TITLE: Safety of Acamprosate in Post-liver transplantation population with Alcohol-associated Liver disease

STUDY PHASE: Enrollment

STUDY ARMS: Acamprosate + Standard of Care, Standard of Care

PRINCIPAL INVESTIGATOR(S): HYOSUN HAN

C1, 2nd Floor 1510 San Pablo Street Los Angeles, CA 90033

323-442-6171

Hyosun.Han@med.usc.edu

CO-INVESTIGATOR(S): Divya Ayyala-Somayajula MD
Stephanie Cho MD
Norah Terrault MD
Vincent Tristan PA

PARTICIPANTS/LOCATONS: Transplant patients from Liver Transplant Program from the USC KECK Transplant Institute's patient census

TABLE OF CONTENTS

1.0 BACKGROUND AND HYPOTHESES

1.1 The prevalence of alcohol-associated liver disease (ALD) has been increasing due to ongoing alcohol use and high-risk drinking over the past decade[1]. ALD now poses a significant burden to the US healthcare system, accounting for 5.4 per 100,00 deaths in 2012, and ALD mortality is increasing particularly in younger demographics[2]. Given the increased prevalence of ALD in conjunction with a 5-fold increase in liver transplant (LT) for severe alcohol associated hepatitis (AH)[3], ALD is now the leading indication for liver transplantation accounting for approximately 30% of LT waitlist additions and 24% of LT recipients in 2016 in the US[1]. Despite excellent surgical outcomes, ~50% liver graft recipients with alcohol use disorder (AUD) relapse (any alcohol use) by 5 years post- (LT)[4]. Those post-LT patients that go on to develop harmful drinking patterns (early onset, moderate to heavy alcohol use) have increased rates of graft failure highlighting a population that would likely benefit from comprehensive treatment of AUD, including pharmacotherapy[5]. Though not contraindicated, to date, no AUD medication has been FDA-approved for use in patients with ALD[6]. Naltrexone and disulfuram are both FDA approved but have a black box warning for hepatoxicity[6]. Although, small studies have shown the benefit of pharmacotherapy in patients with ALD, no studies have been done to validate the use of AUD pharmaceuticals in the post-LT population[7]. Due to combination of factors-provider discomfort, lack of data regarding pharmaceutical effectiveness and safety in this population, and lack of treatment protocols to treat AUD in this specific population, our post- LT population has not received standard of care for AUD[7]. Failure to utilize available and effective interventions predisposes this patient population to alcohol relapse (e.g. slips), subsequent harmful drinking patterns (early onset, moderate to heavy alcohol use), and ultimately graft dysfunction[5].

1.2 Acamprosate is an effective FDA approved adjunct therapy for alcohol dependence in adults[8]. However, there is limited literature on the use of acamprosate in patients with ALD, and there is no literature on the use of acamprosate in post-LT ALD patients[7,8]. It is well established that acamprosate is not metabolized by the liver and unlikely to interfere with medications metabolized via cytochrome P450[8]. Given this unique pharmacokinetic property of acamprosate, there should be no drug-drug interactions with its use in LT recipients[9].

1.3 We hypothesize that acamprosate will be a feasible AUD therapy for post-LT patients.

2.0 OBJECTIVES AND PURPOSE

Keck Medicine of USC's Liver Transplant Program will develop a pilot study to incorporate acamprosate use in suitable post-LT individuals. A research team will provide weekly appointments to administer surveys to assess for alcohol use, alcohol cravings, acamprosate compliance, and drug side-effects. Patients will obtain laboratory values and visit their transplant hepatologist monthly as is standard of care. Patients will also receive a consultation with the program's transplant pharmacist to reconcile medications to avoid drug-drug interactions.

The primary goals of this study are:

2.1 To evaluate the feasibility and safety of acamprosate for management of AUD in post-liver transplant patients

2.2 To determine whether acamprosate use in combination with standard of care (weekly telephone visit) reduces the frequency of alcohol relapse

3.0 STUDY DESIGN

Procedure: Each patient eligible for the study will be contacted by a research assistant via telephone or in-person in the transplant clinic. If patients state they are not interested, we will provide an email address to reach if the patient decides in the future to participate. Interested patients will be consented for study participation. Baseline demographic, social, and medical history, laboratory data, and current medications will be abstracted from the electronic medical record. Baseline alcohol use will be assessed with TLFB and last drink of alcohol. Baseline alcohol cravings will be assessed with PACS survey. Patients randomized to acamprosate arm will then be contacted by a transplant pharmacist to perform a medication reconciliation regardless of whether they are randomized to the acamprosate plus standard of care (SOC) vs SOC alone group. The cost of the medication will be covered by the insurance. Patients without insurance or that decline to use insurance will be excluded or withdrawn if they have already signed consent. Randomization will occur via a 2:1 ratio of acamprosate plus SOC versus SOC alone respectively stratified by sex. The study team and participants will not be blinded to treatment group. For those randomized to the acamprosate plus SOC group, they will be counseled to start acamprosate 666 mg three times daily after this initial visit. All patients (both groups) will undergo weekly phone visits with the research team where interval medical history will be obtained (changes in medications, hospitalizations, and emergency department visits), assessment of alcohol use (TLFB), alcohol craving (PACS), acamprosate side effects (GASE), and acamprosate compliance (self-reported number of missed doses) for those randomized to the acamprosate arm will be obtained. If at any time, patients report side effects to acamprosate or any new symptoms, these will be communicated to the patients' transplant hepatologist to advise appropriate medical care. Patients will then receive standard of care laboratory testing including alcohol metabolites and routine clinic visits with a transplant hepatologist where medication compliance will be assessed (number of pills left and number of refills obtained). This part of the study will last 14 weeks. If patients choose to continue acamprosate they will continue with their primary hepatologist and continue monthly visits, those in the control arm will resume standard of care visits with their primary hepatologist. At 1 year, 3 years, and 5 years, we will abstract data from the electronic medical record (interval social history, medical history, laboratory data, current medications, graft function, pertinent transplant history, continuation of acamprosate or intiation of AUD therapy since time of the study, and current alcohol use). All data will be recorded in the REDCap database.

4.0 DRUG/DEVICE INFORMATION

4.1 Acamprosate is the drug that will be utilized in the proposed study. This is an FDA approved commercially available drug for alcohol dependence and abuse in the United States since 2004. Acamprosate is available in delayed release tablets of 333 mg generically and under the brand name campral. The typical maintenance dose is 666 mg three times daily.

4.2 Acamprosate will be the only drug being utilized in this study.

4.3 IND/IDE number not applicable.

4.4 Acamprosate will be prescribed and sent to patients preferred pharmacy.

4.5 Acamprosate (a kam' proe sate) is N-acetylhomotaurine, a synthetic amino acid analogue similar to gamma aminobutyric acid (GABA) and taurine that has been shown to decrease alcohol craving in

animal models. Acamprosate appears to function as a neurotransmitter with GABA agonist and partial glutamate (N-methyl-D-aspartate [NMDA]) antagonist activity, but its precise mechanism of action in decreasing alcohol craving is unknown[10]. Acamprosate appears safe and well-tolerated for the maintenance of abstinence in alcohol-dependent patients across a wide range of patient groups[8].Flatulence is the only other adverse effect that has been significantly associated with acamprosate over placebo[11] with no statistically significant differences were observed between groups (acamprosate versus placebo) of premature withdrawals from treatment due to adverse effects[12].

Acamprosate has a low propensity for interactions with other drugs[8].Acamprosate is contraindicated in patients with hypersensitivity to acamprosate calcium or any of its components and patients with severe renal impairment (CrCl of 30 mL/min or less) as Acamprosate is primarily renally excreted[13]. There were no sex differences in safety or tolerability for acamprosate[8]. Acamprosate appears generally safe in patients with impaired hepatic function[8].

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

Beginning January 1st, 2022, we will recruit patients from Liver Transplant Program from the USC Transplant Institute's patient census. We will target at least 25-30 patients for this study with 2:1 randomization (acamprosate plus SOC vs SOC alone). All patients must have history of LT with a pre-LT diagnosis of ALD. As our usual number of transplants per year is 120 and 30% of patients have ALD (includes AH) as a diagnosis, we do not anticipate any difficulties in identifying 30 participants for this study.

Enrollment will be on a rolling basis.

5.1 Patients must have received a transplant for liver disease secondary to alcohol-associated hepatitis or alcohol-associated cirrhosis.

5.2 We will exclude patients with hypersensitivity to acamprosate calcium or any of its components, severe renal impairment (creatinine clearance ≤30 mL/min), psychopathology under treatment with psychoactive drug, substance dependence other than THC, alcohol, or nicotine, need for inpatient detoxification or inpatient treatment of alcohol use, participation in a clinical trial within the past 30 days, and women of childbearing potential who do not practice a medically acceptable form of contraception will be excluded.

We will obtain an informed consent for all patients. As part of the informed consent, participants will be expected to complete a weekly telemedicine visit with a research member for at least 3 months, required to fill out weekly surveys (Appendix III) (Penn Alcohol Craving Scale (PACS), Alcohol Timeline Followback (TLFB), and Generic Assessment of Side Effects in Clinical Trials (GASE) prior to these visits and expected to be compliant with acamprosate if randomized to that group. The proportion of patients eligible but who did not agree to participate will be captured.

5.3 Patients may withdraw from study at any time. If patients suffer any severe adverse effects from acamprosate they will be advised to stop the drug immediately and withdraw from the study.

6.0 STRATIFICATION/DESCRIPTIVE FACTORS/RANDOMIZATION SCHEME

6.1 Sex will be balanced across treatment arms – due to the pilot nature of this study, age, race ethnicity and time from transplant will be recorded for planning of future trials.
6.2 Drinking history, social history, pre- liver transplant relapse probability scores, medical history, and medication history will be obtained.

6.3 Randomization will occur via an unblinded 2:1 ratio of acamprosate plus SOC versus SOC alone respectively stratified by sex.

7.0 STUDY AGENT ADMINISTRATION OR INTERVENTION AND TOXICITY MANAGEMENT PLAN

7.1 Treatments

A. Standard of Care (SOC): Participants will be expected to complete a weekly telemedicine visit with a research member for at least 3 months, required to fill out weekly surveys (figure 2) (Penn Alcohol Craving Scale (PACS), Alcohol Timeline Followback (TLFB), and Generic Assessment of Side Effects in Clinical Trials (GASE) prior to these visits and expected to be compliant with acamprosate if randomized to that group.

B. SOC+ Acamprosate: Participants randomized to this arm will participate in SOC + take acamprosate 666 mg TID daily for three months.

7.21

AGENT	DOSE	ROUTE	DAYS	ReRx INTERVAL	NOTES
Acamprosate	666 mg	PO TID	Daily	4 weeks	maximum cumulative dose 500 mg/m^2

7.31 A patient may always be removed from treatment whenever he/she wishes

7.32 Treatment will be discontinued or held at discretion of investigators if patients experience any moderate-severe side effects as evaluated in section 8.0 thought to be secondary to acamprosate.

8.0 ASSESSMENT OF EFFICACY AND SAFETY

8.1 Acamprosate's package insert includes a comprehensive list of adverse events in over 7000 patients exposed to acamprosate[14]. However, adverse events are listed without regard to the causal relationship of the events to the drug[14]. Only diarrhea and flatulence appear to be significantly associated with acamprosate[14]. There is no evidence that acamprosate has additional risks in the liver transplant population[8]. Multiple meta analyses have found that the only side effect significantly associated with acamprosate over placebo is diarrhea[8,15]. Flatulence is the only other adverse effect that has been significantly associated with acamprosate over placebo[11]. In a review of clinical trials, diarrhea was observed in 10-17% of patients treated with acamprosate (versus 10-11% in placebo)[11,12]. Diarrhea appears to be acamprosate dose dependent, settles within a few days, and mostly mild or moderate in severity[11]. If diarrhea was severe, temporary dose reduction was beneficial[8]. Of note, no statistically significant differences were observed between groups (acamprosate versus placebo) in terms of premature withdrawals from treatment due to adverse effects[12]. No clinically meaningful differences have been found comparing acamprosate and placebo regarding the incidence of clinically significant postbaseline abnormalities for any hematology

parameter measured: including mean values for the liver function tests aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT)[11]. Acamprosate therapy has not been associated with serum enzyme elevations over and above rates that occur with placebo therapy. Despite wide-scale use in alcohol treatment programs, there have yet to be published reports of clinically apparent acute liver injury attributed to acamprosate therapy[10]. Pharmacovigilance data in 1.5 million patients has indicated no serious adverse events[8].

Acamprosate's package insert includes a precaution for suicidality due to an increase in adverse events of a suicidal nature (suicidal ideation, suicide attempts, completed suicides) in acamprosate treated patients. The insert recognizes the complex and well-recognized interrelationship between alcohol dependence, depression and suicidality and encourages that "all alcohol-dependent patients, including those patients being treated with CAMPRAL should be monitored for the development of symptoms of depression or suicidal thinking." There is no evidence of a statistically significant association between treatment with acamprosate and adverse events of a suicidal nature[8,14,11,12]. Acamprosate has a low propensity for interactions with other drugs, including those likely to be administered as concomitant drugs in alcohol-dependent patients, including alcohol, diazepam, disulfiram or naltrexone. In vitro studies indicate that acamprosate does not induce cytochrome P450 (CYP) 1A2 or 3A4 isoenzymes, nor does it inhibit the metabolism of drugs that are substrates for CYP1A2, 2C9, 2C19, 2D6, 2E1 or 3A4[16]. Micromedex has no reported drug interactions with acamprosate[13]. However, co-administration of naltrexone with acamprosate significantly increased the maximum plasma concentration and the area under the plasma concentration-time curve of acamprosate[14,17]. No adverse effects were documented[17]. No adjustment of dosages is recommended in patients with co-administration of naltrexone with acamprosate[14].

Acamprosate is contraindicated in patients with hypersensitivity to acamprosate calcium or any of its components and patients with severe renal impairment (CrCl of 30 mL/min or less)[13]. Acamprosate is primarily renally excreted. Peak plasma concentrations after administration of a single dose of 2 x 333 mg Acamprosate tablets to patients with moderate or severe renal impairment were about 2-fold and 4-fold higher, respectively, compared to healthy subjects[13]. Acamprosate is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function[13]. There were no sex differences in safety or tolerability for acamprosate[8]. Acamprosate appears generally safe in patients with impaired hepatic function[8]. There is no evidence, clinical or theoretical, that Acamprosate is not safe in the liver transplant population. Acamprosate may improve morbidity and mortality in liver transplant patients by mitigating the risks associated with continued alcohol use.

The greatest proportion of deaths or re-transplants after liver transplantation occur soon after initial transplantation. The causes of death and graft loss vary according to the interval from transplantation, with infection and intraoperative and perioperative causes accounting for nearly 60% of deaths and graft losses in the first posttransplant year. After the first year, death due to acute infections declines, whereas malignancies and cardiovascular causes account for a greater proportion of deaths. The recurrence of the pretransplant condition, especially hepatitis C virus (HCV) or autoimmune liver disease, is an increasingly important cause of graft loss the longer the patient

survives transplantation for these etiologies [10]. There is no evidence, clinical or theoretical, of a link between acamprosate and any of the above causes of morbidity and mortality in liver transplant patients in the first-year post-transplant[8,15,11,12].

Though no causal relationships to acamprosate have been found, the adverse of acute kidney failure has been reported to be temporally associated with acamprosate in several patient[13]. There is no evidence of a link between acamprosate and any of the other above causes of morbidity and mortality in liver transplant patients following the first-year post-transplant[8,15,11,12].

8.11 Patients will undergo a self-administered weekly survey, Generic Assessment of Side Effects in Clinical Trials (GASE) to evaluate for potential side effects and toxicities. They will also undergo standard of care laboratory testing as well to check renal function and graft function along with immunosuppression levels. Details regarding the survey are listed in Appendix III.

8.12 There are no known long term drug toxicities associated with acamprosate. The recommended long-term dose for acamprosate is 666 mg TID PO daily unless the patient has severe renal impairment (CrCl of 30 mL/min or less) or levels hypersensitivity to acamprosate calcium or any of its components, in which case, acamprosate is contraindicated. If the patients choose to continue acamprosate after this study, they will continue to follow with their primary transplant hepatologist who can monitor for adverse side effects such as kidney dysfunction, hypersensitivity, diarrhea, and flatulence.

8.2 Complete discontinuation is advised if the patient experiences any drug toxicities related to acamprosate. Patients should not restart treatment if toxicity is thought to be related to acamprosate.

8.3
8.31 If a patient experiences an adverse event such as an unexpected or fatal toxicity, the event will be immediately (within 24 hours) reported to the primary medical care team so patient can receive the appropriate care.
8.32 We will then report the event to the IRB and FDA.

9.0 CLINICAL AND LABORATORY EVALUATIONS AND STUDY CALENDAR

Parameter	Pre-Treatment	Day 1	Weekly	Bi-monthly
Targeted History (alcohol history, psychiatric history, liver transplant history, medications history, social history, abdominal imaging, pregnancy test if indicated)	X			
Complete Blood Count (CBC)	X			X
Complete Metabolic panel (CMP)	X			X
Alcohol Metabolites	x			X

Immunosuppression levels	X			X
Penn Alcohol Craving Scale (PACS)	X		X	
Quick Drinking Screen	X		X	
Timeline Follow back	X		X	
General Assessment of Side Effects in Clinical Trials (GASE)			X	
Agent administration		X[1]		
Interval history (hospitalizations, medication changes)			X	

[1]daily

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

Outcomes assessed will include feasibility, safety, and efficacy. Feasibility will be assessed via completion rates, number of missed doses per patient, and number of patients who completed 3 monthly refills for the study. Safety will be measured via % total, minor, moderate, and major side-effects documented via the GASE survey and mortality during the time of the study. Finally, efficacy will be measured via % maintained abstinence, reduction in alcohol cravings determined via PACS score, and % of alcohol relapses determined via TLFB survey, PeTh, and self-reporting. We will then examine acamprosate use and its effect on 1-, 3-, and 5- year graft survival and alcohol usel in our patients transplanted for ALD. Efficacy and safety outcomes will be compared to control group to determine if acamprosate itself is helpful and safe for alcohol use reduction post-LT.

11.0 SPECIAL INSTRUCTIONS:

This is not applicable for this study.

12.0 DATA COLLECTION AND MONITORING

All data collection will be done using the REDCAP database. Only those involved in data collection and analysis who are included on the IRB will have access to the data.

13.0 STATISTICAL CONSIDERATIONS

13.1 The goal of this study is to evaluate the feasibility, safety, and efficacy of acamprosate for management of AUD in post-liver transplant patients. All patients will be post-LT with a pre-LT diagnosis of ALD. As our usual number of transplants per year is 120 and 30% of patients have ALD (includes AH) as a diagnosis, we do not anticipate any difficulties in identifying 30 participants for this study. Feasibility will be assessed via completion rates, number of missed doses per patient, and number of patients who completed 3 monthly refills for the study. Safety will be measured via % total, minor, moderate, and major side-effects documented via the GASE survey. Finally, efficacy will be measured via % maintained abstinence, reduction in alcohol cravings determined via PACS score, % of alcohol relapses determined via TLFB survey, PEth, and self-reporting and patient and graft survival in our patients transplanted for ALD. Demographic variables will be compared between SOC and acamprosate+SOC groups using descriptive statistics. Efficacy and safety outcomes will be compared to control group using wilcoxan pair rank sum. Cox regression analysis will be done to determine determinants of alcohol relapse and graft failure in both SOC and SOC+acamprosate

group. Finally, time to relapse will be measured in both SOC and SOC+acamprosate group via Kaplan meier plots.

13.2 Given the small number of patients (30), we will not perform a stratified randomization based upon age, race, ethnicity and timing from transplant but rather compare frequencies of different ethnicities in our descriptive statistics section.

14.0 REGISTRATION GUIDELINE

14.1 Patients will be contacted by our research coordinator. Patients will be randomized in a 2:1 fashion and stratified based upon sex.

14.2 Patients will undergo an intake session where an informed consent and HIPPA release form will be signed. All patients will receive a signed and dated copy of the Informed Consent Form once enrolled.

15.0 BIOHAZARD COMTAINMENT

No biohazard materials will be produced during this study,hus containment protocol is not applicable.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

` All institutional and Federal regulations concerning the Informed Consent form will be fulfilled. The study will be conducted in adherence to ICH Good Clinical Practice.

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APPENDICES

Appendix I: informed consent and HIPAA form
Appendix II: Questionnaires &/or Survey Forms (if applicable)

APTAP Informed Consent

Please complete the survey below.

Thank you!

Study Title: Safety of Acamprosate in Post-Transplant Alcoholic Liver Disease Patients
Principal Investigator: Hyosun Han, MD

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

You have been asked to participate as a subject in a medical experiment. Before you decide whether you want to participate in the experimental procedure, you have a right to the following information:

CALIFORNIA LAW REQUIRES THAT YOU MUST BE INFORMED ABOUT:

1. The nature and purpose of the study.
2. The procedures in the study and any drug or device to be used.
3. Discomforts and risks reasonably to be expected from the study.
4. Benefits reasonably to be expected from the study.
5. Alternative procedures, drugs, or devices that might be helpful and their risks and benefits.
6. Availability of medical treatment should complications occur.
7. The opportunity to ask questions about the study or the procedure.
8. The ability to withdraw from the study at any time and discontinue participation without affecting your future care at this institution.
9. Be given a copy of the signed and dated written consent form for the study.
10. The opportunity to consent freely to the study without the use of coercion.

I have carefully read the information contained above and I understand fully my rights as a potential subject in this study.

1) Date & Time: _____

2) Signature:

_____
(Research Participant)

USC HIPAA

Please complete the survey below.

Thank you!

USC HIPAA AUTHORIZATION TO USE HEALTH INFORMATION FOR RESEARCH

Principal Investigator: Hyosun Han, MD
Study Title: Safety of Acamprosate in treating Alcohol Use Disorder in the Post Liver Transplant Populations (APTAP)
IRB #: HS-19-00991 1. Purpose of this Form:

A federal law known as the Health Insurance Portability and Accountability Act (HIPAA) protects how your health information is used. HIPAA generally does not allow your health information to be used or released for research purposes without your written permission. Health information protected under the law includes: medical and dental records, bills or other payment records for health care received, tissue samples, x-rays, laboratory results and any other health information that identifies you. State laws also protect how your health information may be used.

By signing this form, you are allowing your health care providers (for example, physicians, dentists, hospitals, clinics) to share your health information with the researchers and others involved in this research study for the uses described below and also described in the informed consent.

2. Who May Release Your Health Information:

This document permits (i) the researcher/health care provider who creates health information about you during this research study; and (ii) the healthcare providers checked below to release health information about you for the research purposes described in this document and the informed consent:

(Check ALL boxes that apply)

- ☐ All health care providers with health information about me
- ☐ Keck Medical Center
- ☐ USC Norris Cancer Hospital
- ☐ Keck Hospital of USC
- ☐ Keck Doctors of USC
- ☐ Children's Hospital Los Angeles
- ☐ LAC+USC Medical Center
- ☐ Herman Ostrow School of Dentistry
- ☐ Other: _____(please specify)

Please specify:

_____

3. What Health Information Will Be Used:

The health care providers listed above are permitted to use and release (i) all health information that is created during this research study; and the health information about you described below:

[CHECK ONE OF THE TWO BOXES BELOW]

◯ All of your health information that the health care provider has in his or her possession, but does not include HIV test results, mental health diagnosis and treatment records, and drug or alcohol treatment records;
◯ Only the following records or types of health information:

(Insert dates of treatment or specific types of treatment, records or reports.)

_____

4. Health Information with Special Protections:

The following information only will be released if you give specific permission by initialing on the line(s) below.

HIV test results.

_____
(Initial)

Mental health diagnosis and treatment records.

_____
(Initial)

Drug and alcohol treatment records.

_____
(Initial)

5. How Your Health Information Will Be Used:

Your health information may be shared with the following individuals or entities for the following purposes:

Researchers (those individuals in charge of the study), research staff, and students to conduct the research described in the informed consent and other activities related to the research, such as conducting safety analyses. The research sponsor(s), OneLegacy Foundation, and its authorized representatives, business partners, clinical research organizations and affiliates for the purposes described in the informed consent and for other activities related to the research, such as assessing the safety or efficacy of the drug, device or treatment included in the study, improving designs of future studies or obtaining approval for new drugs, devices or health care products. The USC Institutional Review Boards that review research involving human subjects in accordance with regulations;

USC's clinical trial organization that supports clinical trials administration at USC, Other USC offices involved in regulatory compliance, including the Offices of General Counsel and Compliance, U.S. government agencies, such as the Food and Drug Administration and the Office for Human Research Protections, government agencies from other countries, and others who are authorized by law to review or oversee this research.

6. Creation of a Research Database:

The following is an optional research activity. You can choose whether or not to participate in these activities and it will not affect your ability to participate in the main research study. Please initial on the line below to give your specific permission to this activity.

Researchers will often study existing health information from large groups of patients in order to test or validate theories that the researcher develops. By initialing above, you allow the USC research team to put your health information in a research database or repository for future research purposes. The USC Institutional Review Board still may review how the researcher uses or releases your health information for future research purposes.

This section of the Authorization will remain in effect indefinitely unless you revoke (cancel) it as described below.

◯ Yes
◯ No
(Initial)

Initial: _____

7. Scope of this Authorization:

The USC research team will use and release your health information for the purposes described in this authorization and the informed consent or as otherwise permitted by law. However, health information that is shared with others outside USC may not be protected by HIPAA once it is released. Certain health information may still be protected under state law.

8. Right to Deny Access to Health Information:

You may not be permitted to access (review or copy) your health information created during this research study while the research study is in progress. You may be entitled to access your health information once the research study is completed.

9. Term of this Authorization:

Except for database research, this authorization expires 25 years from the date the study is completed or terminated.

10. Refusal to Sign/Right to Revoke:

You must sign this Authorization in order to participate in this research. You may change your mind and revoke (withdraw or cancel) this authorization and your participation in this research study at any time. To do so, your revocation must be sent in writing to the Principal Investigator and include: (1) the title of the research study; and (2) your name and telephone number or address. Please send the revocation to the following:

Hyosun Han, MD
USC Transplant Institute
USC Health Care Consultation Center I
1510 San Pablo St, Suite 200
Los Angeles, CA 90033

You will not be permitted to participate in the research and health information that identifies you will no longer be collected as of the date the Principal Investigator receives your revocation. However, we may still use and share health information about you that has already been obtained as necessary in order to maintain the integrity of the research study. Also, if the law requires it, the researchers, sponsor, and government agencies may continue to look at your records to review the quality or safety of the study.

11. Questions Regarding Your Privacy Rights:

Please contact the USC Office of Compliance by telephone at 213-740-8258 or email at compliance@usc.edu if you have questions about your privacy rights.

Agreement:

I have read (or someone has read to me) the information provided above. I have been given the opportunity to ask questions and all of my questions have been answered to my satisfaction. By signing below, I agree that my health information may be used as described in this form.

◯ Yes
◯ No

Participant Signature

_____

Name of Participant

_____

Date Signed

_____

GASE & PACS Week 1

Please complete the survey below.

Thank you!

GASE Survey

Please rate whether you experienced one of the following complaints during the last seven days by
using the scale below. Please indicate by selecting yes or no whether you believe that these symptoms are related to your current medication

0 = Complaint not present
1 = Mild: complaint causes mild distress or discomfort, but no impairment in daily functioning
2 = Moderate: complaint causes moderate distress or discomfort or at least some impairment in daily
functioning
3 = Severe: complaint causes severe distress and discomfort, severe impairment in daily functioning,
or acute danger to health

Please try to choose an answer even if you are not completely sure.

In the last seven days I had the following complaints:

Headache	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Hair Loss	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Dry Mouth	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No

Dizziness	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Chest Pain	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Palpitations, irregular heartbeat	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Breathing Problems	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Low blood pressure, other circulation problems	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Abdominal Pain	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Nausea	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Vomiting	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Constipation	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No

Diarrhea	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Reduced Appetitie	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Increased Appetite	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Difficulty Urinating	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Problems with sexual performance or sex organs	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Females: Painful or irregular menstruation	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No

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3 = Severe: complaint causes severe distress and discomfort, severe impairment in daily functioning, or acute danger to health

Skin Rash or Itching	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No

Tendency to develop bruises	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Fever, increased temperature	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Abnormal sweating	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Hot flashes	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Convulsions or seizures	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Fatigue, loss of energy	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Tremor	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Insomnia, sleeping problems	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Nightmares or abnormal dreams	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No

Back pain	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Muscle pain	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Joint pain	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Agitation	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Irritability, nervousness	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Depressed mood	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Thoughts about suicide	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Anxiety, Fearfulness	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No

0 = Complaint not present **1 = Mild: complaint causes mild distress or discomfort, but no impairment in daily functioning** **2 = Moderate: complaint causes moderate distress or discomfort or at least some impairment in daily** **functioning** **3 = Severe: complaint causes severe distress and discomfort, severe impairment in daily functioning,** **or acute danger to health**

Have you had any further symptoms?	◯ Yes ◯ No (Please name the symptom)
How many additional symptoms have you had?	◯ 1 ◯ 2 ◯ 3 ◯ 4 (Intensity)
What was the first symptom?	_____ (Please name the symptom)
What was the intensity of the first symptom? ([symptom1])	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
What was the second symptom?	_____ (Please name the symptom)
What was the intensity of the second symptom? ([symptom2])	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
What was the third symptom?	_____ (Please name the symptom)
What was the intensity of the third symptom? ([symptom3])	◯ 0 ◯ 1 ◯ 2 ◯ 3 (Intensity)
Is this complaint related to your current medication?	◯ Yes ◯ No
Please list the additional symptom(s) you are experiencing and relay them to your study coordinator at the next study appointment	_____ (Please name the symptom(s))

Penn Alcohol Craving Scale (PACS)

Please read each item carefully and circle the number that best describes your craving during the past week.

1. How often have you thought about drinking or about how good a drink would make you feel during this period?	◯ Never-0 times during this period of time ◯ Rarely-1 to 2 times during this period of time ◯ Occasionally-3 to 4 times during this period of time ◯ Sometimes-5 to 10 times during this period of time ◯ Often-11 to 20 times during this period of time ◯ Most of the time-20 to 40 times during this period of time ◯ Nearly all of the time-more than 40 times or more than 6 times per day
2. At its most severe point, how strong was your craving during this period?	◯ None at all. ◯ Slight, that is a very mild urge. ◯ Mild urge. ◯ Moderate urge. ◯ Strong urge, but easily controlled. ◯ Strong urge and difficult to control. ◯ Strong urge and would have drunk alcohol if it were available.
3. How much time have you spent thinking about drinking or about how good a drink would make you feel during this period?	◯ None at all ◯ Less than 20 minutes. ◯ 21-45 minutes. ◯ 46-90 minutes. ◯ 90 minutes-3 hours. ◯ Between 3 and 6 hours. ◯ More than 6 hours.
4. How difficult would it have been to resist taking a drinking during this period of time if you had known a bottle were in your house?	◯ Not difficult at all. ◯ Very mildly difficult. ◯ Mildly difficult. ◯ Moderately difficult. ◯ Very difficult. ◯ Extremely difficult. ◯ Would not be able to resist.
5. Keeping in mind your responses to the previous questions, please rate your overall average alcohol craving for the stated period of time.	◯ Never thought about drinking and never had the urge to drink. ◯ Rarely thought about drinking and rarely had the urge to drink. ◯ Occasionally thought about drinking & occasionally had the urge to drink. ◯ Sometimes thought about drinking & sometimes had the urge to drink. ◯ Often thought about drinking & often had the urge to drink. ◯ Thought about drinking most of the time & had the urge to drink ◯ Thought about drinking nearly all of the time & had the urge to drink

	Timeline Followback Method Assessment	
	Timeline followback Week Start Date	_____
1.	Have you used any illicit substances or alcohol on Monday	◯ Yes ◯ No
	Substances used on Monday	☐ Alcohol ☐ Cannabinoids/Marijuana ☐ Cocaine ☐ Crack ☐ Amphetamine-type stimulants ☐ Opiod Analgesics, including methadone ☐ heroin ☐ Hallucinogens, including MDMA/ecstasy ☐ sedatives and hypnotics, excluding benzodiazepine ☐ Benzodiazepines ☐ Inhalants ☐ other drugs
	Since you said yes to alcohol, how many standard drinks did you drink. A standard drink is one 12-ounce bottle/can of regular beer, OR One 5-ounce glass of regular (12%) wine, OR 1 1/2 ounces of hard liquor either straight or in a mixed drink OR One 12-ounce wine cooler	_____
	other drugs	_____
2.	Have you used any illicit substances or alcohol on Tuesday	◯ Yes ◯ No
	Substances used on Tuesday	☐ Alcohol ☐ Cannabinoids/Marijuana ☐ Cocaine ☐ Crack ☐ Amphetamine-type stimulants ☐ Opiod Analgesics, including methadone ☐ heroin ☐ Hallucinogens, including MDMA/ecstasy ☐ sedatives and hypnotics, excluding benzodiazepine ☐ Benzodiazepines ☐ Inhalants ☐ other drugs
	Since you said yes to alcohol, how many standard drinks did you drink. A standard drink is one 12-ounce bottle/can of regular beer, OR One 5-ounce glass of regular (12%) wine, OR 1 1/2 ounces of hard liquor either straight or in a mixed drink OR One 12-ounce wine cooler	_____
	other drug	_____
3.	Have you used any illicit substances or alcohol on Wednesday	◯ Yes ◯ No

Substances used on Wednesday	☐ Alcohol ☐ Cannabinoids/Marijuana ☐ Cocaine ☐ Crack ☐ Amphetamine-type stimulants ☐ Opiod Analgesics, including methadone ☐ heroin ☐ Hallucinogens, including MDMA/ecstasy ☐ sedatives and hypnotics, excluding benzodiazepine ☐ Benzodiazepines ☐ Inhalants ☐ other drugs
Since you said yes to alcohol, how many standard drinks did you drink. A standard drink is one 12-ounce bottle/can of regular beer, OR One 5-ounce glass of regular (12%) wine, OR 1 1/2 ounces of hard liquor either straight or in a mixed drink OR One 12-ounce wine cooler	_____
other drug	_____
4. Have you used any illicit substances or alcohol on Thursday	◯ Yes ◯ No
Substances used on Thursday	☐ Alcohol ☐ Cannabinoids/Marijuana ☐ Cocaine ☐ Crack ☐ Amphetamine-type stimulants ☐ Opiod Analgesics, including methadone ☐ heroin ☐ Hallucinogens, including MDMA/ecstasy ☐ sedatives and hypnotics, excluding benzodiazepine ☐ Benzodiazepines ☐ Inhalants ☐ other drugs
Since you said yes to alcohol, how many standard drinks did you drink. A standard drink is one 12-ounce bottle/can of regular beer, OR One 5-ounce glass of regular (12%) wine, OR 1 1/2 ounces of hard liquor either straight or in a mixed drink OR One 12-ounce wine cooler	_____
other drug	_____
5. Have you used any illicit substances or alcohol on Friday	◯ Yes ◯ No

	Substances used on Friday	☐ Alcohol ☐ Cannabinoids/Marijuana ☐ Cocaine ☐ Crack ☐ Amphetamine-type stimulants ☐ Opiod Analgesics, including methadone ☐ heroin ☐ Hallucinogens, including MDMA/ecstasy ☐ sedatives and hypnotics, excluding benzodiazepine ☐ Benzodiazepines ☐ Inhalants ☐ other drugs
	Since you said yes to alcohol, how many standard drinks did you drink. A standard drink is one 12-ounce bottle/can of regular beer, OR One 5-ounce glass of regular (12%) wine, OR 1 1/2 ounces of hard liquor either straight or in a mixed drink OR One 12-ounce wine cooler	_____
	other drug	_____
6.	Have you used any illicit substances or alcohol on Saturday	◯ Yes ◯ No
	Substances used on Saturday	☐ Alcohol ☐ Cannabinoids/Marijuana ☐ Cocaine ☐ Crack ☐ Amphetamine-type stimulants ☐ Opiod Analgesics, including methadone ☐ heroin ☐ Hallucinogens, including MDMA/ecstasy ☐ sedatives and hypnotics, excluding benzodiazepine ☐ Benzodiazepines ☐ Inhalants ☐ other drugs
	Since you said yes to alcohol, how many standard drinks did you drink. A standard drink is one 12-ounce bottle/can of regular beer, OR One 5-ounce glass of regular (12%) wine, OR 1 1/2 ounces of hard liquor either straight or in a mixed drink OR One 12-ounce wine cooler	_____
	other drug	_____
7	Have you used any illicit substances or alcohol on Sunday	◯ Yes ◯ No

Substances used on Sunday	☐ Alcohol ☐ Cannabinoids/Marijuana ☐ Cocaine ☐ Crack ☐ Amphetamine-type stimulants ☐ Opiod Analgesics, including methadone ☐ heroin ☐ Hallucinogens, including MDMA/ecstasy ☐ sedatives and hypnotics, excluding benzodiazepine ☐ Benzodiazepines ☐ Inhalants ☐ other drugs
Since you said yes to alcohol, how many standard drinks did you drink. A standard drink is one 12-ounce bottle/can of regular beer, OR One 5-ounce glass of regular (12%) wine, OR 1 1/2 ounces of hard liquor either straight or in a mixed drink OR One 12-ounce wine cooler	_____
other drug	_____