A PHASE IIA STUDY EVALUATING THE SAFETY OF ACAMPROSATE FOR ALCOHOL USE DISORDER IN ALCOHOL-RELATED LIVER DISEASE

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List of Abbreviations

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUD	Alcohol use disorder
CFR	Code of Federal Regulations
CRF	Case Report Form
DSM	Diagnostic and Statistical Manual
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HE	Hepatic encephalopathy
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
INR	International Normalized Ratio
IRB	Institutional Review Board
MELD-Na	Model for End Stage Liver Disease Sodium
MMSE	Mini mental state examination
PACS	Pennsylvania Alcohol Craving Scale
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure

Study Summary

Title	A phase IIa study evaluating the safety of acamprosate for alcohol use disorder in alcohol-related liver disease
Running Title	Acamprosate for alcohol use disorder in alcohol-related liver disease
Protocol Number	18-010902
Phase	Phase IIa
Methodology	Open label, pilot safety assessment
Overall Study Duration	12 months
Subject Participation Duration	6 months
Single or Multi-Site	Single site
Objectives	To evaluate the safety of acamprosate in individuals with alcohol-use disorder (AUD) and alcohol-related liver disease
Number of Subjects	10
Diagnosis and Main Inclusion Criteria	Adult patients aged 21 or over with a diagnosis of alcohol-related liver disease and AUD
Study Product, Dose, Route, Regimen	Acamprosate will be dosed at 333 mg TID, increased to 666 mg TID after 1 week if tolerated. If GFR is 30-50 ml/min, dosage will remain at 333 mg TID throughout the study.
Duration of Administration	3 months
Reference therapy	No reference or control group
Statistical Methodology	Basic descriptive statistics and a qualitative analysis will be performed

1 Introduction

This document is a clinical research protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Background

Alcohol use disorder (AUD) is a common condition with a lifetime and 12-month prevalence of 29.1% and 13.9%, respectively, identified in the US population (Grant et al., 2015). Although several effective treatments are available, less than one-fifth of individuals seek treatment over their lifetime; most seek help from physicians to manage comorbidities related to AUD (Grant et al., 2015; Lyon, 2017). Alcohol-related liver disease encompasses a wide spectrum of disease, ranging from steatosis and minimal fibrosis to alcoholic hepatitis, cirrhosis and sequelae of portal hypertension. Hepatic steatosis is common, seen in approximately 90% of longstanding heavy drinkers with recent binging (Edmondson et al., 1967). Ongoing alcohol consumption may result in steatohepatitis in one third of patients and an estimated 16% of those with steatohepatitis will develop cirrhosis over five years (Barrio et al, 2004; Deleuran et al., 2012). Individuals with alcohol-related cirrhosis are at high risk for complications from liver disease and death; these risks are increased in the setting of ongoing alcohol use (Jepsen et al., 2010; Jepsen et al., 2012).

Despite the prevalence of liver disease complicating AUD, there are few prospective clinical studies evaluating the efficacy of pharmacologic treatments to promote abstinence and prevent relapse. Naltrexone and acamprosate have been found to be effective for AUD; however, naltrexone carries a significant risk of hepatocellular injury, and it is contraindicated in those with acute hepatitis or liver failure (Jonas et al., 2014; Alkermes, Inc., 2010). Other promising medications that require further study include baclofen, topiramate, gabapentin, varenicline and ondansetron, of which baclofen is the only drug that has been evaluated in liver disease (Addolorato et al., 2007).

Acamprosate has not been evaluated formally in individuals with AUD and liver disease. It is an N-methyl-D-aspartate glutamate receptor antagonist approved by the Food and Drug Administration to aid in maintaining abstinence in individuals with alcohol dependence (Frye et al., 2016). Acamprosate has an unclear mechanism of action, although it is thought that its effect on decreased alcohol craving intensity is mediated through a reduction in glutamate levels (Frye et al., 2016). The efficacy of acamprosate has been demonstrated in several meta-analyses, most recently exhibiting a number needed to treat of 12 to prevent return to any drinking (Jonas et al., 2014; Rosato et al., 2015). Acamprosate is not metabolized by the liver and thus has been considered as a potential therapeutic option in those with liver disease. However, as acamprosate antagonizes the glutamate receptor, there have been concerns it may increase the risk of hepatic encephalopathy. Previously, a single dose of acamprosate 666 mg was administered to 12 patients with Child-Pugh A or B cirrhosis with no identifiable induction of subclinical hepatic encephalopathy; however, transient diastolic hypotension was noted (Delgrange et al., 1992). No further studies on acamprosate have been performed in individuals with liver disease.

To evaluate the safety of acamprosate in individuals with AUD and alcohol-related liver disease, an initial pilot study in five patients with a Model for End Stage Liver Disease Sodium (MELD-Na) score less than 20 will be conducted. If no safety concerns are identified, the study will then

be performed in five patients with MELD-Na scores of 20 or more. If again no safety concerns are identified, a larger, placebo-controlled efficacy study is planned and will be submitted as a separate protocol.

1.2 Investigational Agent

Per the manufacturer, Merck (2005): "*CAMPRAL*® (acamprosate calcium) is supplied in an enteric-coated tablet for oral administration. Acamprosate calcium is a synthetic compound with a chemical structure similar to that of the endogenous amino acid homotaurine, which is a structural analogue of the amino acid neurotransmitter γ-aminobutyric acid and the amino acid neuromodulator taurine. Its chemical name is calcium acetylaminopropane sulfonate. Its chemical formula is $C_{10}H_{20}N_2O_8S_2Ca$ and molecular weight is 400.48.

Each *CAMPRAL* tablet contains acamprosate calcium 333 mg, equivalent to 300 mg of acamprosate. Inactive ingredients in *CAMPRAL* tablets include: crospovidone, microcrystalline cellulose, magnesium silicate, sodium starch glycolate, colloidal anhydrous silica, magnesium stearate, talc, propylene glycol and Eudragit® L 30 D or equivalent. The drug product will appear in tablet form."

Acamprosate is now available as a generic in the USA.

1.3 Preclinical Data

n/a

1.4 Clinical Data to Date

Acamprosate has been studied extensively in individuals without liver disease. The efficacy of acamprosate has been demonstrated in several meta-analyses, most recently exhibiting a number needed to treat of 12 to prevent return to any drinking (Jonas et al., 2014; Rosato et al., 2015).

Previously, a single dose of acamprosate 666 mg was administered to 12 patients with Child-Pugh A or B cirrhosis with no identifiable induction of subclinical hepatic encephalopathy; however, transient diastolic hypotension was noted (Delgrange et al., 1992). No further studies on acamprosate have been performed in individuals with liver disease.

1.5 Dose Rationale

Acamprosate will be dosed at 333 mg TID, increased to 666 mg TID after 1 week if tolerated. If GFR is 30-50 ml/min, dosage will remain at 333 mg TID throughout the study. The dosing and dose regimen of acamprosate has varied in prior trials; however, the regimen used herein is largely considered standard for use in AUD (Plosker, 2015; Higuchi, 2015). Based on prior studies and for practical purposes, route of administration will be by mouth.

1.6 Risks and Benefits

Individuals with alcohol-related cirrhosis are at high risk for complications from liver disease and death; these risks are increased in the setting of ongoing alcohol use (Jepsen et al., 2010; Jepsen et al., 2012). A profound difference in five-year survival after an episode of alcoholic hepatitis in seen in those who are able to maintain abstinence compared to those who continue to drink or relapse, with rates of 75% and 21-27%, respectively (Potts et al., 2013).

Adverse events associated with acamprosate use are considered minimal and primarily have included anxiety, diarrhea and vomiting (Jonas et al., 2014; Reus et al., 2018). Specific rates of the following adverse events have been reported: pruritus (4%), diarrhea (17%), flatulence (3%), nausea (4%), dizziness (3%), insomnia (7%), anxiety (6%) and depression (5%) (Merck, 2005). More rare risks include cardiomyopathy, deep thrombophlebitis, heart failure, mesenteric arterial occlusion, shock and suicide (Merck, 2005). There has been no increased risk of withdrawal from trials with acamprosate due to adverse events (Jonas et al., 2014). Given the high risk of adverse outcomes associated with ongoing alcohol consumption in this patient population, including death, the risks of acamprosate use are reasonable in comparison.

2 Study Objectives

Primary Objective:

To assess the safety and tolerability of acamprosate for treatment of AUD in alcohol-related liver disease as measured by adverse event reporting.

Secondary Objective:

To assess treatment effect of acamprosate on alcohol relapse in alcohol-related liver disease as measured by Pennsylvania Alcohol Craving Scale (PACS) scores and reporting of alcohol use.

3 Study Design

This study is a phase IIa trial of the safety of acamprosate in treating AUD in alcohol-related liver disease. Subjects will be screened for eligibility at outpatient clinic visits and during hospitalizations; interested qualified subjects will be consented and offered participation in this trial. At study enrollment, initial MELD-Na score must be less than 20 for the five individuals enrolling in the first phase of the pilot safety assessment. The second phase of the pilot safety assessment will include individuals with a MELD-Na of 20 or more at enrollment. Once consent has been obtained, baseline characteristics will be established and then patients will be initiated on acamprosate treatment. Acamprosate will be administered for three months, during which time, patients will complete monthly blood work, weekly telephone assessments for the first month, followed by telephone assessments and urine testing on a monthly basis thereafter. A final clinic visit for evaluation and collection of lab samples will be conducted at the end of the study at 3 months. Patients will be contacted by telephone at weeks 13 and 24 after study enrollment for final follow up assessments off of study medication.

3.1 General Description

Adult patients aged 21 or over with a diagnosis of alcohol-related liver disease and AUD will be identified in the outpatient clinic or while admitted to hospital and seen by the gastroenterology or hepatobiliary service at Mayo Clinic, Rochester. This population is evaluated for potential eligibility for other alcohol-related liver disease studies by a research coordinator on a weekly basis. The diagnosis of alcohol-related liver disease will be determined by a hepatologist based on history of regular and excessive alcohol consumption in the absence of other causes of liver cirrhosis or acute hepatitis, compatible clinical, imaging and laboratory findings and typical histology on liver biopsy, if performed. Underlying liver disease may include alcoholic hepatitis, advanced (F3-F4) fibrosis, and/or portal hypertension. The diagnosis of AUD will be determined by a hepatologist based on history obtained that is consistent with DSM-5 diagnostic criteria for AUD (all categories of mild, moderate and severe considered eligible).

Patients need not be abstinent from alcohol prior to initiating acamprosate treatment (but not abstinent for more than 6 months). At study enrollment, initial MELD-Na score must be less than 20 for the five individuals enrolling in the first phase of the pilot safety assessment. The second phase of the pilot safety assessment will include individuals with a MELD-Na of 20 or more at enrollment. Patients with heart failure (NYHA class II or higher) or hypotension requiring the use of vasoconstrictors (i.e. midodrine) will be excluded. Individuals with a glomerular filtration rate (GFR) of less than 30 ml/min will be excluded. Acamprosate will be dosed at 333 mg TID, increased to 666 mg TID after 1 week if tolerated. If GFR is 30-50 ml/min, dosage will remain at 333 mg TID throughout the study. Acamprosate will be administered for a total of 3 months.

Prior to enrollment, known risks and benefits of acamprosate in treating AUD will be discussed with patients including pruritus (4%), diarrhea (10% to 17%), flatulence (3%), nausea (4%), dizziness (3%), insomnia (7%), anxiety (6%) and depression (5%). More rare risks include cardiomyopathy, deep thrombophlebitis, heart failure, mesenteric arterial occlusion, shock and suicidal intent (1%).

At enrollment, collected baseline characteristics will include patient age, sex, race, martial and employment status, education level, social support, presence of children, age of children, underlying liver disease etiology, MELD-Na score, presence of ascites, esophageal varices, spontaneous bacterial peritonitis, diabetes, corticosteroid or other medical treatment for alcoholic hepatitis (Maddrey and Lille scores if relevant), medical comorbidities, prescription and non-prescription medications. With regard to alcohol use, patients will have the 11 DSM-5 questions regarding AUD answered at screening (American Psychiatric Association, 2013), as well as the following history obtained: duration of excess alcohol consumption in years, level of alcohol consumption prior to study enrollment, interval of alcohol abstinence prior to study enrollment, family history of alcoholism, history of alcohol-related legal issues, psychiatric comorbidity (requiring medication, outpatient care or hospitalization), other addictions including smoking and number of prior rehabilitation attempts for alcohol or other addictions. The PACS questionnaire will be administered. Vital signs and a physical examination will be performed. West Haven HE score will be graded and modified telephone version of MMSE completed. Blood work will be completed including a complete blood count, electrolytes, creatinine, blood urea nitrogen, total bilirubin, direct bilirubin, albumin, INR, AST, ALT and alkaline phosphatase. A urine ethyl

glucuronide will be performed. A urine pregnancy test will be conducted before admission into the trial for women of child-bearing potential.

Study duration will be six months. During the study, patients will complete monthly MELD-Na labs and receive a phone call weekly for the first month, then monthly for a total of 3 months. Urine ethyl glucuronide will be done at enrollment and once monthly. Patients will then have a follow up visit at 12 weeks, with labs, urine ethyl glucuronide, vital signs and physical exam. During telephone assessments and at the follow up visit, patients will be asked about potential side effects and hepatic decompensation. Other variables to be collected at enrollment and at the 3 month visit include Child-Pugh score, West Haven grading of HE, vital signs at enrollment and current medications. At enrollment, during phone calls and at the follow up visit, patients will be asked standardized questions to assess for HE based on the abbreviated telephone version of the mini-mental state examination (MMSE). Follow up telephone visits at 13 and 24 weeks will be conducted, primarily to monitor for adverse events and alcohol relapse.

The Pennsylvania Alcohol Craving Scale (PACS) will be applied before treatment initiation, weekly for the first month on treatment, then monthly thereafter. This will include the need severity scale (mild, moderate, severe) at baseline and at each assessment by phone call and in clinic.

Alcohol use relapse will be monitored. Any amount of alcohol use as revealed during follow-up considered a relapse event. Alcohol use will be captured and categorized as none, slip (no longer drinking at most recent follow up) or sustained alcohol use (minimum 100 days drinking). Slips and sustained alcohol use will be categorized as binge drinking, frequent drinking, or both (binge drinking as more than 6 units/day for men and 4 units/day for women and frequent drinking as alcohol use in 4 or more days/week regardless of quantity per day) (Lee et al., 2018).

Basic descriptive statistics and a qualitative analysis will be performed. Analyses will be performed using SPSS 25 (Chicago, IL). Results will not contain any patient-specific information.

3.2 Number of Subjects

10 individuals.

3.3 Duration of Participation

6 months.

3.4 Primary Study Endpoints

The primary endpoint is an estimation of the safety profile of acamprosate for treatment of AUD in alcohol-related liver disease as measured by adverse event reporting. The safety parameters to be measured include clinical symptoms, vital signs, physical examination, blood work and urine testing.

3.5 Secondary Study Endpoints

Secondary endpoints will detail extent of alcohol cravings and relapse during treatment with acamprosate for treatment of AUD in alcohol-related liver disease as measured by Pennsylvania Alcohol Craving Scale (PACS) scores and reporting of any amount of alcohol use.

3.6 Primary Safety Endpoints

See 3.4.

3.7 Identification of Source Data

The following source data will be directly recorded on the Case Report Form (CRF):

- Vital signs
- Weight
- Clinical history
- Adverse events
- Medication list including new medications, change in medications
- Alcohol use
- Other substance use including nicotine and recreational drug use
- PACS responses and score
- MMSE responses and score
- West Haven HE grade
- Laboratory results and clinical interpretation of the values.
- Clinical significance of observations (when applicable)

The following source data will not be directly collected in the Case Report Form (CRF), but will be captured in supportive documentation (Demographics form, Concurrent Medications form):

- All data to be obtained at enrollment as detailed in 6.1.

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

Eligible individuals:

- Aged 21 or over
- Diagnosis of alcohol-related liver disease and AUD.
    - The diagnosis of alcohol-related liver disease will be determined by a hepatologist based on history of regular and excessive alcohol consumption in the absence of other causes of liver cirrhosis or acute hepatitis, compatible clinical, imaging and laboratory findings and typical histology on liver biopsy, if performed. Underlying liver disease may include alcoholic hepatitis, advanced (F3-F4) fibrosis, and/or portal hypertension.
    - The diagnosis of AUD will be determined by a hepatologist and/or addiction psychiatrist based on history obtained that is consistent with DSM-5 diagnostic criteria for AUD (all categories of mild, moderate and severe considered eligible) (American Psychiatric Association, 2013; questions from NIH, 2016).

- Patients need not be abstinent from alcohol prior to initiating acamprosate treatment (but not abstinent for more than 6 months).
- At study enrollment, initial MELD-Na score must be less than 20 for the five individuals enrolling in the first phase of the pilot safety assessment. The second phase of the pilot safety assessment will include individuals with a MELD-Na of 20 or more at enrollment.
- Have capacity to provide consent themselves

4.2 Exclusion Criteria

Exclusion criteria:

- Individuals with a glomerular filtration rate (GFR) of less than 30 ml/min
- Congestive heart failure (NYHA class II or higher)
- Hypotension, requiring the use of vasoconstrictors (i.e. midodrine)
- Pregnancy, lactation or refusal to use a reliable method of birth control if a sexually active female of childbearing potential. Although no human trial data is available, animal studies suggest possible teratogenic effects of acamprosate (Merck, 2005).

4.3 Subject Recruitment, Enrollment and Screening

Patients will be identified in the outpatient hepatobiliary clinic or while admitted to hospital and seen by the gastroenterology or hepatobiliary service at Mayo Clinic, Rochester. This population is evaluated for potential eligibility for other alcohol-related liver disease studies by a research coordinator on a weekly basis. Physicians that identify eligible patients that are not captured by the research coordinator may refer the patient. Both male and female subjects must use 2 reliable forms of birth control from screening to at least up to 4 weeks after the study treatment is over. No recruitment material will be created.

Using clinical information obtained from the electronic medical record, patients will be screened for eligibility. Documentation of inclusion and exclusion criteria will be included in the participant database.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Patients will be withdrawn from the study prior to study completion if:

1. Subjects elect to withdraw consent
2. Subject is found to be ineligible for the protocol as per the Inclusion/Exclusion criteria.
3. Subjects experience a serious adverse event felt to possibly be related to acamprosate administration as determined by PI and/or DSMB.
4. Failure of the subject to comply with protocol requirements.
5. Exhibition of unacceptable toxicity which would make it difficult or dangerous to comply with further protocol requirements such as study visits, blood draws, etc.
6. There are changes in medical status of the subject such that the Investigator believes that subject safety will be compromised or that it would be in the best interest of the subject to stop participation in the study.

7. Death of the subject.
8. Subjects with a test consistent with pregnancy such as a positive beta-hCG.
9. Subject is lost to follow-up.
10. Any complication that requires prolongation of the hospitalization or change in treatment and in the opinion of the investigator is related to the study drug.

If subjects are withdrawn from the study, they will be replaced to ensure a total of 10 patients complete the study in its entirety. The data collected up until the time of withdrawal from the study will be included in analysis.

Follow up from subjects withdrawn from study treatment will include:

- Clinic visit at time of withdraw from study will be recommended. Beyond risk of returning to alcohol consumption, sudden study treatment termination should not include any subject safety considerations.
- Follow up phone call 3 months after withdrawal from study

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

If a subject withdraws consent to participate in the study, for subject safety reasons, attempts will be made to obtain permission to collect follow up information whenever possible. Attempt will be made when the patient reports withdrawal of consent.

5 Study Drug

5.1 Description

Per Merck manual (2005):

"*CAMPRAL*® (acamprosate calcium) is supplied in an enteric-coated tablet for oral administration. Acamprosate calcium is a synthetic compound with a chemical structure similar to that of the endogenous amino acid homotaurine, which is a structural analogue of the amino acid neurotransmitter γ-aminobutyric acid and the amino acid neuromodulator taurine. Its chemical name is calcium acetylaminopropane sulfonate. Its chemical formula is C10H20N2O8S2Ca and molecular weight is 400.48.

Acamprosate calcium is a white, odorless or nearly odorless powder. It is freely soluble in water, and practically insoluble in absolute ethanol and dichloromethane. Each *CAMPRAL* tablet contains acamprosate calcium 333 mg, equivalent to 300 mg of acamprosate. Inactive ingredients in *CAMPRAL* tablets include: crospovidone, microcrystalline cellulose, magnesium silicate, sodium starch glycolate, colloidal anhydrous silica, magnesium stearate, talc, propylene glycol and Eudragit® L 30 D or equivalent. The drug product will appear in tablet form.

CLINICAL PHARMACOLOGY
Pharmacodynamics
The mechanism of action of acamprosate in maintenance of alcohol abstinence is not completely understood. Chronic alcohol exposure is hypothesized to alter the normal balance between

neuronal excitation and inhibition. *In vitro* and *in vivo* studies in animals have provided evidence to suggest acamprosate may interact with glutamate and GABA neurotransmitter systems centrally, and has led to the hypothesis that acamprosate restores this balance.

Pharmacodynamic studies have shown that acamprosate calcium reduces alcohol intake in alcohol-dependent animals in a dose-dependent manner and that this effect appears to be specific to alcohol and the mechanisms of alcohol dependence. Acamprosate calcium has negligible observable central nervous system (CNS) activity in animals outside of its effects on alcohol dependence, exhibiting no anticonvulsant, antidepressant, or anxiolytic activity. The administration of acamprosate calcium is not associated with the development of tolerance or dependence in animal studies. *CAMPRAL* is not known to cause alcohol aversion and does not cause a disulfiram-like reaction as a result of ethanol ingestion.

Pharmacokinetics

Absorption: The absolute bioavailability of *CAMPRAL* after oral administration is about 11%. Steady-state plasma concentrations of acamprosate are reached within 5 days of dosing. Steady-state peak plasma concentrations after *CAMPRAL* doses of 2 x 333 mg tablets three times daily average 350 ng/mL and occur at 3-8 hours post-dose. Coadministration of *CAMPRAL* with food decreases bioavailability as measured by Cmax and AUC, by approximately 42% and 23%, respectively. The food effect on absorption is not clinically significant and no adjustment of dose is necessary.

Distribution: The volume of distribution for acamprosate following intravenous administration is estimated to be 72-109 liters (approximately 1 L/kg). Plasma protein binding of acamprosate is negligible.

Metabolism: Acamprosate does not undergo metabolism.

Elimination: After oral dosing of 2 x 333 mg of *CAMPRAL*, the terminal half-life ranges from approximately 20 - 33 hours. Following oral administration of *CAMPRAL*, the major route of excretion is via the kidneys as acamprosate."

5.2 Treatment Regimen

Acamprosate will be dosed at 333 mg PO TID, increased to 666 mg PO TID after 1 week if tolerated. If GFR is 30-50 ml/min, dosage will remain at 333 mg PO TID throughout the study. Treatment duration is 3 months.

5.3 Method for Assigning Subjects to Treatment Groups

n/a

5.4 Preparation and Administration of Study Drug

Subjects will collect the study drug from their local pharmacy and self-administer by mouth.

5.5 Subject Compliance Monitoring

At weekly telephone assessments for the first month, and then monthly telephone assessments and then clinic visit at 3 months, the study team will ask the patient if he or she has missed any acamprosate doses. Subjects will be asked to count their remaining pills and detail how many they were initially prescribed and when. If patients are significantly non-compliant, defined as taking less than 75% of prescribed medication, they will be withdrawn from the study.

5.6 Prior and Concomitant Therapy

All prescription and non-prescription medications will be documented at enrollment and throughout the study. There are no known significant drug interactions and no concomitant medications will be considered exclusion criteria to the study (Merck, 2005).

5.7 Packaging

Acamprosate will be administered in tablets by mouth. The drug will be picked up at the patient's preferred pharmacy. The study is not blinded. Labeling will be per manufacturer.

5.8 Masking/Blinding of Study

The study is not blinded.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

The drug will be picked up by the patient at the patient's preferred pharmacy.

5.9.2 Storage

It will be recommended that patients store acamprosate at room temperature. Merck indicates recommended storage at 25ºC (77ºF); excursions permitted to 15º - 30ºC (59º - 86ºF).

5.9.3 Dispensing of Study Drug

Regular study drug reconciliation will be performed during assessments to document drug remaining, and will be logged on the Case Report Form.

5.9.4 Return or Destruction of Study Drug

Study drug is an FDA-approved prescription medication that patients will be picking up at their local pharmacies. Should the patient stop taking the study drug for any reason, it will be recommended that they return the drug to their local pharmacy for disposal.

6 Study Procedures

6.1 Visit 1 – Screening/enrollment day

Informed consent will be obtained. Inclusion and exclusion criteria will be evaluated. Collected baseline characteristics will include patient age, sex, race, martial and employment status, education level, social support, presence of children, age of children, underlying liver disease etiology, MELD-Na score, presence of ascites, esophageal varices, spontaneous bacterial peritonitis, diabetes, corticosteroid or other medical treatment for alcoholic hepatitis (Maddrey and Lille scores if relevant), medical comorbidities, prescription and non-prescription medications. With regard to alcohol use, patients will fill out the Alcohol Use Disorder Identification Test (AUDIT) and the following history will be obtained: duration of excess alcohol consumption in years, level of alcohol consumption prior to study enrollment, interval of alcohol abstinence prior to study enrollment, family history of alcoholism, history of alcohol-related legal issues, psychiatric comorbidity (requiring medication, outpatient care or hospitalization), other addictions including smoking and number of prior rehabilitation attempts for alcohol or other addictions. The PACS questionnaire will be administered.

Vital signs and a physical examination will be performed. West Haven HE score will be graded and modified telephone version of MMSE completed. Blood work will be completed including a complete blood count, electrolytes, creatinine, blood urea nitrogen, total bilirubin, direct bilirubin, albumin, INR, AST, ALT and alkaline phosphatase. A urine ethyl glucuronide will be performed. A urine pregnancy test will be conducted before admission into the trial for women of child-bearing potential.

6.2 Visit 2-5

Visits 2-5 will be conducted by telephone and include data to be included on the Case Report Form including

- Clinical history
- Adverse events
- Medication list including new medications, change in medications
- Alcohol use
- Other substance use including nicotine and recreational drug use
- PACS responses and score
- MMSE responses and score
- West Haven HE grade
- Laboratory results and clinical interpretation of the values.
- Clinical significance of observations (when applicable)

6.3 Visit 6

Visit 6 will occur at week 12 of acamprosate therapy. Interval clinical history, adverse events, medication list and alcohol and other substance use will be detailed. PACS score will be evaluated. Case Report Form will be completed.

Vital signs and a physical examination will be performed. West Haven HE score will be graded and modified telephone version of MMSE completed. Blood work will be completed including a complete blood count, electrolytes, creatinine, blood urea nitrogen, total bilirubin, direct bilirubin, albumin, INR, AST, ALT and alkaline phosphatase.

6.4 Visit 7 Follow up

Patients will receive a telephone call at week 13 for reassessment. Interval clinical history will be obtained, all adverse events, medication list and alcohol and other substance use will be detailed. PACS score, modified telephone version of MMSE and West Haven HE score will be calculated. Case Report Form will be completed.

6.5 Visit 8 Follow up

Patients will receive a telephone call at week 24 for reassessment. Interval clinical history will be obtained, history of any serious adverse events, medication list and alcohol and other substance use will be detailed. PACS score, modified telephone version of MMSE and West Haven HE score will be calculated. Case Report Form will be completed. Final blood tests will be requested.

	Screening/ Enrollment day	Treatment Period													
Test/Procedure Name	(D1)	W1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	W 13	W 24
Study Visit	x												x		
Follow-Up Phone Calls		x	x	x	x				x					x	x
Physical Exam	x												x		
Complete blood count	x												x		x
Electrolytes	x				x				x				x		x
Creatinine	x				x				x				x		x
Urea	x												x		x
Total Bilirubin	x				x				x				x		x
Direct bilirubin	x												x		x
INR	x				x				x				x		x
Urine Ethyl Glucuronide	x				x				x				x		x
Albumin	x												x		x
AST, ALT, alkaline phosphatase	x												x		x
Child Pugh Score	x												x		x
West Haven HE Score	x												x	x	x
MMSE	x	x	x	x	x				x				x	x	x
Med Review	x	x	x	x	x				x				x	x	x
Pennsylvania Alcohol Craving Scale	x	x	x	x	x				x				x	x	x

Adverse event evaluation	x	x	x	x	x				x				x	x	x
Alcohol consumption documentation	x	x	x	x	x				x				x	x	x

7 Statistical Plan

7.1 Sample Size Determination

As the study is a phase IIa safety trial, no power analysis was completed.

7.2 Statistical Methods

Descriptive Statistics

Univariate descriptive statistics and frequency distributions will be calculated, as appropriate for all variables. Baseline values for demographic, clinical, and outcome variables (primary and secondary) will be tabulated.

Safety analyses will be conducted using all subjects, and presented overall. Safety data will be analyzed using descriptive statistics and tabulation.

7.3 Subject Population(s) for Analysis

All subjects that received at least one dose of study drug will be evaluated.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)
Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) breach of confidentiality and (6) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event
An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event
Adverse events are classified as serious or non-serious. Serious problems/events include;

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant disability or incapacity

and/or per protocol may be problems/events that in the opinion of the investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All adverse events that do not meet any of the criteria for serious, will be regarded as **non-serious adverse events**.

Adverse Event Reporting Period

For this study, the study treatment follow-up period is defined as 12 weeks following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality will be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report, to the investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
Determination of whether worsening of liver biochemical tests is due to the alcohol-related hepatitis or study drug induced liver injury (DILI) is difficult. An AST or ALT increase >500 IU/L would be considered an indication that the patient might have DILI since AST and ALT are typically < 300-400 U/L in AH. Such an increase of > 500 IU/L would trigger prompt evaluation and consideration of discontinuation of the study drug. Considering how difficult it is to distinguish potential DILI from worsening of the underlying liver disease, we have incorporated an external adjudication of all suspected DILI events. An increase in MELD-Na score >5 points from baseline, or doubling bilirubin (2 times the baseline level at enrollment) would warrant urgent review by the DSMB.

The study will be **stopped** if three or more patients develop AST or ALT > 500 U/L or as or as determined by the DSMB.
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Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization will be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery will be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery will **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should recorded in the source document.

All adverse events occurring during the study period will be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs during the Adverse Event Reporting Period and is considered to be at least possibly related to the study treatment or study participation will be recorded and reported immediately.

Adverse events will be classified per the CTCAE Version 5.0, November 27, 2017.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The investigator will evaluate the event and determine the necessary follow-up and reporting required.

8.3.1 Investigator reporting: notifying the Mayo IRB

The investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

Information collected on the adverse event worksheet (*and entered in the research database)*:

- Subject's name:
- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research drug:
- If the adverse event was expected:
- The severity of the adverse event: (use a table to define severity scale 1-5**)
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

The investigator will review all adverse event reports to determine if specific reports need to be made to the IRB. The investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

*** Relationship Index**
The relationship of an AE to the Investigational Drug is a clinical decision by the principal investigator (PI) based on all available information at the time of the completion of the CRF and is graded as follows:

1. Not related: a reaction for which sufficient information exists to indicate that the etiology is unrelated to the study drug; the subject did not receive the study medication or the temporal sequence of the AE onset relative to administration of the study medication is not reasonable or the event is c1early related to other factors such as the subject' s clinical state, therapeutic intervention or concomitant therapy.

2. Unlikely: a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs, chemicals, or underlying disease provide plausible explanations.

3. Possible: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but which could also be explained by concurrent disease or other drugs or chemicals; information on drug withdrawals may be lacking are unclear.

4. Probable: a clinical event including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals and which follows a clinically reasonable response on withdrawal (de-challenge): re-challenge information is not required to fulfi1 this definition.

5. Definite: a reaction that follows a reasonable temporal sequence from administration of the drug, or in which the drug level has been established in body fluids or tissues, that follows a known or expected response pattern to the suspected drug, and that is confirmed by improvement on stopping or reducing the dosage of the drug, and reappearance of the reaction on repeated exposure (re-challenge).

Severity Index
The maximum intensity of an AE during a day will be graded according to the definitions below and recorded in details as indicated on the CRF. If the intensity of an AE changes over a number of days, then separate entries should be made having distinct onset dates.

1. Mild: AEs are usually transient, requiring no special treatment, and do not interfere with patient’s daily activities.

2. Moderate: AEs typically introduce a low level of inconvenience or concern to the patient and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.

3. Severe: AEs interrupt a patient's usual daily activity and traditionally require systemic drug therapy or other treatment.

8.3.2 Investigator reporting: Notifying the FDA

n/a

8.4 Unmasking/Unblinding Procedures

n/a

8.5 Stopping Rules

The study will stop for an individual patient if any of the following occur:

1. The participant decides to withdraw from the study.
2. The participant experiences a Serious Adverse Event (SAE) that, in the opinion of the investigator, is possibly, probably or definitely related to the study drug utilizing the National Cancer Institute's CTCAE system as a guide.
3. The participant experiences a UPIRTSO **AND**, in the opinion of the investigator and study adjudicator, is related to the study drug
4. The participant experiences a grade 3 or higher CTCAE develop that are determined to be possibly or likely attributable to study drug
5. The participant experiences a medical condition that, in the opinion of the investigator, continuation on the study drug would be detrimental.
6. Decision by the DSMB. If a participant experiences a MELD-Na score increase by more than 5 points from baseline or doubling bilirubin level from enrollment, the DSMB will review the records to determine whether DILI is suspected or changes are attributed to natural course of disease
7. The participant experiences an increase of AST or ALT >500 U/L

Determination of whether worsening of liver biochemical tests is due to the alcoholic hepatitis or study drug induced liver injury (DILI) is difficult. An AST or ALT increase >500 IU/L would be considered an indication that the patient might have DILI since AST and ALT are typically < 300-400 U/L in AH. Such an increase of > 500 IU/L would trigger prompt evaluation and consideration of discontinuation of the study drug. Considering how difficult it is to distinguish potential DILI from worsening of the underlying liver disease, we have incorporated an external adjudication of all suspected DILI events. An increase in MELD-Na score >5 points from baseline, or doubling bilirubin (2 times the baseline level at enrollment) would warrant urgent review by the DSMB.

The study will be put on hold for review with the DSMB if one patient experiences a serious adverse event. The study will be restarted if the DSMB considers the serious adverse events to be unrelated to study drug.

The study will stop overall if any of the following occur:

1. The participant experiences a Serious Adverse Event (SAE) that, in the opinion of the investigator, is possibly, probably or definitely related to the study drug utilizing the National Cancer Institute's CTCAE system as a guide.
2. Two or more patients have an adverse event grade 3 or above on the CTCAE scale that is determined to be possibly or likely attributable to study drug as per the study adjudicator.
3. Three or more patients develop AST or ALT > 500 U/L.
4. If recommended by the DSMB.

In the event of a SAE, the site will report this to the Mayo Clinic study team. If the SAE is attributable to study drug, the Mayo Clinic study team will report the event to the Institutional Review Board.

8.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.6.1 Internal Data and Safety Monitoring Board

See DSMB charter.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated

instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

Data Management

Source documents will be kept that include, but are not limited to, medical records, charts, appointment books, patient questionnaires, original laboratory records, equipment printouts. All source documents must be made available to the CRA. The following data must be included in the source data:

- Consent to participate in Trial
- Letter to Primary Care Physician, if applicable
- Patient visit dates
- Screening Numbers
- Demographic Information
- Medical history
- Disease history
- Physical examination
- Vital signs
- Laboratory assessments (copy of laboratory reports)
- AEs and concomitant medications
- Dates of administering study medication
- Patient questionnaires responses
- Issues with protocol compliance
- Completion of, or withdrawal from, trial
- Entirety of Case Report Forms

Data Processing

This is a single center study. Flow of data will be between study coordinators and PIs. De-identified data will be available to DSMB.

Data Security and Confidentiality

All information obtained during the conduct of the trial with respect to the patient will be regarded as confidential and confidentiality of all patients will be maintained. Clinical monitors (e.g. CRAs), auditors and inspectors will require access to a patient's medical notes for the purpose of source document verification source document verification but the patient's confidentiality will be maintained at all times. An agreement for disclosure of any such information will be obtained in writing and is included in the statement of informed consent. The trial data shall not be disclosed to a third party (with the exception of auditors and/or regulatory authorities) without the written consent of the PIs. All data shall be secured against unauthorized access.

Apart from the investigators, no one will have access to participant's identity. The site will securely maintain the code that links participants' identity to their study numbers to prevent access to unauthorized third parties. Participants will be identified according to their study numbers in the data management system and by the investigators during any communications.

Data Quality Assurance

Logic and consistency checks will be performed on all data entered into the CRF to ensure accuracy and completeness.

Training sessions, regular monitoring of the trial, instruction manuals, data verification, cross-checking and data audits will be performed to ensure quality of all trial data.

Data Clarification Process

The data manager for the study will conduct periodic data queries.

9.4 Records Retention

The investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents. The investigator should retain all correspondence relating to this trial in the Investigator Site File (ISF).

All research documentation during the duration of the study will be kept in both secured binders by the study coordinator and in a secured electronic environment (electronic data capture). Documents stored in the secured binders will be kept for the duration of the study. Once the study has been completed, the information in these binders (should it be less than 15 years since the start of the study) will be sent to a medical record warehouse as indicated by Mayo Clinic or stored in a locked research cabinet in the clinical area for at least 15 years. Access to the source documents in study binders will be monitored and only granted on an as needed basis to ensure the welfare of the patients and regulatory responsibilities are maintained through monitoring. There will be a list maintained by study personnel with patient names and identifying information (clinic number, unique patient number), this will not be given to monitors. Those who require access to patient records will be required to sign an agreement for disclosure of any

such information and will not be left unattended by study staff with the records. No copies will be authorized to be made by monitors.

The electronic data capture system will only have de-identified data from subjects as qualified patients will be assigned a unique four-digit number and their initials. This electronic system will be secure meeting the federal requirements and access will be limited only on an authorized basis from the system administrator for purposes of the study.

All documents relating to the trial including the ISF itself, source documents and patient medical files (retained per country specific regulations), completed trial patient log and confidential patient identification list will be retained by the investigator for a minimum period of 15 years, in accordance with regulations as above

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be

obtained before that subject undergoes any study procedure. The consent form must be signed by the subject, and the individual obtaining the informed consent.

It will be made clear throughout the consent process that subjects are under no obligation to participate in the study and that participation will not affect the health care they receive otherwise. Spoken and written communication during consent and throughout the study will be targeted at a maximum sixth grade reading level.

12 Study Finances

12.1 Funding Source

The study is not financed.

13 Publication Plan

The study will be registered to ClinicalTrials.gov prior to subject recruitment and enrollment, as well as posting of results to ClinicalTrials.gov within 12 months of final data collection for the primary outcome. This study will be planned for publication in a peer-reviewed journal. Dr. Douglas Simonetto holds the primary responsibility for publication of the results of the study and will be the primary responsible party from whom approval will need to be obtained before any information can be used or passed onto a third party.

14 References

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15 Attachments

- DSMB
- Case report form
- Adverse event form
- Con Med Form