996 (HIPAA), including your name, initials, and other identifying information will not be released or published without your permission unless required by law. The following protected health information will be collected and used for research:

- Name
- Address
- Valid form of ID
- Telephone number
- Information from a brief psychiatric examination
- Emergency contact information
- Initial telephone screening information
- Current and past medications and therapies
- Information from a physical examination that includes body weight, blood pressure, and heart rate
- Electrocardiogram results
- Blood alcohol test results
- Urine drug screen results
- Pregnancy test results if you are female
- Clinical laboratory test results
- Genetics test results
- Healthcare, drinking, mood, sleep, and questionnaires/forms

To participate in this research, you must allow the study team to use your protected health information. If you do not want us to use your protected health information, you may not participate in this study.

Research data are assessments and information collected by the clinical site from you during this research study.

Documents that contain your name, such as the consent form signed by you, will be securely stored separately from your research data. All research data will be coded in a way that does not identify you by name or initials and will be kept in a secure place that allows only selected study personnel to have access to this information. However, there may be some rare cases beyond our control where your data could be accidentally disclosed, and we cannot protect your privacy.

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As required by law (HIPAA), special steps will be taken to keep confidential any information that can be used to personally identify you (for example: your name, initials, birthdate, address, telephone number, and social security number). This personally identifying information will not be released or published without your permission unless required by law.

If you withdraw your permission:

- We will no longer use or share medical information about you for this research study, except when the law allows us to do so.
- We are unable to take back any information we have already shared with your permission.
- We may continue using and sharing the information obtained before your withdrawal if it is necessary for the soundness of the overall research.
- We will keep a record of your research data as long as the law requires.

If you would like to revoke your HIPAA Authorization, please provide written notice to the study doctor. If you revoke your HIPAA Authorization, you can no longer participate in this study.

WHO MAY USE AND SHARE YOUR PROTECTED HEALTH INFORMATION

You have the right to know who will be able to access your protected health information and why they may access it. Staff designated by the agencies named below may review records that identify you for the purpose of monitoring and quality control. However, it is the policy of these agencies and the study researchers that every effort will be made not to release information that identifies you.

Representatives of the following people/groups within the study site may use your protected health information.

- The principal investigator
- The Institutional Review Board (if applicable)
- The study site's Human Subjects Protection Office
- The study site's Financial Analyst for Clinical Research, if applicable

The above people/groups may share your protected health information with the following people/groups outside the study site for their use in connection with this research study. These groups include:

- The Office of Human Research Protections in the U. S. Department of Health and Human Services
- Food and Drug Administration (FDA)
- IntegReview IRB
- NIAAA (the Funding Sponsor)
- NIAAA research collaborators from Amygdala Inc. (the company that provides the investigational products)
- Fast-Track Drugs & Biologics, LLC (a company hired by NIAAA to monitor your study information and health and welfare during the study)
- AiCure (the company that provides the smart phone application)

In all disclosures outside of the study site, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier. In records and information disclosed outside of the study site, you will be assigned a unique code number.

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The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to the study site's procedures developed to protect your privacy.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

_____ _____
Signature of Subject Date