IND # 114497
Date submitted: July 2, 2014
Title: Glucocorticoid Antagonist Treatment of Alcohol Use Disorder
Responsible Investigator: Barbara J Mason, Ph.D.

INTRODUCTORY STATEMENT

Available medications for alcohol use disorders are of limited efficacy and grossly underutilized. Risk for relapse is highest in the first 90 days[1] and the development of safe and effective medications to increase rates of initial recovery in Alcohol Use Disorder (AUD) that can be implemented by a wide range of treatment providers is a high public health priority. With chronic heavy alcohol use and in alcohol dependence the neuroendocrine stress system becomes dysregulated*, i.e.,* the CORT response of the HPA axis becomes blunted and CRF systems in the amygdala become sensitized, conditions associated with greater craving and risk for relapse in protracted abstinence.

Mifepristone is a GR antagonist that, with 1-week of treatment, restores normal HPA feedback for prolonged periods across a range of disorders and ameliorates cognitive deficits associated with HPA axis dysregulation. Mifepristone produced dramatic effects in blocking compulsive alcohol seeking in animal models of alcohol dependence and protracted abstinence. Similarly, 1-week of treatment with mifepristone reduced cue- and stress-induced craving in a human laboratory POC study of risk factors for relapse in protracted abstinence, with significant effects on decreased drinking and craving persisting for 1-month post treatment in 50 non treatment seeking subjects with alcohol dependence relative to placebo. Improvement on tests of learning, memory and executive function were also found with mifepristone relative to placebo in our AUD sample. Mifepristone is FDA-approved for two indications and was well tolerated in our POC study in AUD and in studies involving 1-week of treatment aimed at "re-setting" the HPA/CRF axis at doses up to 1200 mg/d without titration. We propose to study a treatment seeking sample, with 1-week of mifepristone to increase rates of initial response by re-setting the HPA axis, followed by 8 weeks of counseling to consolidate and sustain medication effects. Based on the association between drinking outcome and mifepristone plasma concentration found in our POC study, we propose to conduct a 3-arm dose-ranging study with randomization to double-blind treatment with 600 or 1200 mg/d of mifepristone or matched placebo to identify optimal dosing for AUD.

Furthermore, a collaboration with Dr. David Goldman, Director, Neurogenetics Lab, NIAAA, will permit an exploratory evaluation of genetic predictors of response; the high affinity of mifepristone for the glucocorticoid receptor makes mifepristone a good candidate for pharmacogenetic analysis that may guide future studies and clinical applications.

GENERAL INVESTIGATIONAL PLAN

SUBJECTS

Sample Size

Power and sample size estimates are based on the change in the number of drinks per week found in our POC study that involved 1-week of mifepristone 600 mg/d vs placebo in 50 subjects with AUD and in our 12-week clinical trial of gabapentin 900mg, 1800mg and placebo in 150 subjects with AUD.[2] Repeated measures ANCOVA performed on the change in number of

drinks per week from baseline through Week 5 in the POC study found significant (F=3.82, df=2, p=0.03) slope effects between mifepristone (-9.19, SEM 7.5) and placebo (+3.62, SEM 7.5), yielding a Cohen's d=0.485 (medium effect size). Continuous outcomes will be assessed for trend dose effects. Based on estimates of change of 0, -2.2 and -6.7 (SE 1.6) drinks per week for placebo, 900mg and 1800mg, respectively, in our gabapentin study, the test for linear trend contrast resulted in highly significant (p<0.001) linear trends with post hoc power at least 99% at the target alpha. Power calculation of cumulative mean drinks per week vs. dose with a planned linear contrast indicates that with 50 subjects per arm (placebo, low dose, high dose), and means which decrease by at least 32% as dose increases, we achieve 91% power to detect a non-zero contrast of the means versus the alternative that contrast is zero using an F test. These calculations assume an alpha=0.05, a common SD+/-12, and hypothesized means of approximately 16, 11 and 8 drinks per week based on the gabapentin data. Estimating early termination by approximately 40% subjects based on clinical trials of similar design,[2,3] the same power analysis for a conservative total of 30 subjects per arm indicates 82% power to test the interactive term (week*treatment) at the alpha of 0.05.

Subject Characteristics

A total of 150 subjects will be randomly assigned to 1 week of double-blind treatment with mifepristone 600 mg/d (n=50), 1200 mg/d (n=50) or placebo (n=50); all subjects will receive 8 weeks of counseling, 4 scheduled phone calls and a Week 12 follow up visit. Subjects will be medically healthy male or female volunteers, 18-*65* years of age. Subjects must meet DSM-V criteria for current alcohol use disorder of moderate or greater severity, defined in DSM-V as ≥ 4 symptoms, because this is the level of severity likely to merit pharmacotherapy and to involve neuroadaptations in the stress systems that mifepristone is hypothesized to treat. Subjects must be abstinent ≥ 3 days (but ≤ 30 days) prior to randomization, as verified by the TLFB and BAC and have a CIWA ≤ 9, to eliminate acute alcohol or withdrawal effects on study measures. Abstinence at randomization will be verified retrospectively by ethyl glucuronide/ethyl sulfate (EtG/Ets) testing, which can reliably detect alcohol metabolites in the urine 80 hours after alcohol consumption. EtG/EtS testing showed only 1 of 50 participants in our mifepristone lab study violated the 3-day abstinence requirement at baseline. Additionally, breathalyzer and Timeline Followback data are collected at every study visit; GGT data are collected monthly.

Inclusion Criteria:

- *Male or female volunteers, 18-65 years of age*
- *Meets DSM-V criteria for current alcohol use disorder of moderate or greater severity, defined by DSM-V as ≥ 4 symptoms*
- *In the month prior to screening, reports drinking > 21 standard drinks per week if male, > 14 if female, with at least one heavy drinking day (males: ≥ 5 drinks, females: ≥ 4 drinks) per week*
- Seeking research-based outpatient treatment for AUD and willing to comply with the protocol, take daily oral medication for 1-week and complete 11 study visits
- *Abstinent a minimum of 3 days (but not more than 30 days) prior to randomization*
- *Negative BAC and a CIWA score of ≤ 9 at randomization*
- *In acceptable health in the judgment of the study physician, on the basis of interview, medical history, physical exam, ECG, urine test and lab tests*
- *Females with childbearing potential must have a negative serum pregnancy test on the screening visit and a negative urine pregnancy test at randomization and agree to use non-hormonal effective birth control for the study duration and one month thereafter*
- *Subjects must be able to complete and understand questionnaires and study procedures in English and sign an informed consent*

- *Willingness to comply with the provisions of the protocol and take daily oral medication*

Exclusion Criteria

- *A medical condition that contraindicates the administration of mifepristone, such as:*
  - *history of adrenal failure, Addison's disease, or adrenal insufficiency*
  - *concurrent systemic corticosteroid therapy*
  - *hemorrhagic disorders*
  - *concurrent anticoagulant therapy*
  - *cardiovascular, hypertensive, hepatic, respiratory or renal disease*
  - *insulin dependent diabetes mellitus*
  - *severe anemia (< 12 hemoglobin)*
  - *inherited porphyria*
  - *females with history of unexplained vaginal bleeding, endometrial hyperplasia with atypia or endometrial carcinoma*
- *Significant medical disorders or clinically significant findings on ECG (e.g., prolongation of the QT_c interval), urine or blood tests that increase potential risk or interfere with study participation as determined by the Study Physician. Note: serum potassium below the normal range must be replaced to normal prior to randomization; individuals with serum potassium outside the range of normal will not be randomized*
- *Liver function tests more than 3 times the upper limit of normal or elevated bilirubin*
- *Female subjects with childbearing potential who are pregnant, nursing, or refuse to use effective non hormonal birth control for the 1-week of medication administration and one month thereafter*
- *Active suicidal ideation*
- *Meets DSM-V criteria for a major Axis I disorder including mood or anxiety disorders or substance use disorders other than alcohol or nicotine use disorders*
- *Positive urine drug screen at screening*
- *Treatment within the month prior to screening with an investigational drug or vaccine, or drugs that may influence study outcomes, e.g., disulfiram, naltrexone, acamprosate*
- *Chronic use or need for psychotropic drugs. Note: some drugs with psychotropic properties (e.g., anti-hypertensive drugs) are allowed if their use is judged by both the investigator and study physician not to pose a safety risk or impact the results of the study*
- *Current use of drugs that are CYP3A substrates and inhibitors (such as calcium channel blockers, azole antifungals, macrolide antibiotics, crythromycin, protease inhibitors) due to risk of interactions with mifepristone; CYP3A inducers (such as rifampin, rifabutin, rifapentine, phenobarbital, phenytoin, carbamazepine, and St. John's wort), which may decrease mifepristone exposure and possibly compromise efficacy or consuming grapefruit juice or chronic use of drugs that are CYP2C8/2C9 substrates (such as NSAIDs, warfarin, and repaglinide), or as determined by the Study Physician*
- *No fixed domicile and/or no availability by home or mobile telephone*
- *Treatment mandated by a legal authority*

Subject Recruitment and Retention

This is the first test of the clinical efficacy of mifepristone for AUD, and as such, requires recruiting individuals with AUD who are both treatment-seekers and free from clinically significant medical and psychiatric disorders or use of concomitant medications that could influence study outcomes. Our experience conducting two N=150, 12-week clinical trials in AUD

with similar admission criteria at Scripps reliably shows we must recruit about 5 subjects for each subject who is successfully randomized, resulting in a rate of randomization of approximately 33 subjects per year. This rate of randomization is consistent with the average rate of 30-36 subjects randomized annually by single sites in recent AUD trials with similarly restrictive admission criteria.

Per procedures established by NIAAA's Clinical Investigations Group,[4] progressive incentive payments will be provided for attendance and completion of study assessments to enhance compliance with study procedures and retention. Subjects will earn a base rate starting at $25 that will increase by $5 for each subsequent consecutive visit. The 4 weekly phone calls will be compensated at a flat rate of $10 each. Perfect attendance and participation in 4 phone calls will result in a subject earning $590 over the 12 weeks of study and follow up.

PROCEDURES

This is a Phase II, single-site, randomized, double-blind, placebo-controlled, 3-arm, parallel groups, dose-ranging study of 1-week of treatment with mifepristone (0, 600, 1200 mg/d) given in conjunction with 8 weeks of manual-guided counseling, and a follow up visit at Week 12. Subjects will be 150 outpatient men and women seeking treatment for current AUD of moderate severity or greater, who are abstinent ≥ 3 and ≤ 30 days and not in acute withdrawal (CIWA ≤ 9) at time of randomization.

Initial Phone Screening: Clinically trained study personnel provide information about the study. Interested individuals who appear eligible are scheduled for a face-to-face intake evaluation.

Week -1, Screening: After providing written informed consent, subjects complete a Screening Visit for evaluation of eligibility (see Table 2). The Structured Clinical Interview for DSM-V (SCID-V) will be administered to determine the inclusion criteria of current AUD with ≥ 4 symptoms and to rule our AXIS I disorders that would warrant study exclusion. The subject's demographic information, medical and alcohol use history, and use of concomitant treatments will be recorded using standardized forms. Vital signs and breath alcohol concentration (BAC) will be assessed, and specimens for urinalysis, serum pregnancy test (if female), urine drug screen, blood chemistry that includes liver function tests (LFT's) and gamma glutamyl transferase (GGT), and complete blood count with differential (CBC w/diff) will be collected by the medical assistant and prepared for same day pick up by LabCorp for analyses. An electrocardiogram (ECG) will be performed. Subjects at risk of clinically significant symptoms of alcohol withdrawal (CIWA≥9) are ineligible and will be referred for detoxification treatment. However, our community dwelling subjects typically do not require medical detoxification, and are advised to reduce their alcohol intake incrementally such that 3 consecutive days of abstinence are achieved prior to their baseline (Week 0) visit. The CIWA is then repeated at Week 0 to further rule out risk of significant withdrawal symptoms during double-blind treatment.

Week 0, Randomization: Subjects complete evaluation for eligibility. Study physicians review all laboratory results, EKG's, vital signs, medical and alcohol histories, use of illicit substances and concomitant treatments, and perform a physical exam to medically clear an individual for admission to study. Medically cleared subjects complete baseline assessments and are randomized to receive a 1-week supply of double-blind drug.

Weeks 1-8: Subjects complete weekly study assessments and counseling described below and in Table 2. Subjects will be seen by the same study personnel and have their visits scheduled at

the same time of day (typically midday) across the study to avoid effects of uncontrolled sources of variance on study measures.

Weeks 9-11: Weekly phone calls are scheduled to maintain contact with the participant and obtain TLFB data.

Week 12: Subjects complete a follow up visit to assess persistence of treatment effects on outcome and safety assessments. *Procedures to maximize the likelihood of participation in the follow-up visit include: scheduled weekly phone calls to maintain contact with subjects, paying for the follow up visit, obtaining multiple back-up addresses and phone numbers, to assist in locating subjects. Patients who are found to have relapsed, or who display other clinically significant symptoms, will be offered referral for appropriate treatment.*

Table 2. Schedule of Procedures for Study Visits

Scheduled Procedures Week	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**12**
Informed consent, demographics, medical and alcohol history, SCID-V	X										
Alcohol Dependence Scale; Fagerstrom Test for Nicotine Dependence; Illicit Drug Use Index; Childhood Trauma Questionnaire; Treatment Goals Checklist	X										
BAC, Vital signs Adverse events, Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[1]	*X*	*X*		*X*	*X*						
Clinical Institute Withdrawal Assessment-Revised (CIWA)	X	X									
CBC w/diff, blood chemistry[2], UA, UDS	X		X			X				X	X
ECG		X									
Plasma cortisol, ACTH		X	X	X		X				X	X
Mifepristone plasma concentration			X								
Alcohol Craving Questionnaire (ACQ); Timeline Follow Back Interview (TLFB); Pittsburg Sleep Quality Index (PSQI); Beck Depression Inventory-II (BDI-II), State-Trait Anxiety Inventory (STAI)	X	X	X	X	X	X	X	X	X	X	X
Neurocognitive Assessment, EtG/EtS		X								X	
Physical exam, saliva and WBC for pharmacogenetics, dispense study drug		X									
Manual-guided counseling	X	X	X	X	X	X	X	X	X	X	

[1] Females of child-bearing potential only, with serum pregnancy at Week -1 and *urine at Week 0, 2 and 3.*

[2] Chemistry panel to include: Glucose, GGT, ALT, AST, alkaline phosphates, bilirubin, uric acid, serum creatinine, BUN, electrolytes, calcium, inorganic phosphorus, total protein and albumin. Only GGT and UDS will be obtained at Weeks 4, 8 and 12.

OUTCOME MEASURES AND ASSESSMENTS

Study Measures to Characterize the Sample:

Alcohol Dependence Scale (ADS)[5] provides a reliable and valid quantitative measure of severity of alcohol dependence (Week -1, self-report, 5 minutes). Ethyl glucuronide/Ethyl sulfate (EtG/EtS): EtG/EtS's presence in urine can reliably detect alcohol metabolites in the urine 80 hours after alcohol consumption and will be used to retrospectively validate abstinence at randomization (Week 0). Childhood Trauma Questionnaire (CTQ) [6] provides a reliable and valid retrospective measure of childhood abuse and neglect (Week -1, self-report, 5 minutes). Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-AR)[7] is a reliable and valid scale to assess severity of alcohol withdrawal symptoms; scores ≥ 9 indicate pharmacological treatment may be warranted (Weeks -1 and 0, Study Physician or Research Nurse, 5 minutes). Fagerstrom Test for Nicotine Dependence (FTND)[8] is a 6-item rating scale of nicotine dependence (Week -1, self-report, 2 minutes). Illicit Drug Use Index[9] is a composite index of frequency and duration of illicit drug use (Week -1, Study Clinician, 7 minutes). Standardized History form will record demography, medical and alcohol history, including age of onset of alcoholism, prior detoxifications, treatments and durations of abstinence, and family history of

alcoholism (Week -1, Study Clinician, 10 minutes). Structured Clinical Interview for the DSM V (SCID V; expected to be released in the winter of *2014* – http://www.scid4.org) will be used to establish the DSM-V categorical diagnosis of current alcohol use disorder of ≥ moderate severity (≥4 symptoms) and to rule out exclusionary Axis I disorders[10] (Week -1, Study Clinician, 30 minutes). Treatment Goals Checklist[11] is a 6-choice checklist subjects use to indicate their treatment goal, e.g., to quit drinking entirely, to quit but realizes a slip is possible, controlled use, etc. (Week -1, self-report, 2 minutes).

Primary Outcome Measure:
Timeline Followback Interview (TLFB)[12] provides quantity and frequency estimates of alcohol consumption for the 90-day period prior to and throughout study. A standard drink is defined as 14g of absolute ethanol content which is equivalent to 12 oz beer, 1.5 oz hard liquor or 5 oz wine.[10] A heavy drinking day is defined as ≥ 4 drinks per day for women and ≥ 5 for men.[10] TLFB drinking data will be supported with weekly drinking diaries as a memory guide, and validated by weekly breathalyzer determination, and monthly GGT values. If unresolved inconsistencies between sources occur, then the most negative outcome will be assumed accurate. (Assessment Coordinator, 10 minutes at Week -1, 5 minutes thereafter).

Secondary Outcome Measures:
Alcohol Craving Questionnaire-Short Form (ACQ-SF)[13] provides an assessment of current drinking urges, difficulty resisting urge and anticipation of positive outcome or relief from negative affective state by drinking (every study visit, 2 minutes). Neurocognitive Functioning The California Verbal Learning Test-II (CVLT-II)[14] and the Verbal Fluency, Trail Making, Color-Word Interference, Design Fluency and Towers tests from the Delis-Kaplan Executive Function System (D-KEFS)[15] and Letter Number Sequences from the Wechsler Adult Intelligence Scale-IV (WAIS-IV)[16] will be used to measure aspects of executive functioning, learning and memory, which are thought to be impacted by the hypothalamic-pituitary-adrenal (HPA) axis and alcohol use and to expand on the mifepristone POC study findings (Weeks 0 and 8, Neuropsychologist, 45 minutes).

Exploratory Measures:
Genetic Indicators of Mifepristone Effects Saliva samples will be collected using Oragene DNA (OG-500) 2 ml saliva kits (DNA Genotek, Inc) and genotyped on the Illumina Human Omni Express Exome beadchip, with analysis limited to selected candidate genes. Differences in response to mifepristone may also be reflected in cellular differences in response to the drug and to cortisol. To study this, blood samples will be collected and sent by same day transport to Dr. Bruce Barshop's Biochemical Genetics Laboratory at UCSD, which is located less than 1 mile from our lab and where peripheral white blood cells (PWBC's) will be extracted and cryopreserved. PWBCs will be isolated by density centrifugation through Nycoprep from whole blood (2 x 8ml) stabilized with acid citrate dextrose and stored at -140°C in tissue culture medium supplemented with 10% DMSO to maintain viability. Dr. Goldman's lab at NIAAA will generate lymphoblastoid cell lines and iPSC lines from cryopreserved PWBCs. Cell lines established from high and low responders to mifepristone will be analyzed for gene expression and methylation differences by RNA-seq and whole genome methylation analysis (Week 0, samples collected by Medical Technician). Cortisol and ACTH Blood is collected, spun, prepared, frozen and stored in Dr. Mason's lab for periodic batch analysis in the Parsons' lab using Enzyme Linked ImmunoSorbent Assay (ELISA) kits to provide quantitative determination of ACTH and cortisol in plasma (Weeks 0, 1, 2, 4, 8 and 12).

Safety Measures:

Breath Alcohol Concentrations (BAC) Subjects are informed prior to the screening visit that if they present with positive BAC's, they will not be paid and will be rescheduled, and have to wait until BAC is normal or will be accompanied home by a friend or taxi driver (beginning of every study visit, Research Nurse, 2 minutes). Adverse Event– Case Report form records each adverse event and onset, duration, severity, relation to study medication and clinical action (every study visit, Research Nurse, 5 minutes). Urine screen for illicit drug use (Weeks -1, 1, 4, 8 *and 12*).

PHARMACOTHERAPY CONDITIONS AND MEDICATIONS DISPENSED

Pharmacotherapy Conditions

Simple randomization procedures will be followed to randomly assign subjects to double-blind treatment with 600 mg/d or 1200 mg/d mifepristone or matched placebo in a 1:1:1 ratio, using a computer-generated randomization code provided by our laboratory biostatistician. Dose titration is not indicated.

Rationale for Dose Selected

The daily doses selected (600 and 1200 mg) are consistent with those used in a recent large scale (N=433) efficacy and safety study of mifepristone for the treatment of psychotic depression[17] which found no significant differences between mifepristone 600mg, 1200 mg and placebo for the percentages of patients with $\geq$ 1 adverse event or with serious adverse events. The most commonly reported side effects were: headache, dizziness and dyspepsia for mifepristone, and nausea and somnolence for placebo.

Rational for Study Duration

Dosing duration (1-week) provides a duration of drug exposure that is compatible with optimal drug effects for resetting the HPA axis and for maintaining subject safety.

Medication Supply

Mifepristone 300 mg tablets and matched placebo tablets will be provided by Corcept Therapeutics.

Medication Compliance

Subjects will receive a 1-week supply of double-blind study medication in a blister card package. Blistercards are consecutively numbered for each participant and prepared according to the randomization code. Neither subject nor study personnel involved in subject care or assessment will know the identity of the randomly assigned study drug. Medication will be identical in appearance and all subjects will be given the same number of double-dummy tablets to preserve the blind. Subjects will be instructed to take the study drug each morning, preferably with food, and to return the blistercard and any unused drug at the next visit (Week 1). A brief scripted phone call will be scheduled on Day 3 of medication to assess medication compliance, any AE's and subject concerns that could prompt study discontinuation. Compliance will be verified with returned medication package and pill count. Mifepristone plasma determinations will be obtained at Week 1 and will be analyzed retrospectively to verify correct medication assignment per the randomization code and ingestion of active medication and will be examined for an association with outcome.

Drug Accountability

All study medication is kept in a locked metal cabinet in the medication preparation room. The research technician labels and prepares the blinded medication in blistercards which are

identified by randomization code, and keeps a record of all medication dispensed and returned throughout the study.

Concomitant Pharmacological Treatments
Subjects will be instructed to not use any herbal, over-the-counter or prescribed medication without consulting the study physician, who will consult with the P.I. to determine the continued eligibility of the subject for participation in the study. All approved medications, e.g., NSAIDS or antihypertensives, will be recorded in the case report form with any changes recorded throughout the study.

Data and Safety Monitoring Plan
Potential risks and benefits for participants
Stringent procedures will be followed to minimize the risk of adverse reactions for participants, including the following:

- The P.I. is experienced and qualified to distinguish a serious adverse event (SAE) from a non-serious adverse event (AE). The P.I. will be responsible for monitoring the conduct of this single-site clinical trial to ensure the safety of participants and the integrity of the data. The P.I. will monitor subject side effect complaints, clinically significant lab abnormalities and findings on physical exam in consultation with study physicians and Dr. Michael Skinner, MD, Pharm D, our independent Medical Safety Monitor, who has over a decade of experience as a Research Physician in the pharmaceutical industry involved in Phase I, II and III clinical trials. Dr. Mason will meet with members of her staff and the Medical Safety Monitor, Dr. Skinner, on a weekly basis to discuss progress of the study, subject enrollment and retention, the clinical status of active subjects and any safety issues as they arise.
- If a SAE occurs, the P.I., in consultation with the chief Study Physician, Farhad Shadan, M.D., and the Independent Medical Safety Monitor, Michael Skinner, M.D., PharmD., will report it to the Scripps-IRB, our NIAAA Project Officer and the US FDA within 48 hours of becoming aware of the event. The written report will capture all safety information including the date of SAE onset, a description of the event, action taken, and whether a relationship between the SAE and drug exists. A summary of all AE's and SAE's that occurred during the previous year will be included in an annual progress report to the FDA, our NIAAA Project Officer and the Scripps-IRB.
- The study physician will be responsible for managing the SAE and/or making referrals for appropriate care, as needed, until the problem has resolved or stabilized with no further change expected, or is clearly unrelated to study medication, or results in death.
- Female subjects who are pregnant and nursing, or not using effective non-hormonal methods of birth control will be excluded from study.
- Participants who are found to require additional treatment at their follow up visit due to significantly increased alcohol consumption or serious psychiatric/medical symptoms will be offered referral for appropriate treatment. Treatment resources include the adjacent Scripps Green Hospital and Clinic where our study physicians have staff privileges and the nearby Scripps MacDonald's Center for Chemical Dependency that provides inpatient and outpatient services. We also provide referral to no-fee and sliding fee facilities.
- SAE's during follow up will be reported to the Scripps-IRB, our NIAAA Project Officer and the FDA within 48 hours of our becoming aware of the event, using the procedures for SAE's described above. All AE's and SAE's during follow up will be compiled in our annual reports to the Scripps-IRB, our NIAAA Project Officer and the FDA.

- Data forms and behavioral ratings for each subject will be formatted into a standardized case report form (CRF) upon which participants will only be identified by an assigned study number. Each CRF will be checked for accuracy and completeness. Data will be entered into a computerized database immediately after each subject completes the study. All data are routinely checked after entry, and distributional statistics are calculated and examined to identify outlying and/or potentially inaccurate data values and missing data. Data entry errors are promptly corrected and missing data verified with the CRF. All data are backed up on a nightly basis. Data will be stored and analyzed using computer facilities at the Laboratory of Clinical Psychopharmacology.
- Confidentiality will be preserved by the following measures: keeping CRF's in locked metal cabinets; CRF's and computerized data will be identified only by numerical code so that neither the subject's name nor initials will be used; the electronic database is password protected and accessible only to designated research personnel; no information will be released to non-study personnel regarding the identity or progress of subjects without written request by the individual subject to the Principal Investigator. A Certificate of Confidentiality will be applied for to protect against involuntary disclosure of the identities of research participants.

Stringent procedures will be followed to minimize the risk of adverse reactions for participants, including the following:

- *Study medication will be administered according to a protocol reviewed for safety by the FDA and conducted under an approved amendment to IND #114497 that we hold for our POC study in AUD.* The medication studied is considered safe when used in accordance with the procedures to be employed in the study.
- Subjects are required to be abstinent ≥ 3 days prior to randomization and some subjects may be at risk for withdrawal. Withdrawal risk is evaluated at the screening visit with the Clinical Institute Withdrawal Assessment-Alcohol Revised (CIWA-AR). Subjects with CIWA scores ≥ 9 are ineligible for randomization and referred for medical detoxification. However, our community dwelling subjects typically do not require medical detoxification, and are advised to reduce their alcohol intake incrementally such that 3 consecutive days of abstinence are achieved prior to their randomization (Week 0) visit. The CIWA-AR is then repeated at Week 0 to further rule out risk of significant withdrawal symptoms during double-blind treatment.
- Subjects will be excluded who are at increased risk through an extensive medical history, complete physical exam, including ECG, complete blood chemistry (CBC), liver function tests (LFT's), urinalysis, and urine toxicology screen for drug of abuse.
- Subjects with any conditions that would expose them to unusual risk (e.g., use of contraindicated medications, suicidal ideation, significant medical disorders *including prolongation of the QT_c interval*, or pregnancy) will be excluded.
- A menstrual history, *2* negative pregnancy tests, and birth control will be documented in women of childbearing potential, to avoid giving study drug to women with unrecognized pregnancies.
- Female subjects of childbearing potential will be informed that mifepristone may interfere with the effectiveness of hormonal contraceptives and will be required to use effective non-hormonal birth control for the 1-week duration of medication and for one month thereafter.
- Subjects will be advised neither to drive a car nor operate complex machinery until they have gained sufficient experience on drug to gauge whether or not it affects their mental and/or motor performance adversely.

- Subjects will be provided with their Study Clinician's business card and a copy of the informed consent that includes 24/7 phone numbers for study physicians.
- Participants will be asked about adverse events and concomitant medications at the scheduled phone call on Day 3 of medication and at each study visit.
- Participants will be instructed about signs and symptoms of adrenal insufficiency and how to contact the study physician in case they occur. The following language will be used in the informed consent:

  Tell your doctor right away if you have any of these symptoms:
  * Unusual tiredness or weakness
  * Nausea and/or vomiting
  * Dizziness when standing
  * Aches and pains
  * Loss of appetite
  * Being depressed
- Female participants will be instructed to report unexplained vaginal bleeding.
- Participants reporting symptoms of adrenal insufficiency or unexplained vaginal bleeding during the 1-week of study medication will be discontinued from study drug and seen promptly for medical evaluation.
- Laboratory evaluations and electrocardiogram will be repeated at the conclusion of medication to identify any abnormalities potentially related to drug exposure. Any clinically significant abnormalities persisting at the end of medication will be followed by the investigator until resolution or until a clinically stable endpoint is reached.
- Participants will be evaluated at the end of study medication for:
  - Evidence of QT prolongation (ECG) and if present will be monitored until resolution
  - Signs and symptoms of adrenal insufficiency. If adrenal insufficiency is suspected, it will be followed-up closely. *We note that no case of adrenal insufficiency or QT prolongation has been reported in studies of similar duration and dosing (also see Darpo et al., 2013).*
- Following 1-week of study drug, subjects will be evaluated weekly through Week 8 and provided with manual-guided counseling, and will complete a follow up visit at Week 12. *Project MATCH found that 4 sessions of Motivational Enhancement Therapy (MET) in 12 weeks was as efficacious as 12 weekly sessions of Cognitive Behavioral Therapy or Twelve Step Facilitation for reducing drinking, leading to the conclusion that multiple types of behavioral interventions of varying intensity are equally helpful in early recovery.[18] The manual-guided counseling we provide is most similar to MET. We chose 8 weeks of counseling and assessment based on the 8-weeks of aftercare and assessment in the 1-week mifepristone psychotic depression studies.[17, 19, 20] Duration of mifepristone effects beyond 8-weeks has not been evaluated in controlled trials, but we will collect outcome data for Weeks 9, 10, and 11 by scheduled phone calls, and conduct an in person assessment at Week 12, in conjunction with referral for additional treatment if warranted.*
- Highly trained and experienced personnel will provide a degree of supervision that might not be available under usual treatment conditions.
- Subject clinical status will be carefully monitored by the P.I. and Michael Skinner, M.D., PharmD, Safety Monitor, during weekly laboratory meetings with all personnel involved in the study *and by quarterly review of blinded tables of safety data, including rates per group of adverse events, serious adverse events and discontinuation due to adverse events, provided by our statistician. Dr. Skinner will advise the PI and study physicians if trends emerge that warrant changes to the study protocol to protect the safety of research*

participants. Dr. Mason will present any safety findings and proposed remedial actions to the Scripps-IRB and our NIAAA Program Officer.

- The clinical ratings and blood tests will be performed by experienced personnel to minimize complications and unnecessary fatigue and distress.
- The study physician will evaluate any subject experiencing clinical deterioration and make a clinically-based decision regarding study discontinuation and referral for appropriate care in consultation with the P.I. Criteria for study termination include: development of intolerable side effects; development or worsening of a physical or psychiatric disorder that requires treatment that would be in violation of the protocol. If a subject is discontinued, every attempt will be made to perform the evaluations specified for the final visit at the time of discontinuation. Reason(s) for premature termination will be documented in the case report form.
- At the follow-up visit, subjects who report significantly increased alcohol consumption or serious psychiatric/medical symptoms will be offered a referral to treatment specific to their needs.
- Importantly, the research group has a well-established record of subject safety in the conduct of analogous clinical trials and subjects will receive careful monitoring of their health status while in the study.

Risks to patient confidentiality will be mitigated by the following measures:

- Keeping the subject case report forms in locked metal file cabinets.
- Case report forms and computerized data will be identified only by numerical code so that neither the subject's name nor initials will be used.
- Access to computerized data will be password protected and available only to authorized study personnel
- No information will be released to non-study personnel regarding the identity or progress of subjects without written request by the individual subject to the P.I. In addition to the aforementioned protection of privacy, a Certificate of Confidentiality will be applied for to protect against involuntary disclosure of the identities of research participants.
- Published results will not reveal the identity of individual participants.
- *Confidentiality of genetic data will be protected including by coding and anonymization of samples and maintaining data under lock and key and limiting access to electronic data to authorized personnel. No genetic results will be communicated to study participants. The following language will be used in the informed consent to advise participants of available protections against discrimination based on genetic information obtained in this study, should confidentiality not be preserved:*
  "A new federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:
    - *Health insurance companies and group health plans may not request your genetic information that we get from this research*
    - *Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premium*
    - *This new Federal Law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance or long-term care insurance"*

Collection and Reporting of AEs and SAEs

The P.I. will be responsible for monitoring the conduct of this single-site human laboratory study to ensure the safety of participants. The P.I. will monitor subject side effect complaints, clinically significant lab abnormalities and findings on physical exam in consultation with study physicians and Dr. Michael Skinner, MD, Pharm D, our independent Medical Safety Monitor, who has over a decade of experience as a Research Physician in the pharmaceutical industry involved in Phase I, II and III clinical trials. If a SAE occurs, the P.I., in consultation with the Study Physician, Farhad Shadan, M.D., and the Independent Clinical Safety Monitor, Michael Skinner, M.D., PharmD., will report it to the IRB, our NIAAA Project Officer and the US FDA within 48 hours of becoming aware of the event. The written report will capture all safety information including the date of SAE onset, a description of the event, action taken, and whether a relationship between the SAE and drug exists. In addition, a summary of all SAEs that occurred during the previous year, and their outcomes, will be included in the annual progress report to the FDA, NIAAA and our IRB. AEs will be documented at each study visit on the Adverse Event case report form by recording of each adverse event and onset, duration, severity, relation to study medication and any clinical action. These will be compiled and reported to the FDA, NIAAA and our IRB in the annual progress report.

Management of SAEs or Other Study Risks

The study physician will be responsible for managing a drug-related SAE and/or making referrals for appropriate care, as needed, until the problem has resolved or stabilized with no further change expected, or results in death.

DSM Plan Administration

Responsibility for data and safety monitoring
The P.I. is responsible for monitoring this single-site human laboratory trial. Dr. Mason will meet with members of her staff and the Study Safety Monitor, Dr. Skinner, on a weekly basis to discuss progress of the study, subject enrollment and retention, the clinical status of active subjects and any safety issues as they arise.

Frequency of DSM
All case report form data will be entered into an electronic file on a daily basis as they are completed. Data safety monitoring will be conducted by the P.I. and Safety Monitor who will review adverse events on a weekly basis. The Safety Monitor will advise the P.I. and the study physicians if any changes in the study plan may be needed to improve subject safety.

Data safety and monitoring reports will be provided annually to the IRB, NIAAA and the FDA. We will use pre-established criteria and procedures for reporting AEs, SAEs, issues potentially arising from conflicts of interest significant protocol changes, and/or cause for trial termination to the IRB, NIAAA and the FDA.

DSM board plan
Per NIAAA guidelines, no DSM board is required for this single-site, early Phase II trial.

References

1. Miller WR. What is relapse? Fifty ways to leave the wagon. *Addiction.* 1996; 91(Suppl:S15-27).
2. Mason BJ, Quello S, Goodell V, Shadan F, Kyle M, Begovic A. Gabapentin treatment for alcohol dependence: a randomized clinical trial. *The Journal of the American Medical Association Internal Medicine.* 2014;174(1):70-77. NIHMSID#533947
3. Maisel NC, Blodgett JC, Wilbourne PL, Humphreys K, Finney JW. Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful? *Addiction.* 2013;108(2):275-293.
4. Fertig J. NIAAA Clinical Investigations Group. Paper presented at Alcohol and Stress: A Framework for Future Treatment Strategies. May 2011; Volterra, Italy.
5. Skinner H, Horn J. *Alcohol Dependence Scale: Users Guide.* Addiction Research Foundation: Toronto;1984.
6. Bernstein DP, Fink L, Handelsman L, Foote J, Lovejoy M, Wenzel K, Sapareto E, Ruggiero J. Initial reliability and validity of a new retrospective measure of child abuse and neglect. *The American Journal of Psychiatry.* 1994;151(8):1132-1136.
7. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *British Journal of Addiction*. 1989;84(11):1353-1357.
8. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *British Journal of Addiction*. 1991;86(9):1119-1127.
9. Clayton RR, HL Voss. Young men and drugs in Manhattan: a causal analysis*. NIDA Research Monograph.* 1981;39:1-187.
10. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition*. Washington, DC: American Psychiatric Press; 2013.
11. Hall SM, Havassy BE, Wasserman DA. Commitment to abstinence and acute stress in relapse to alcohol, opiates, and nicotine. *Journal of Consulting and Clinical Psychology.* 1990;58(2):175–81.
12. Sobell LC, Sobell MB. Timeline follow-back: a technique for assessing self-reported alcohol consumption. In: Litten RZ, Allen JP eds. *Measuring Alcohol Consumption: Psychosocial and Biochemical Methods.* New Jersey: Humana Press, 1992:41-72.
13. Singleton EG, Henningfield JE, Tiffany ST. *Alcohol Craving Questionnaire: ACQ-Now: Background and Administration Manual.* Baltimore, MD: NIDA Addiction Research Center;1994.
14. Delis, D., Kramer, J., Kaplan, E., Ober, B., *California Verbal Learning Test-Second Edition* 2000, San Antonio, TX: The Psychological Corporation.
15. Delis, D., Kramer, J., Kaplan, E., *Manual for the Delis-Kaplan Executive Function System (D-KEFS)* 2001, San Antonio, TX: Psychological Corporation.
16. Wechsler, D. *Wechsler Adult Intelligence Scale – Fourth Edition* 2008, San Antonio, TX: Pearson.
17. Blasey CM, Block TS, Belanoff JK, Roe RL. Efficacy and safety of mifepristone for the treatment of psychotic depression. *Journal of Clinical Psychopharmacology*. 2011;31(4):436-440.
18. Project MATCH Research Group. Matching alcoholism treatments to client heterogeneity: treatment main effects and matching effects on drinking during treatment. *Journal of Studies on Alcohol.* 1998;59(6):631-639.

19. Simpson GM, Sheshai AE, Loza N, Kingsbury SJ, Fayek M, Rady A, Fawzy W. An 8-week open-label trial of a 6-day course of mifepristone for the treatment of psychotic depression. *Journal of Clinical Psychiatry.* 2005;66(5):598-602.
20. Blasey CM, Debattista C, Roe R, Block T, Belanoff JK. A multisite trial of mifepristone for the treatment of psychotic depression: a site-by-treatment interaction. *Contemporary Clinical Trials.* 2009;30(4):284-288.

Request for Modification-Amendment (Version 20.0)

1.0

REQUEST FOR MODIFICATION/AMENDMENT

Attach copies of any revised or new documents in the last section of this form.

Questions that require an answer are marked with a red asterisk.

1.1 Study Information

IRB#

IRB-14-6372

Principal Investigator

Barbara J Mason, Ph.D.

Title of Project:

Glucocortoid Antagonist Treatment of Alcohol Use Disorder

1.2 *Are you requesting approval for subject information?

○ Yes ◉ No

If Yes, indicate the type of information and attach a copy of your tracked/revised documents or new documents associated with this modification.

- ☐ Newsletter
- ☐ Patient diaries
- ☐ Instruction sheets
- ☐ Subject incentive
- ☐ Sponsor gifts
- ☐ Advertisements (including flyers, posters, etc.)
- ☐ Other

If Other, describe.

2.0

2.1 *Are you requesting approval for an increase in the number of subjects to give consent, undergo screening or enroll? (IMPORTANT: If you are increasing enrollment, remember to notify the Contracts/Finance Services department. If your study has any hospital procedures, notify ARCIS to see if it requires further review.)

○ Yes ◉ No

If Yes, indicate :

Current approved enrollment.

Proposed Enrollment

Reason for increasing enrollment:

3.0

3.1 Conflict of Interest Disclosure

As of January 2009, the Scripps IRB has a new policy concerning Conflict of Interest disclosure. *Disclosure forms must be submitted for ALL personnel on all New and Continuing Review studies that are sponsored, funded or have any involvement of an outside institution.* You can access the new policy document and the new Conflict of Interest disclosure form by clicking on the 'Help' link in the upper right of your screen (has a question mark next to it).

To download the disclosure form, click on the 'Scripps IRB Conflict of Interest Form' link. This will open the form in another window. Press the F12 key on your keyboard. This will open a 'Save As' dialog box for you to save the form to your computer.

This form can be completed electronically in Word on your computer. But you will have to print it out in order to get a signature. Fax completed and signed forms to (858) 652-5554. Or you can upload and attach a scanned copy of the completed and signed forms by clicking on the green button below.

Version	Sponsor Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
No Document(s) have been attached to this form.							

3.2 *Are you requesting approval to add new personnel to the study team or delete personnel from the study team? IMPORTANT: If this is an FDA regulated study, you must attach (in the Attachments section at the end of this form) FDA form 1572. The names and sites on this form must match exactly the sites and investigators listed in iRIS for this study.

(•) Yes ( ) No

If Yes, will the new personnel be obtaining informed consent from subjects?

( ) Yes (•) No

If you are requesting to add new personnel, list the names and roles (sub-investigator, coordinator, etc.) of the personnel you wish to add and *describe what their duties will involve* :

Jenny Miller, B.S., will serve as our Medical Assistant. She will obtain vital signs, ECGs, blood, and urine. Ms. Miller will also administer self-report questionnaires to subjects.

If you are requesting to remove personnel, list the names and roles (sub-investigator, coordinator, etc.) of the personnel you wish to remove:

Melissa St. John, Medical Assistant, as she no longer works at TSRI.

4.0

4.1 *If you are requesting additional or other modifications to the protocol, please describe these changes. Also, attach a copy of your tracked/revised documents or new documents associated with this modification.* Describe the proposed modification(s):

We request permission to amend the protocol to remove the 600 mg/day dose of mifepristone from the remainder of the study. We will focus on 1200 mg/day of mifepristone versus placebo. The decision to remove the lower dose of mifepristone is based on literature in psychotic depression showing a plasma: dose response with plasma concentrations above threshold associated with clinical response; plasma concentration above threshold is more likely to be

achieved with 1200 mg/day than with 600 mg/day. To date, both doses have been very well tolerated in our study population and we believe that the 1200 mg dose would provide the most adequate test of our study hypotheses.

4.2 *Will the proposed modifications change the population, purpose or procedures?

○ Yes ◉ No

If yes, outline those changes:

4.3 *Will the requested modification(s) change the risks or benefits to subjects?

○ Yes ◉ No

If Yes, explain:

4.4 *Will the proposed changes require notification to subjects in a revised informed consent form or addendum?

○ Yes ◉ No

5.0

ATTACHMENTS

Attach a copy of any revised or new documents associated with this modification. For updated protocols and IDBs include a summary of the changes and sponsor letter.

(Highlight or track the changes in a revised document).

5.1 Consent Revisions or New Consent Form:

Version	Title	Category	Language	Expiration Date	Consent Outcome	Checked Out	View Document
1.35	Revised Consent. 1.9.18 (Clean /Approved)		English	05/11 /2018	Void		287.71 KB

5.2 Normal Blood Donor Service consent form:

Version	Title	Category	Language	Expiration Date	Consent Outcome	Checked Out	View Document
No Consent(s) have been attached to this form.							

5.3 Attach any other documents associated with this request:

Version	Sponsor Version	Title	Category	Expiration Date	Document Outcome	Checked Out	View Document
1.0		Jenny Miller CITI Certificates	Other				2.11 MB

1.0		Blasely et al 2010	Other				691.02 KB
1.0		Blasely et al 2009	Other				193.75 KB

Scripps

Scripps IRB
4275 Campus Point Court, CPB 200
San Diego, CA 92121

Office for the Protection of Research Subjects

Approval Notice (Modification)

Investigator: Barbara J Mason, Ph.D.

Department: The Scripps Research Institute – Dept. of Neuroscience

Approved Research Sites: The Scripps Research Institute

Project Title: Glucocortoid Antagonist Treatment of Alcohol Use Disorder

Protocol No: IRB-14-6372

Risk Category: Greater than Minimal

Type of Review: Expedited

The modification to the protocol above was reviewed and approved by an IRB Officer. This modification does not extend the expiration date of the protocol's last IRB review.

Current, approved study documents can be downloaded from iMedRIS at https://research.scripps.org

(Revised Informed Consent dated 1-09-18: Removes the 600mg/day dosing arm of the study. Jenny Miller, BS, is added as a medical assistant and Melissa St. John is removed)

Signature applied by Jennifer Holmes on 01/18/2018 06:47:42 PM PST

IRB Officer