Clinical Study Protocol

Study Title: Efficacy and safety of combination EMB-001 as a potential smoking cessation treatment

Sponsor: Embera Neurotherapeutics, Inc.

Protocol Number: ERL-T002

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Medical Monitor and Serious Adverse Contact Information:

[redacted]

Authors:

[redacted]

APPROVAL FOR PROTOCOL ERL-T002

The study will be completed according to regulations and guidelines of Good Clinical Practice. Compliance with this practice provides public assurance that the rights, safety, and well-being of trial subjects are protected consistent with the principles that have their origin in the Declaration of Helsinki.

The signature below constitutes the approval of this protocol and attachments and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and International Council on Harmonisation guidelines.

Sponsor signatory:

Signe[redacted] Date: 07 APR 2022

Name[redacted]

Title: Chief Medical Officer
Embera NeuroTherapeutics, Inc.

INVESTIGATOR AGREEMENT

Confidentiality and Good Clinical Practice Compliance Statement: I, the undersigned, have reviewed this protocol, including appendices, and I will conduct the study as described and will adhere to the ethical and regulatory considerations stated. I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

I understand that all information obtained during the conduct of the study regarding the subjects' states of health will be regarded as confidential. No participants' names may be disclosed. All participants will be identified by assigned numbers on all Case Report Forms, laboratory samples, or source documents forwarded to the sponsor. Clinical information may be reviewed by the sponsor or its agents or regulatory agencies. The US Food and Drug Administration has the right to see subject identifiers. Otherwise, agreement must be obtained from the subject before disclosure of subject identifiers to a third party.

Information taken from the study protocol may not be disseminated or referred to without the express consent of the sponsor.

Signed: _____ Date: _____

Name:
Title:

Address:

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LIST OF ABBREVIATIONS

AE	Adverse event
ACTH	Adrenocorticotropic hormone
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
BE	Benzoylecgonine
BID	Twice daily
BMI	Body Mass Index
BP	Blood pressure
BUN	Blood urea nitrogen
CC	Conventional cigarette
CFR	Code of Federal Regulations
CO	Carbon monoxide
CRF	Case report form
CUD	Cocaine Use Disorder
DHEA-S	Dehydroepiandrosterone-sulfate
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
e.g,	*exempli gratia* (latin abbreviation that means “for example”)
etc.	*et cetera* (latin abbreviation that means “and the rest”)
EOS	End of Study
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
FTND	Fagerström test for nicotine dependence
GCP	Good Clinical Practice
GIRC	Glucocorticoid Insufficiency Review Checklist
HCG	Human chorionic gonadotropin

HIV	Human immunodeficiency virus
HPA	Hypothalamic-pituitary-adrenal
HTTPS	Hypertext Transfer Protocol Secure
ICF	Informed consent form
ICH	International Council for Harmonisation
i.e.	*id est* (Latin abbreviation which means “in other words”)
IM	Intramuscular
IRB	Institutional Review Board
Kg	Kilograms
kg/m^2	Kilograms per square meter
mCEQ	Modified Cigarette Evaluation Questionnaire
MD	Medical Doctor
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDMA	3-4 methylenedioxymethamphetamine (Ecstasy)
mg	Milligram
mIU/ml	Milli international unit per milliliter
mL	Milliliter
mmHg	Millimeters of Mercury
MNWS	Minnesota Nicotine Withdrawal Scale
msec	Millisecond
PA	Physician Assistant
PCP	Phencyclidine
pH	Potential hydrogen (a scale representing relative acidity)
PHQ-9	Patient Health Questionnaire
PK	Pharmacokinetics
ppm	Parts per million

PSS	Perceived stress scale
QTc	Corrected QT interval
RBC	Red blood cell
RCT	Randomized Control Trial
RRC	Rose Research Center, LLC.
SAE	Serious adverse event
Sheehan-STS	Sheehan suicidality tracking scale
SOC 2	Service Organization Control 2
SOP	Standard operating procedure
SSL	Secure Sockets Layer
TSH	Thyroid Stimulating Hormone
THC	Tetrahydrocannabinol
TLS	Transport Layer Security
TUD	Tobacco Use Disorder
UAE	Unexpected Adverse Event
µg/dL	Micrograms per deciliter
W	Wattage
WBC	White blood cell
WI-PREPARE	The Wisconsin Predicting Patients' Relapse Questionnaire

1 INTRODUCTION

1.1 STUDY DESIGN AND PLAN

This open-label study will evaluate EMB-001, comprised of metyrapone, a cortisol synthesis inhibitor marketed as a diagnostic drug for testing hypothalamic-pituitary-adrenal (HPA) axis function, combined with oxazepam, an anxiolytic and sedative/hypnotic benzodiazepine, to help smokers abstain from smoking during a 12-week trial period.

1.2 BACKGROUND

Cigarette smoking remains the leading cause of preventable death in the U.S., and is one of the leading causes of preventable morbidity and mortality (1,2). An estimated 540,000 smokers die each year from smoking-related diseases (3). Existing treatments for tobacco cessation yield, on average, less than 25% long-term abstinence rates, with many of the cessation failures occurring within the first month of abstinence (4). There is an urgent need to develop new therapies for smoking cessation (5). Current pharmacological approaches (e.g., nicotine replacement therapy, bupropion, or varenicline) increase efficacy for smoking cessation, but continue to have poor long-term abstinence rates, with potentially concerning adverse events.

EMB-001 is a proprietary combination of metyrapone and oxazepam. Metyrapone is a cortisol synthesis inhibitor marketed as a diagnostic drug for testing hypothalamic-pituitary-adrenal (HPA) axis function in the US and elsewhere, and for Cushing's syndrome in Europe. Oxazepam is an anxiolytic and sedative/hypnotic benzodiazepine and is commercially available in the US and other countries.

It has been hypothesized that stress can precipitate relapse to addictive behaviors; adequate down-modulation of stress responsivity may mitigate relapse, and therefore aid in the maintenance of abstinence across addiction disorders (6–8). Metyrapone and oxazepam are pharmacologically distinct stress modulators, and when administered individually are effective in an animal model of cocaine use disorder (CUD) (9). However, each drug has potential side effects, including abuse potential for oxazepam (a Schedule IV controlled substance) and adrenal insufficiency for metyrapone. This led to the hypothesis that lower dosages of each might be combined to retain efficacy while reducing side effects.

Results from animal models of cocaine, methamphetamine, and nicotine use disorders all suggest that the combination of metyrapone and oxazepam may be effective in these substance use disorders (9–11).

1.3 EFFICACY OF METYRAPONE AND OXAZEPAM FOR SMOKING CESSATION

Based on data from the previous studies listed above, EMB-001 is being investigated as a treatment for cocaine use disorder (CUD), tobacco use disorder (TUD), and potentially other disorders in the future. In the clinical setting, co-administration of metyrapone and oxazepam has been evaluated in three clinical studies of patients with substance use disorders; one of these studies examined exploratory smoking measures and two studies examined cocaine-related endpoints. These are detailed below.



[redacted]

Finally, with regard to special safety topics, metyrapone is approved for a single day of dosing for testing hypothalamic-pituitary ACTH function. It is approved for chronic administration to normalize the excessive cortisol production in Cushing's syndrome only in Europe. Therefore, administration of metyrapone to patients with normal HPA axis function for longer durations is of particular importance from a safety perspective. In addition to the clinical studies described above, there have been five published papers examining repeated use of metyrapone for the treatment of depression, either alone or in combination with other medications (16–20), and one paper investigating heavy drinkers (21). Two of these studies used some cortisol supplementation: 20 mg hydrocortisone at bedtime (18) and hydrocortisone 7.5 mg QID (19). Doses ranged from 250 mg/day to 4 g/day for 2 to 8 weeks. Only 2 discontinuations due to AEs (dizziness and headache) were reported in these studies. Only 1 study reported any serious adverse events (SAEs), but none of them were deemed to be related to treatment and the rate was numerically greater in the placebo group.(17)

[redacted]

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 STUDY DESIGN AND OBJECTIVE

This an exploratory, single-group, open-label study of up to 50 subjects with the objective to evaluate the effects on smoking cessation and the safety and tolerability of EBM-001 in smokers.

2.2 STUDY ENDPOINTS

2.2.1 Efficacy Endpoints

The primary efficacy endpoint will be the continuous abstinence from smoking over weeks 9-12 as assessed by self-reports of smoking and expired CO breath tests.

The following secondary efficacy endpoints will be assessed:

- Subject reports of smoking status
- Expired CO breath test
- Modified Cigarette Evaluation Questionnaire (mCEQ)
- Minnesota Nicotine Withdrawal Scale (MNWS)
- The Fagerström Test for Nicotine Dependence (FTND)
- Wisconsin Predicting Patients' Relapse Questionnaire (WI-PREPARE)
- 10-Item Perceived Stress Scale (PSS-10)

2.2.2 Safety Endpoints

The following safety endpoints will be assessed:

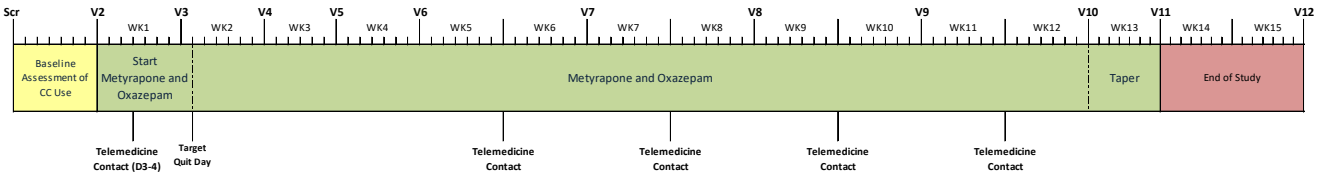
- AEs, including SAEs
- Physical Examinations
- Vital sign measurements
- Laboratory investigations
- ACTH stimulation testing
- ECGs
- Glucocorticoid Insufficiency Review Checklist (GIRC)
- Sheehan-Suicidality Tracking Scale (S-STS)

3 INVESTIGATIONAL PLAN

3.1 STUDY PLAN

After obtaining informed consent, adult smokers will be enrolled into the study. There will be an observational period of at least five days to obtain baseline data on use of combustible cigarettes.

Figure 1: Overall Study Design



3.2 POINT OF ENROLLMENT

Participants will be enrolled after screening once all safety laboratory results have been received and reviewed by the Investigator or qualified designee. Study drugs will be dispensed starting at V2, and at each subsequent visit through Visit 10.

3.3 STUDY AND SESSION DURATIONS

The expected duration of the study, from first participant, first visit, through last participant, last visit will be approximately 18 months. The total duration for a participant will be approximately 16 to 17 weeks.

1. The Screening Session (Visit 1) and Visit 3 will last approximately three hours.
2. The other study sessions will last approximately one hour.

4 PARTICIPANT INVOLVEMENT

4.1 SELECTION OF STUDY POPULATION

Healthy, cigarette smoking adults, age 21-65 years, with no restriction on gender, race and ethnicities, or social-economic status, who have smoked an average of at least 10 commercially available cigarettes per day for the last 12 months will be screened for enrollment in this study.

The study will screen and enroll at multiple centers.

4.1.1 Inclusion Criteria

Each participant must meet all the following inclusion criteria before enrollment:

Table 1: Inclusion Criteria

Inclusion Criteria
1. Has signed the ICF and is able to read and understand the information provided in the ICF.
2. Healthy smokers 21 to 65 years of age (inclusive) at screening.
3. Smokes an average of at least 10 commercially available cigarettes per day for the last 12 months.
4. Has an expired air CO reading of at least 10 ppm at screening.
5. Expressed desire to quit smoking within the next 30 days at screening.
6. Serum Cortisol $\geq$ 3 µg/dL at screening.
7. Willing and able to comply with the requirements of the study.
8. For participants at the Rose Research Center: owns a smart phone with data capabilities compatible with *eResearch*.

4.1.2 Exclusion Criteria

Potential participants who show or report indications of or self-report a diagnosis of conditions listed below may be excluded from the study. If the study physician (or designee) determines through the course of pre-screening, or a physical screen, medical history, physical findings, current medications, ECG, or laboratory findings suggest one of the conditions listed below, or findings reveal other information that may potentially jeopardize the participants' safe participation, then they also may be excluded. For medical conditions that do not appear below, the participant may be enrolled if the study physician (or designee) does not feel that the medical condition would jeopardize safe study participation or data validity.

Table 2: Exclusion Criteria

Exclusion Criteria
1. Is unhealthy or cannot participate in the study for any reason (e.g., medical, psychiatric, and/or social reason) as judged by the Investigator or designated medical staff based on all available assessments from the screening period (e.g., safety laboratory, vital signs, physical examination, ECG, concomitant medications and medical history).
2. PHQ-9 score greater than 9, or a score greater than 0 on item #9 ("Thoughts that you would be better off dead, or of hurting yourself in some way") at screening.
3. Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than two times the upper limit of normal or history of liver disease.
4. Have positive serology test results for human immunodeficiency virus (HIV)-1/HIV-2 antibodies, hepatitis B surface antigen, or hepatitis C antibody.
5. High blood pressure (systolic > 150 mmHg or diastolic >95 mmHg) at screening.
6. Body mass index (BMI) less than 18.5 kg/m^2 or greater than 35.0 kg/m^2.
7. Coronary heart disease, structural cardiac disease, cardiac dysrhythmias, abnormal ECG, syncope, cardiac chest pain, or history of heart attack or heart failure. For males, QTc $\geq$ 450 msec. For females QTc $\geq$ 470 msec (using Fridericia correction formula).
8. Has a history of clinically significant drug/alcohol overdose as judged by the Investigator.
9. Has alcohol breathalyzer > 0% at screening.
10. Has a current DSM-5 opioid or benzodiazepine use disorder of any severity or use of these substances or alcohol in amounts that would increase risk of receiving oxazepam as part of EMB-001 or has received psychotherapy or behavioral treatments potentially impacting symptoms of depression, anxiety, or nicotine withdrawal within 30 days of screening, or during the study.
11. Has history of mental illness that, in the opinion of the Investigator, may interfere with subject safety or data integrity.

Exclusion Criteria
12. Taking antidepressants, CNS or psychoactive medications (e.g., antipsychotics, benzodiazepines, hypnotics) or medications that prolong QT_c within the last 30 days of screen or during study.
13. Use of any of these products in the past 30 days: a. Illegal drugs (or if the urine drug screen is positive for cocaine, THC, amphetamines, methamphetamines, MDMA (Ecstasy), phencyclidine, benzodiazepines, barbiturates, or opiates at screening); b. Experimental (investigational) drugs or biologic; c. Chronic opiate use; d. Biotin products (Vitamin B7 or B8, Vitamin H, or coenzyme R).
14. Use of glucocorticoids including: a. Oral glucocorticoids within 90 days of screen or during study; b. Inhaled glucocorticoids within 90 days of screen or during study; c. Topical glucocorticoids within 7 days of screen or during the study (except when applied to a small body surface area); d. Joint injection within 90 days of screening or during the study.
15. Donation of any blood components within 84 days of screening or during the study or loss of blood ≥ 400 mL within 84 days of screen.
16. Use of smokeless tobacco (chewing tobacco, snuff), cigars (except for cigarillos), pipes, hookah, e-cigarettes, nicotine replacement therapy or other smoking cessation treatments within 14 days of enrollment.
17. Pregnant or nursing (by self-report) or has a positive pregnancy test.
18. Unable to meet requirements of section 4.1.3 (Woman of Childbearing Potential).
19. Known hypersensitivity to or intolerance of oxazepam, metyrapone, or any benzodiazepine, or severe hypersensitivity reaction (e.g., angioedema) to any drug.
20. Treatment with an investigational drug or biologic within the 30 days preceding the first dose of study medication or plans to take another investigational drug or biologic within 30 days of study completion (including the follow-up visit).
21. Enrollment requirements met.

4.1.3 Women of Childbearing Potential

Female subjects must be of non-childbearing potential. Evidence of non-childbearing potential includes documented surgical sterilization (hysterectomy or bilateral oophorectomy) or being postmenopausal. Postmenopausal is defined clinically as 12 months of amenorrhea in a woman over 45 years of age in the absence of other biological or physiological cause. In addition, women must have a documented serum follicle stimulating hormone (FSH) level ≥ 40 mIU/mL during the Screening Period.

Male subjects must agree to use one of the following accepted contraceptive regimens during the study and for at least 90 days after the last dose of the study drug:

a. Abstinence from heterosexual intercourse.
b. Use of condom with spermicide by male study subject.
c. Male sterilization with absence of sperm in the post-vasectomy ejaculate.
d. Female partner using hormonal contraceptives (birth control pills, injectable/implant/insertable hormonal birth control products, transdermal patch).
e. Female partner with intrauterine device (with or without hormones).
f. Female partner of non-childbearing potential.
g. Female partner using diaphragm with spermicide.

Male subjects must agree not to donate sperm during the study and for at least 90 days after the last dose of the investigational product.

Female subjects must agree not to donate eggs during the study and for at least 90 days after the last dose of the investigational product.

4.2 RECRUITMENT STRATEGIES

Rose Research Center

Participants will be selected through IRB approved generic recruitment advertisements which are specifically designed to recruit participants into the volunteer database for future smoking and tobacco use related research at the Rose Research Center. For this database, many of the participants have provided basic smoking history data along with demographic information, which will allow selection of potentially interested participants.

Participants who call in will be screened into the volunteer database, and if they pre-qualify, will be offered the option to prescreen for this protocol.

Participants will be contacted only with IRB approved appropriate materials and information submitted along with this protocol. These documents will include a brief description of the study and information on how to prescreen for participation. Participants will be contacted by phone, email and text message prompting interested participants to prescreen through an electronic screen form.

Segal Trials

Participants will be selected through IRB approved recruitment advertisements which are specifically designed to recruit participants into this study.

4.2.1 Pre-Screening

Pre-screening will be completed prior to Visit 1 for all participants. Participants will be provided with a set of IRB approved questions directly related to the inclusion and exclusion criteria. Based upon the outcome of these questions, potential participants may be scheduled for a screening visit (V1).

4.3 PARTICIPANT RETENTION IN THE STUDY

All candidates who schedule a screening visit (V1) will receive a series of email, text, and telephone reminders; participants are also permitted through these communications to confirm, cancel, or reschedule all their appointments.

4.4 DISCONTINUATION OF PARTICIPANTS FROM STUDY

Discontinued participants will include both participants who withdraw from the study (participant's decision) or participants who are discontinued from the study (following Investigator's decision). A participant can only be discontinued from the study after enrollment. Participants that are not enrolled are considered screen failures.

Participants will be informed that they are free to withdraw from the study at any time. Participants should be questioned for the reason of premature withdrawal from the study, although they are not obliged to disclose it.

Participants discontinued from the study cannot re-enter the study.

If a subject is withdrawn from the study at any time after randomization, the assessments and procedures for the follow-up/early termination visit must be completed. The assessments will be the same as the assessments done at the final study visit (V12). Additional safety assessments may be performed if clinically indicated.

If there are ongoing unstable medical issues at the time of discontinuation, the subject should be followed or referred for appropriate care until stable. If referral is necessary, the subject's consent should be obtained before divulging medical information per standard HIPAA requirements.

Information pertaining to subject withdrawal will be recorded in the electronic case report form (eCRF).

Participants will be discontinued from the study for any of the following reasons:

- Withdrawal of informed consent.
- Any adverse effect or condition that would jeopardize continued safe study participation.
- Pregnancy test is positive.
- Discontinuation is considered to be in the best interest for the participant or for other participants in the study, as judged by the Investigator or designee.
- Subjects with peak stimulated cortisol <18 µg/dL following an ACTH stimulation test, or who are symptomatic for glucocorticoid insufficiency.
- Subjects with adrenal/glucocorticoid crisis
- Active SARS-CoV-2 infection
- Sponsor/FDA decision to stop study.

Subjects may be discontinued from the study for any of the following reasons based on the judgment of the Investigator:

- No-show to appointments and unable to reschedule within the visit window.
- The misuse or abuse of study related equipment.
- Potential loss of the subject's data validity.
- Unwilling or unable to comply with study procedures.
- Enrollment discontinuation.

4.5 ENROLLMENT DISCONTINUATION

Enrollment in the study will be stopped based on the totality of the safety data. All HPA axis related SAEs and cases of clinically significant glucocorticoid/adrenal insufficiency will trigger a review by the Investigator(s) (and/or designee), and the medical monitor.

4.6 REASONS FOR WITHHOLDING THE STUDY MEDICATION

Subjects with a positive finding on the GIRC may be symptomatic for adrenal insufficiency. The Investigator (or designee) will withhold study drug until the ACTH Stimulation Test results are available. Additionally, the Investigator (or designee) may contact the study endocrinologist to discuss an appropriate treatment course for any subject exhibiting signs and symptoms of adrenal insufficiency.

Subjects who have symptoms suggestive of COVID-19 (based upon available local guidelines) will have study medication withheld while the subject is evaluated for active SARS-CoV-19 infection. Due to the limited availability of SARS-CoV-19 testing, a subject will need to be evaluated for SARS-CoV-19 infection outside of this study's procedures. Study subjects who test positive for active infection will be discontinued independent of their symptom status. Subjects whose test result for active infection is negative may restart study drug. Subjects whose SARS-CoV-19 test results are not known or a test is not available will be discontinued unless their symptoms fully resolve within 72 hours of study drug withholding (if symptoms have fully resolved within 72 hours of study drug withholding, study drug may be restarted). Subjects whose study drug is withheld due to symptoms suggestive of COVID-19 will be flagged in the database.

4.7 LOST TO FOLLOW-UP

A reasonable number of attempts to contact the participant (including written correspondence and phone calls) should be made and documented in the source documents. The date of the last contact (e.g., last visit, last phone call) should also be recorded in the source document. When the Investigator (or designee) declares a participant is lost to follow-up, the lost to follow-up date will be recorded and will correspond to the date of the end of study (EOS) of the participant.

4.8 VIOLATION OF INCLUSION/EXCLUSION CRITERIA

Participants who, after signing the ICF, do not meet the inclusion and exclusion criteria will not be enrolled in the study and will be considered screen failures. Re-screening for the study is not permitted.

4.9 PARTICIPANT COMPENSATION

Participants will receive compensation for study participation, as detailed in the site specific Informed Consent.

Participants who decide to withdraw from the study will be paid for the part of the study they have completed.

4.10 SESSION AND RESPONSE WINDOWS

4.10.1 V2 Session Window

Participants may attend V2 up to 30 days post Screening Session (V1).

4.10.2 All other visit Windows

Participants may attend sessions up to three-calendar days pre or post the scheduled visit.

4.10.3 Daily Message Response Window (Rose Research Center ONLY)

The daily message response window will be open until the next message is sent.

5 EMB-001 (METYRAPONE AND OXAZEPAM)

5.1 DESCRIPTION OF EMB-001

EMB-001 is a proprietary combination of metyrapone (a cortisol synthesis inhibitor) and oxazepam (a short to medium acting benzodiazepine).

Metyrapone is approved in the US and elsewhere as a diagnostic drug for the testing of hypothalamic-pituitary ACTH function. It acts by inhibiting 11B-hydroxylase, which converts 11-deoxycortisol to cortisol and deoxy-corticosterone to corticosterone. The dose of metyrapone used as a diagnostic is a single dose of 30 mg/kg (max 3000 mg) or 750 mg every four hours for 6 doses (adults). An average person who weighs approximately 70 kg would receive a single dose of approximately 2100 mg, with no adjustments necessary for renal or hepatic function. Maximum dosing of metyrapone in this study will be 720 mg twice daily and it will be given for a total of 12 weeks, with a one-week taper at 240 mg twice daily.

Oxazepam is a Schedule IV medication that is approved in the U S and elsewhere for anxiety, and for tremulousness, inebriation or for anxiety associated with acute alcohol withdrawal. The FDA approved dosages range from 10 mg to 30 mg, up to four times a day, with no adjustments required for renal or hepatic function. Tapering is normally required after extended therapy. Maximum dosing of oxazepam in this study is 24 mg twice daily, and it will be given for a total of 12 weeks, with a one-week taper at 8 mg twice daily.

EMB-001 will be provided as capsules [redacted]

5.2 DOSING OF EMB-001

EMB-001 will be administered utilizing capsules which contain 240 mg of metyrapone and 8 mg of oxazepam (240/8 mg). Subjects will be prescribed 3 capsules (total of 720 mg metyrapone and 24 mg oxazepam) taken twice daily for a total of 12 weeks. After week 12, or if indicated and possibly for a subject who is being discontinued early, subjects will take one capsule of EMB-001, 240/8 mg, twice a day for one additional week (taper dose). All medication will be dispensed under the supervision of a licensed provider that holds an unrestricted DEA license to dispense Schedule 4 medications.

All doses of study drugs are to be taken with milk, or with yogurt, or after a meal, because food affects absorption.

For subjects experiencing tolerability issues, the Investigator may consult the medical monitor to discuss possible reductions in the dosing regimen by administering fewer than 3 capsules per dose. Any changes to the planned course of treatment of 3 capsules BID, must be properly documented in the CRF.

5.3 STORAGE OF EMB-001

EMB-001 capsules will be stored refrigerated (2 to 8°C; 36 to 46°F) prior to dispensing to subjects.

All capsules will be stored in a secure area. Access to and administration of EMB-001 will be limited to the Investigator and authorized site staff. EMB-001 will be administered only to subjects enrolled in the study and in accordance with the protocol.

Subjects should store EMB-001 capsules either refrigerated or at room temperature (2 to 25°C; 36 to 77°F).

5.4 ACCOUNTABILITY AND COMPLIANCE

5.4.1 Dispensing Product

EMB-001 will be dispensed by the Investigator or designated study staff. Each dispense and collection of the product will be recorded during each study visit (Visit 2 through Visit 11). All study-related drugs will be expected to be returned by the participant at the End-Of-Study (Visit 12 or early termination).

Prior to dispensing, the site will ensure that the product packaging is labelled with the protocol number and unique participant identifiers, date it was dispensed, and the statements “For investigational use only” and “Keep out of reach of children”.

5.4.2 Compliance

Compliance will be ensured by strict distribution of the product, daily messages, and collection of unused products at each study session. This information will be documented in appropriate logs.

6 STUDY PROCEDURES AND ACTIVITIES

Personnel performing study assessments must have appropriate and documented training. An overview of all study assessments is shown in the Schedule of Events. Study personnel will adhere to standard operating procedures (SOPs) for all activities. Appropriate medical advice will be provided to the participant in case of any medical findings requiring health care.

6.1 INFORMED CONSENT AND GUIDANCE

Prior to any study assessments being performed, the participant will be asked to provide their written consent to participate in the study on an informed consent form (ICF). All assessments must start after the time of ICF signature by the participant.

Designated staff will obtain written consent from each participant under the supervision of the Investigator. The person obtaining consent provides the participants with a written document explaining the procedures and risks and will answer any questions. A signed copy of the informed consent form will be given to each participant. Participants are informed that they may withdraw from participation in the study at any time without penalty.

Because of the nature of this study and the number of questionnaires that participants are expected to complete, we do not recruit potential participants who do not read, are blind or who do not read/understand English. We are not equipped to validate alternate versions of our questionnaires. Questionnaires cannot be administered orally by a translator or by technicians to illiterate or blind participants because the data obtained would not be comparable to self-administered questionnaires.

6.2 PATIENT EDUCATION

All subjects will receive enhanced patient education regarding signs/symptoms of glucocorticoid insufficiency. Subjects will be instructed to call the clinical study site with any of the following:

- Signs/symptoms of any illness, in which case the site can conduct an unscheduled study visit and assess them with the GIRC, potentially an ACTH stimulation test, etc.
- Signs/symptoms of glucocorticoid insufficiency.

Each subject will be provided with identification noting the potential risk for adrenal insufficiency as a result of participation in this study and will be instructed to carry the information with them at all times in case of emergency. All subjects will receive a wallet card and a MedicAlert necklace or bracelet, which includes the specific instruction, “In emergency, give hydrocortisone 100 mg IV or IM.” The wallet card will include subject information, contact information for the Investigator, and information about the potential need for glucocorticoids in the settings of shock, surgery, etc.

All subjects with adrenal/glucocorticoid crisis will be discontinued from the study and emergently referred for appropriate assessment, treatment (including hydrocortisone replacement and/or other action as clinically indicated), and regular monitoring until resolution. The medical monitor and study endocrinologist will be available by telephone 24/7 for the sites to consult as needed. Additionally, a board-certified endocrinologist will be available to address medical concerns and for face-to-face follow up for individual subjects who experience endocrinological effects.

6.3 BASELINE ASSESSMENTS

Baseline assessments will be performed according to the Schedule of Events. Descriptions of the baseline assessments can be found in Sections 6.4 and 6.5.

6.4 EFFICACY ASSESSMENTS

Efficacy assessments will be performed according to the Schedule of Events.

6.4.1 Smoking Status

6.4.1.1 *Daily*

Subjects will answer the following questions daily about their smoking status and study medication use:

- Have you smoked any cigarettes today?
  - If yes, how many?
  - And how soon after you woke up did you smoke your first cigarette?
    1-Within 5 Minutes, 2-6 to 30 Minutes, 3-31 to 60 Minutes, 4-After 60 Minutes

At the Rose Research Center, participants will receive a push notification with a prompt to a daily survey to assess the questions. Participants at sites other than Rose Research Center will complete these questions via paper diary.

Rose Research Center will utilize *eResearch*, an IRB approved proprietary mobile electronic application for clinical research studies available in both the iOS and Android app stores. For the purposes of this protocol, the Survey's feature will be utilized to push the daily messages to enrolled participants.

For participants at the Rose Research Center, daily text reminders and/or push notifications may be paired with these daily messages in order to remind participants about the request to complete these assessments.

6.4.1.2 *6 Months*

At the Rose Research Center only, participants who complete the study will be contacted six months after the quit day utilizing *eResearch*, to ascertain their current smoking status.

Participants will receive a push notification with a prompt to a survey to assess the following:

- Have you smoked any cigarettes since your last study visit?
    - If yes, are you currently smoking?

6.4.2 Expired Air CO Breath Test

Carbon Monoxide (CO) in participant's exhaled breath (expressed as ppm) will be measured using a Vitalograph CO Monitor. Participants must have an expired air CO reading at V1 of at least 10 ppm for inclusion into this study. This test will be repeated at each of the laboratory sessions.

6.4.3 Efficacy Questionnaires

The questionnaires will be administered to the participants using paper questionnaires and/or an electronic data collection system.

6.4.3.1 *Modified Cigarette Evaluation Questionnaire (mCEQ)*

The mCEQ assesses the degree to which participants experience the reinforcing effects of smoking. This questionnaire will be administered after enrollment and prior to commencing the investigational products (V2 and V3).

6.4.3.2 *MNWS –Minnesota Nicotine Withdrawal Scale*

The MNWS will be used at all visits after "quit day" (V4 through V12) to assess nicotine withdrawal symptoms including craving and mood effects. Participants will be asked to assess the following seven symptoms (on a 5-point scale ranging from 0 to 4, where 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe):

1. Desire or craving to smoke
2. Anger, irritability, frustration
3. Anxiety or nervousness
4. Difficulty of concentrating
5. Impatience, restlessness
6. Hunger
7. Depression

6.4.3.3 *FTND -- The Fagerström Test for Nicotine Dependence*

The Fagerström Test for Nicotine Dependence is a six-item questionnaire developed by Karl-Olov Fagerström and is used to determine someone's level of nicotine dependence. The scores obtained on the test allow the classification of nicotine dependence in three different levels: mild (0-3 points), moderate (4-6 points), and severe (7 -10 points). This questionnaire will be given at all visits (V1 through V12).

6.4.3.4 *WI-PREPARE – Wisconsin Predicting Patients' Relapse Questionnaire*

The WI-PREPARE is a seven-item questionnaire that is designed to assess a participant's susceptibility to smoking relapse. The questionnaire includes measures of physical dependency, environmental factors and smoking characteristics. Participants will respond to this questionnaire after enrollment and prior to the selected "quit day" (V2 and V3).

6.4.3.5 *10-Item Perceived Stress Scale (PSS-10)*

Self-report questionnaires are the simplest method for obtaining a rapid evaluation of a participant's realized stress levels. The Perceived Stress Scale (PSS) was developed in 1983 as a psychometrically valid measure of perceived stress. A 2011 study reviewed the use of the PSS in a sample of participants who smoked, evaluating three different versions: the PSS-14 (14-item questionnaire), the PSS-10 (10-item questionnaire), and the PSS-4 (4-item questionnaire). The results from this 2011 study confirmed the psychometric properties of all three versions (22). Our study will utilize the PSS-10 during V2, V6, V8, V10, and V12 to evaluate self-reported perceived stress levels.

6.5 Safety, Laboratory and Other Assessments

An overview of all assessments is provided in the Schedule of Events.

Fasting blood samples (nothing but water for 8 hours) and urine samples will be collected by qualified and trained site personnel. Participants will be in a seated or in a supine position during blood collection.

Samples for clinical chemistry, hematology, urinalysis, and serum pregnancy test will be sent to a central laboratory for analysis. Urine pregnancy, urine drug testing, and serum sodium will be performed on-site.

The results of the clinical chemistry, hematology and urinalysis safety panel will not routinely be given to participants. However, if the participant's laboratory results are clinically relevant (including positive pregnancy tests), the medical staff will send the participant a copy of the laboratory results. Participants who are accepted into the study but need medical follow up due to minor abnormalities in laboratory results will also receive a copy of the laboratory results.

6.5.1 Blood Samples

Blood samples will be collected by qualified and trained site personnel. Participants should be in a seated or supine position during blood collection.

Blood samples should be drawn between 6 am and 10 am and, during treatment, pre-dose.

Hematology and Clinical Chemistry will be drawn at screening, every 4 weeks while subjects are taking the Investigational Product, and at the end of the study.

Blood sample for serum sodium will be drawn at each study visit during treatment.

ACTH and cortisol will be drawn at Screening, Baseline, every 4 weeks while subjects are taking investigation product, and at follow-up. Cortisol will also be measured when triggered by a positive finding on the GIRC and as part of an ACTH stimulation test (see Section 6.5.14).

Table 3: Hematology

Hematology
Red blood cell (RBC) count
Hemoglobin
Hematocrit
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration (MCHC)
Red cell distribution width
White blood cell (WBC) count
WBC differential
Platelet count

Table 3: Clinical Chemistry

Clinical Chemistry	
Sodium	Potassium
Chloride	Carbon Dioxide
Blood Urea Nitrogen (BUN)	Creatinine
Glucose	Total Protein
Albumin	Total Bilirubin
Alkaline Phosphatase (AP)	Direct Bilirubin
Aspartate aminotransferase (AST)	Alanine aminotransferase (ALT)
Estimated Glomerular Filtration Rate	Phosphorus (inorganic)
Calcium	FSH (females only, for verification of post-menopausal state, screening only)
Triglycerides	Magnesium
Lactate dehydrogenase	Gamma glutamyl transpeptidase
TSH (screening only)	Uric Acid
Creatine phosphokinase	Cholesterol

6.5.2 Steroid panel

DHEA-S, 11-deoxycortisol, 11-deoxycorticosterone, free and total testosterone (Baseline V2 (Week 0), End of Treatment V11 (Week 13), and End of Study V12 (Week 15).

6.5.3 Serology

Table 5: Serology

Serology
Human immunodeficiency virus (HIV 1/2 antibodies and HIV-1 p24 antigen)
Hepatitis B surface antigen
Hepatitis C virus antibody

6.5.4 Serum Pregnancy Test

A serum qualitative human chorionic gonadotropin (HCG) pregnancy test will only be performed during the screening visit for all female participants.

6.5.5 Urine Samples

Urine samples will be collected for the urine drug screen (at screening session), urine pregnancy test (at all sessions except screening), and safety urinalysis (at screening session and at Visit 16). The urine drug screen and pregnancy tests will be performed by study personnel at the study site. The urine sample collected for urinalysis will be sent to an external laboratory for testing.

A urine drug screen for benzodiazepines will be performed at the end the treatment period to confirm compliance with the study medication.

In case of any positive pregnancy test, the Investigator (or designee) will inform the participant about the risks associated with smoking during pregnancy.

Table 6: Urinalysis Assessments

Urinalysis
pH
Red blood cell traces
Bilirubin
Protein
Glucose
Specific gravity
Nitrite
WBC Esterase

Table 7: Drug Screening

Drug Screening
Cocaine
THC
Amphetamines
Methamphetamines
Ecstasy (MDMA)
Phencyclidine (PCP)
Benzodiazepines
Barbiturates
Opiates

6.5.6 Alcohol Breathalyzer

Alcohol breathalyzer testing will be performed on subjects during the screening visit.

6.5.7 Urine Pregnancy Test

The urine pregnancy tests will be performed by site personnel. Urine pregnancy tests will be performed for all females at all visits except screening.

6.5.8 Medical History and Concomitant Disease

Relevant medical history and concomitant disease will be documented at the screening visit (V1). Medical history is defined as any condition that started and ended prior to V1. A concomitant disease is defined as any condition that started prior to V1 and is still ongoing at V1 (this may also include findings detected during the screening visit).

6.5.9 Prior and Concomitant Medication

All medication taken four weeks prior to the screening visit (V1) and during the study will be documented using a source document. Medications which are stopped before V1 will be considered as prior medication. Medication which was started prior to V1 and which is still being taken by the participant during the study as well as medication that is initiated after V1 will be considered as a concomitant medication. This applies to both prescription and over-the-counter products (e.g., vitamins).

Records of prior and concomitant medications taken include the drug name (preferably both generic and trade name), route of administration, dose/unit, frequency of use, indication, the start and if applicable, the stop date. Any therapy changes (including changes of regimen) during the study will be documented.

The questionnaires will be administered to the participants using paper questionnaires and/or an electronic data collection system. The timing of these questionnaires is outlined in the Schedule of Events.

6.5.10 Demographics

Sex, date of birth, race and ethnicity will be recorded for each participant.

6.5.11 Height and Weight

Height and weight will be measured (and BMI calculated) according to the Schedule of Events.

6.5.12 Physical Examination

A physical examination will be performed according to the Schedule of Events. The physical examination will include review of general appearance, hair and skin, head, eyes, ears, nose and throat, neck, chest, abdomen, dentition, cardiovascular, musculoskeletal and neurological systems. The physical examination is to be conducted by a designated fully trained and licensed medical staff.

Appropriate medical advice will be provided to the participant if any medical findings requiring health care are identified.

6.5.13 AE/SAE Reporting

AEs/SAEs will be assessed using questionnaires and interviews at the indicated time points and spontaneous reporting from the time of ICF signature until the EOS for the participant (see Section 9).

6.5.14 ACTH Stimulation Testing

An ACTH stimulation test will be performed when each subject has reached steady-state concentrations of EMB-001, at Visit 3, when there is the greatest risk of adrenal suppression. It will also be triggered by positive results on the GIRC.

The ACTH stimulation test must be performed early in the morning at trough study drug concentration. After subjects have undergone the Day 3 ACTH stimulation test, they should administer the study drug—which they have brought with them to clinic—upon completion of the ACTH stimulation test.

If a patient should forget to hold the study drug morning dose, and instead takes their morning study dose before coming to the study site, the ACTH stimulation testing must be rescheduled for the next day.

ACTH stimulation test (standard high-dose short cosyntropin [ACTH1-24] test)

- Testing will occur between 6 am and 10 am (approximately 8 am).
- An IV will be placed and kept open with a saline drip.
- 250 µg (0.25 mg) of ACTH (Cortrosyn®*) will be given IV over 1-2 minutes. If an IV cannot be established, Cortrosyn® may be administered IM, usually in the deltoid.
- 30 minutes after Cortrosyn® is administered, blood will be withdrawn from the IV line for laboratory cortisol measurement. 1 mL of blood should be drawn and discarded before drawing the cortisol sample (to avoid dilution by residual saline). If a blood sample cannot be obtained from the IV line, then another site should be used to obtain the sample.
- 60 minutes after Cortrosyn® is administered, blood will be withdrawn from the IV line for laboratory cortisol measurement. 1 mL of blood return should be discarded before drawing the cortisol sample. If a blood sample cannot be obtained from the IV line, then another site should be used to obtain the sample.

Cortisol is drawn in a 2-mL red-top tube (no additives) and processed at room temperature.

Actions to be taken based on ACTH stimulation test results are provided in the Table 8 below.

Table 8: Actions to be Taken Based on ACTH Stimulation Test Results

Cortisol Result	Action(s) to be Taken
Normal (≥18 µg/dL)	The subject can continue on study with no modifications.
Abnormal (<18 µg/dL) or with clinically significant signs/symptoms of adrenal insufficiency.	The subject must be withdrawn from the study. Stimulation tests to be conducted at least 1, 2, and 4 weeks after initial test for these subjects, unless they return to normal levels, and at other time points dependent upon ACTH stimulation test results and evolution of symptoms (if present). These subjects may also be referred for urgent and ongoing endocrinological evaluation during the presence of abnormal ACTH test results and signs/symptoms (if present).

6.5.15 Adrenal/Glucocorticoid Crisis

All subjects with adrenal/glucocorticoid crisis will be treated with hydrocortisone replacement, discontinued from the study, and emergently referred for appropriate assessment and further treatment. A serum cortisol and ACTH level should be drawn prior to administering hydrocortisone if it will not impact the medical intervention for adrenal/glucocorticoid crisis.

6.5.16 Electrocardiogram (ECG)

ECG recording will be performed as per Standard Operating Procedures at screening. A standard 12-lead ECG will be recorded after the participant has rested for at least 5 minutes in a supine position.

The following parameters will be documented: heart rate, PR interval, QRS interval, QT interval, and QTc interval (Fridericia). Every ECG will be assessed as normal, abnormal – not clinically significant, or abnormal – clinically significant.

ECG printouts will be interpreted by a qualified physician or physician assistant. Any printouts of ECGs on thermo-sensitive paper will be photocopied and stapled together for inclusion in the source documents and signed by the qualified physician or physician assistant.

6.5.17 Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature) will be measured in sitting position after the participant has rested for at least 5 minutes and according to the Schedule of Events. Orthostatic vitals will be obtained at all visits (2 minutes from sitting to standing).

6.5.18 Safety and Other Questionnaires

The questionnaires will be administered to the participants using paper questionnaires and/or an electronic data collection system. The questionnaires will be asked according to the Schedule of Events.

6.5.18.1 *Sheehan Suicidality Tracking Scale (Sheehan-STS)*
The Sheehan-STS is a 16-item prospective rating scale that tracks suicidal ideation and behaviors. This questionnaire will be administered at each study session.

6.5.18.2 *PHQ-9 -- The Patient Health Questionnaire*
The Patient Health Questionnaire PHQ-9 for Depression will be used to screen for current (within 2 weeks) depression at Screening. Potential participants who score >9 (or who score >0 on item #9 ("Thoughts that you would be better off dead, or of hurting yourself in some way")) will be excluded from study participation, and, at the discretion of the study physician/physician assistants, referred to appropriate psychiatric treatment.

6.5.18.3 *Prior and Concomitant Medication*
At each visit, participants will report any changes in medication use, including the use of supplements, vitamins, over-the-counter medications, and prescription medications.

6.5.18.4 *Smoking History Questionnaire*
The Smoking History is a questionnaire designed to help assess the participant's current and past smoking habits. This questionnaire will be administered at screening (V1) and will include questions about the number of years participants have smoked combustible cigarettes (CC), the number of CCs per day smoked over the last 12 months, brand of CCs, use of other tobacco products and use of nicotine replacement therapy or other smoking cessation treatments. This questionnaire will also be used to check eligibility criteria.

6.5.18.5 *Registration Form*
This form is an internal questionnaire designed to collect demographic information about participants. It will be administered at screening (V1).

6.5.18.6 *Medical History Form*
The Medical History form is an internal questionnaire designed to help assess the participant's current health and any health history. This questionnaire also includes questions about all medications (include prescription medications, over-the-counter medications or supplements) taken in the past 30 days. It is designed to help assess the participant's current health and health history and is used to help determine eligibility. This form is administered at the initial screening visit (V1).

6.5.18.7 *Review of Systems*
The Review of Systems is an internal questionnaire administered at screening (V1) to help assess the participant's current health and health history by asking about the presence of a list of symptoms.

6.5.18.8 *Employment History*
The Employment History is an internal questionnaire designed to collect information about a participant's social economic status. Participants will be presented this questionnaire after enrollment, at the second visit (V2).

6.5.18.9 *Glucocorticoid Insufficiency Review Checklist*

The GIRC is an extensively edited (by the current Embera Endocrine Advisory Board) version of the previously employed Adrenal Insufficiency Review Checklist used in EMB-001 Studies ERL-001 and ERL-002. As the name change implies, it is focused on surveillance for the key symptoms, signs, and laboratory changes seen during the onset of glucocorticoid insufficiency, which metyrapone could potentially induce (e.g., orthostatic hypotension, hyponatremia, fever, and prostration), as well as for other signs of acute intercurrent illness (nausea, vomiting, diarrhea, etc.) that might reflect glucocorticoid insufficiency or be a risk factor for it.

If there is any positive finding on the GIRC, study medication will be withheld, and an ACTH stimulation test will be performed the following morning. Based on the cortisol results from the ACTH stimulation test, subjects may continue on study (cortisol levels rise to at least 18 µg/dL) or will be discontinued (cortisol levels rise to less than 18 µg/dL).

The GIRC will be assessed at Treatment Visits and during telemedicine contacts with each subject. When assessed via telemedicine contact, only symptom and sign items of the GIRC will be assessed (appetite/gagging, nausea/vomiting/diarrhea/acute illness, unexplained abdominal pain and unexplained persistent fever). GIRC items not assessed during phone contact include orthostatic vital signs and serum sodium. Treatment Visits are scheduled every week for the first four weeks, then every other week until the start of the taper week (Week 13), plus a Treatment Visit at the end of the taper week. Telemedicine contacts are scheduled on Day 3 or 4, then, starting after Week 4, every other week alternating with Treatment Visits until the start of the taper week. Treatment Visits and telemedicine contacts, therefore, allow weekly monitoring.

6.5.18.10 *Medication Compliance*

Participants will complete a daily diary or be queried via daily messages (the latter at Rose Research Center) whether they have been compliant with taking the study specific medications. The diary/messages will commence after the second visit and continue through the End of Study.

Subjects will answer the following question daily about their study medication use:

- Did you take your study drugs this morning? (Only after V2)
- Did you take your study drugs this evening? (Only after V2)

6.6 SCHEDULE OF EVENTS

Table 9: Schedule of Events

Visit Assessments and Procedures	Screening	Study Visits														6-month F/U Contact
		Treatment Period												Taper		
	V1	V2	V3	V4	V5	V6		V7		V8		V9		V10	V11	V12	
Weeks on Study Drug		Wk0	Wk1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Wk9	Wk10	Wk11	Wk12	Wk13	Wk15	
Informed Consent and Guidance	•																
Inclusion/Exclusion Criteria	•	•															
Enrollment		•															
Questionnaires																	
Smoking History Questionnaire	•																
Registration and Demographics	•																
Employment History		•															
Medical History/Review of Systems	•																
Glucocorticoid Insufficiency Review Checklist (GIRC) - Visit Based		•	•	•	•	•		•		•		•		•	•	•	
Glucocorticoid Insufficiency Review Checklist (GIRC) - Telephone Based^		•					•		•		•		•				
10-item Perceived Stress Scale (PSS-10)		•				•				•				•		•	
Wisconsin-Predicting Patient's Relapse (WI-PREPARE)		•	•														
Modified Cigarette Evaluation Questionnaire (mCEQ)		•	•														
The Fagerström Test for Nicotine Dependence (FTND)	•	•	•	•	•	•		•		•		•		•	•	•	
Sheehan Suicidality Tracking Scale		•	•	•	•	•		•		•		•		•	•	•	
Patient Health Questionnaire (PHQ-9)	•																
Minnesota Nicotine Withdrawal Scale (MNWS)				•	•	•		•		•		•		•	•	•	
MINI for opioid or benzodiazepine use disorder	•																
Smoking Status	•	•	•	•	•	•		•		•		•		•	•	•	•
Medication Compliance		•	•	•	•	•		•		•		•		•	•	•	
Blood Samples																	
Hematology and Clinical Chemistry	•					•				•				•		•	
TSH	•																
Serology	•																
ACTH and cortisol levels*	•	•				•				•				•		•	
Steroid Panel		•													•	•	
Sodium Check		•	•	•	•	•		•		•		•		•	•	•	
ACTH Stimulation Testing^^			•														
Serum Pregnancy Test (Females)	•																
Urine Samples																	
Urinalysis Safety Panel	•															•	
Urine Pregnancy Test (Females)		•	•	•	•	•		•		•		•		•	•	•	
Urine Drug Screen	•														•		
Other Assessments																	
Prior and Concomitant Medication Assessment	•	•	•	•	•	•		•		•		•		•	•	•	
Concomitant Disease Assessment		•	•	•	•	•		•		•		•		•	•	•	
CO Breath Test	•	•	•	•	•	•		•		•		•		•	•	•	
Alcohol Breath Test	•																
ECG	•							•								•	
Blood Pressure - Sitting and Standing Positions	•	•	•	•	•	•		•		•		•		•	•	•	
Heart rate	•	•	•	•	•	•		•		•		•		•	•	•	
Temperature	•	•	•	•	•	•		•		•		•		•	•	•	
Respiratory rate	•	•	•	•	•	•		•		•		•		•	•	•	
Weight	•	•	•	•	•	•		•		•		•		•	•	•	
Height	•																
BMI Calculation	•																
Physical Examination	•	•#	•#	•#	•#	•#		•#		•#		•#		•#	•#	•#	
Procedures																	
Brief Smoking Cessation Counseling		•	•	•	•	•		•		•		•		•	•	•	
Patient Handout on Glucocorticoid Insufficiency and MedicAlert		•															
Collect Used/Unused Pill Bottles			•	•	•	•		•		•		•		•	•	•	
Dispense Study Drugs in Pill Bottles		•	•	•	•	•		•		•		•		•			

^The telephone-based GIRC will be performed between visits. This GIRC will include only symptom and sign-based items of the GIRC (ie will not include assessment of orthostatic hypotension or measurement of serum sodium).

Targeted examination as needed

^^Also done if GIRC is positive and the post-positive GIRC morning cortisol is <18 mcg/dL or unavailable

* Cortisol will also be measured when triggered by a positive finding on the GIRC and as part of an ACTH stimulation test

7 RISK / BENEFIT INFORMATION

7.1 POTENTIAL BENEFITS

The participants will be encouraged to quit smoking, which would significantly reduce their risk of smoking-related diseases.

7.2 IMPORTANCE OF KNOWLEDGE TO BE GAINED

By conducting the proposed research, we may develop a new approach to smoking cessation treatment that promises to help a significantly larger proportion of smokers to quit successfully. This would have a major positive impact on public health.

7.3 POTENTIAL RISKS

Continuing to smoke carries significant health risks; if participants are successful at maintaining abstinence (and possibly quit), the participants in the studies will realize a significant improvement in their health and a decrease in their risk of morbidity and mortality associated with smoking combustible cigarettes.

7.3.1 Metyrapone

The most common potential side-effects of metyrapone include nausea, upset stomach, headache, dizziness, and drowsiness. Previous participants from studies of EMB-001 have also noted diarrhea and extremity pain. A complete summary of safety data can be found in Section 7 Guidance for the Investigator of the Investigator Brochure Version 4.0.

7.3.2 Oxazepam

Common side-effects of oxazepam are those normally encountered with any benzodiazepine. This includes drowsiness, blurred vision, headache, forgetfulness, trouble concentrating, constipation, urinary retention, changes in sleep, and decreased libido. A complete summary of safety data can be found in Section 7 Guidance for the Investigator of the Investigator Brochure Version 4.0.

7.3.3 Nicotine Withdrawal

Participants may experience nicotine withdrawal symptoms, including craving, difficulty concentrating, nausea, insomnia, headache, mood disturbance and increased appetite/weight gain.

7.3.4 Blood Draw

The risks associated with venipuncture are minimal and include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, and fainting are also possible, although unlikely.

7.4 CONCOMITANT MEDICATIONS

7.4.1 Prohibited Medications

Subjects are prohibited from taking any medications (including herbal remedies or supplements, etc.) with central nervous system activity within 30 days prior to administration of their first study medication dose and for the duration of the study. Medications which prolong QT interval will also exclude subjects from participation.

Subjects should use caution when using acetaminophen or acetaminophen-containing products. Metyrapone may reduce the metabolism of acetaminophen and increase the risk of acetaminophen toxicity. Subjects should not exceed acetaminophen daily limits (4,000 mg per day from all sources) and preferably use less than the daily total limit for acetaminophen. Subjects should avoid the consumption of alcohol during acetaminophen usage.

Diabetics who are taking insulin or any sulfonylureas will receive written guidance on proper monitoring of blood glucose levels while participating this study (Appendix 19).

Concomitant medications that are used because they are required to treat an AE should be recorded on the appropriate eCRF page and in the medical record. The reason for the use of the concomitant medication should be documented.

7.5 PROTECTION AGAINST RISKS

Participants will be screened medically and monitored throughout the study. Participants will be instructed to report any side effects to study staff, who will communicate these reports immediately to the medical staff. The most appropriate course of action will be determined, which may include options for dose reduction or termination of treatment. Participants whose treatment is terminated will be encouraged to remain in the study for assessment of outcomes and to receive continuing social support for quitting smoking. Participants will, however, be reminded that they have the option to withdraw from the study at any time. Participants will also be given the 24-hour emergency contact number in the event that side effects or adverse events occur between sessions.

7.5.1 Blood Pressure Monitoring

After study enrollment, if blood pressure during laboratory visits is above 160/100, then the following actions will be taken to enhance participant safety:

- If BP >210/120 with symptoms of malignant hypertension, all experimental interventions will be stopped immediately, and the participant will be referred to appropriate medical treatment. Participation may resume, with continued monitoring, if BP is no greater than 150/100.
- If BP > 160/100 for 2 consecutive sessions, the Center will request that the participant have their BP checked weekly by their primary care provider, local pharmacy, or home machine and call us with results. Participants will also be encouraged to see their primary care provider regarding evaluation, treatment, and further monitoring.

8 QUALITY CONTROL AND QUALITY ASSURANCE

8.1 TRAINING OF STAFF

The Investigator or designee will ensure that appropriate training relevant to the study is provided to all staff involved in the study, and that any new information relevant to the performance of this study is forwarded in a timely manner to the staff.

8.2 AUDITS AND INSPECTIONS

Good Clinical Practice regulations require independent inspections of clinical program activities. Such inspections may be performed at any time before, during, and after the study.

Authorized representatives of the Sponsor, regulatory agencies and/or an IRB may perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed and accurately reported, according to the protocol, ICH/GCP guidelines and any applicable regulatory requirements. The Investigator or designee will inform the Sponsor immediately if contacted by a regulatory agency about an inspection at their site.

The Investigator and study staff are responsible for maintaining a comprehensive and accurate filing system of all study-related documentation that will be suitable for inspection at any time by the Sponsor, its authorized representative, and other regulatory agencies.

9 REPORTING OF ADVERSE EVENTS

9.1 DEFINITIONS

9.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered to have a causal relationship with the medicinal product.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication (overdose per se will not be reported as an AE/SAE).

Events that do not meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

9.1.2 Serious Adverse Event

A Serious Adverse Event is any untoward medical occurrence that, at any dose:

- results in death.
- is life-threatening.
- NOTE: The term life-threatening in the definition of serious refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- results in inpatient hospitalization or prolongation of existing hospitalization.
- NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE or SAE.
- results in persistent or significant disability / incapacity.
- NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- results in a congenital anomaly / birth defect.
- requires immediate medical or surgical intervention.
- NOTE: Medical or scientific judgment should be exercised in deciding whether an event should be considered a possible SAE in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of

the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The terms *serious* and *severe* are not synonymous. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. The term *severe* is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as *serious*, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning.

9.1.3 Unexpected Adverse Event (UAE)

An adverse event is considered unexpected if the nature or severity of the event is not consistent with information already known about the study product.

9.1.4 Laboratory and Other Safety Assessment Abnormalities

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline and are considered to be clinically significant in the medical and scientific judgment of the Investigator are to be recorded as AEs or SAEs.

9.2 Collection of Safety Events from Participants

Information recorded when collecting AEs will include: thorough description of the AE, seriousness assessment, start and stop dates (if known), circumstances leading up to the event, clinical elements such as clinical course, specific vital signs and test results that may explain the pathophysiology of the event, as well as alternative explanations to its occurrence, the action taken with the investigational product/procedures due to the AE, the participant`s disposition in the study after the occurrence of the AE and the final outcome of the AE (if known).

Any exacerbation/worsening or increased frequency of an AE or pre-existing condition shall be evaluated and recorded.

AEs should be collected using interviews with the participant.

Whenever a medically meaningful diagnosis is available to comprise a set of reported signs and/or symptoms, it should be preferentially provided as the AE or SAE term, rather than the individual signs and/or symptoms. Otherwise, each one of those signs and/or symptoms should be reported separately as event terms.

All AEs will be recorded in the subjects' charts and will then be transcribed into the eCRFs. A description of the event including its severity, duration, any action taken (e.g., treatment and follow-up tests), and the outcome should be provided, along with the Investigator's assessment of the relationship to the study treatment.

9.2.1 Period of Collection

All existing health conditions identified during the Screening Period will be recorded as concomitant disease and the participant's eligibility will be reviewed. Any AEs which occur during the screening session will be captured by the study site staff and assessed by the Investigator or designee in order to establish relationship or relatedness in respect to study procedures.

Any new, clinically relevant, abnormal finding detected during the study or worsening of a pre-existing condition/concomitant disease will be documented as an AE or an SAE.

Adverse events will be collected from the time of randomization to (and including) the follow-up contact at the end of Week 15 (Visit 12). SAEs will be collected from the time the informed consent is signed to (and including) the follow-up contact at the end of Week 15 (Visit 12).

9.3 Assessment of Adverse Events

9.3.1 Intensity of Adverse Events

For each AE/SAE, the intensity will be graded on a 5-point intensity scale:

- Grade 1 – Mild: The AE is easily tolerated, causes minimal discomfort, and does not interfere with daily activity.
- Grade 2 – Moderate: The AE interferes with daily activity; intervention may be needed
- Grade 3 – Severe: The AE is incapacitating and requires medical intervention.
- Grade 4 – Life-threatening or disabling
- Grade 5 – Death

9.3.2 Relationship to Study Procedures

All AEs and SAEs will be assessed by the Investigator or designee as either 'related' or 'not related'.

9.4 Follow-up of Non-serious and Serious Adverse Events

Non-serious AEs will not be followed-up by the Investigator or designee after the follow-up visit. The Investigator or designee will refer the participant to their Primary Care Provider for follow up of those AE(s) until they have resolved, stabilized (i.e., no worsening of condition), or until an acceptable explanation has been found.

Serious AEs will be followed up by the Investigator or designee, despite their continuation after the end of study, until their resolution, stabilization (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g., a chronic condition).

9.5 Reporting of Safety Events

Prompt reporting of SAEs by the Investigator to Embera is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

Investigator safety reports are prepared for suspected unexpected SAEs according to local regulatory requirements and Embera policy and are forwarded to Investigators, as necessary.

An Investigator who receives an Investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from Embera will file it with the Investigator's Brochure and will notify the IRB, if appropriate, according to local requirements.

9.5.1 Reporting a Serious Adverse Event

Type of Event	Initial Reports		Follow-Up Information	
	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hours	SAE eCRF or SAE form	24 hours	SAE eCRF or SAE form

eCRF: electronic case report form; SAE: serious adverse event

To ensure subject safety, the Investigator must report within 24 hours of identification to Embera any SAEs, regardless of relationship to EMB-001, including those listed in the protocol or the Investigator's Brochure, and must include an assessment of whether there is a reasonable possibility that EMB-001 caused the event. The Investigator must obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide Embera with a complete case history; and inform the IRB of the SAE within their requirements for reporting SAEs. All information relevant to the SAE must be recorded on the appropriate eCRF page. The Investigator is obligated to pursue and obtain information requested by Embera in addition to that information reported on the eCRF.

9.6 Reporting of Safety Events to the IRB

The Investigator will report all serious adverse events relating to the study in an expedited manner to the Institutional Review Board (IRB) office in accordance with the Center's standard operating procedures and GCP reporting guidelines.

9.7 Adverse Event Leading to Discontinuation

If a participant is discontinued from the study because of an AE, the Investigator or designee will follow up until the AE(s) has/have been resolved, stabilized (*i.e.*, no worsening of condition), or until an acceptable explanation has been found.

10 Data Management

10.1 Data Collection Procedures

Trained study personnel will be responsible for capturing the data from the observations, tests, and assessments specified in the protocol and in the source documents.

The Investigator has ultimate responsibility for the collection and reporting of all data related to the clinical study and ensuring that the data are accurate, authentic/original, legible, timely (contemporaneous), enduring, and available when required. Any corrections made to source documents must be clearly recorded, without obscuring the original values and be accompanied by the date of change and identification of the person making the change.

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of participants. Study staff will permit authorized representatives and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

10.2 PROTOCOL DEVIATIONS / NONCOMPLIANCE

Protocol deviations are defined as deviations from the study procedures as defined in this document, whether intentional or unintentional that may affect the participant's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the data.

Noncompliance that meets the above definition must be reported to the IRB according to IRB requirements.

10.3 DATA CAPTURE

All data are collected from participants using paper documents or an electronic data capture system. All applicable data, as specified in the protocol, will be transferred to the database or applicable Case Report Forms.

10.3.1 Screening Data

Data will be collected for recruitment and screening purposes as stated within an Advarra IRB generic recruitment protocol. Unrelated to that recruitment protocol, pre-screening questionnaires will be attached to potential participant's records on whether they qualify or are disqualified for this study. Pre-Screening questionnaires utilized for this study will be permanently attached to that potential volunteer's record unless that information is requested to be removed by the participant.

10.3.2 At-home Data Collection

At the Rose Research Center, short message service (SMS), [redacted], and [redacted] will be used to collect diary study data. Non-Rose Research Center sites will collect this data via a paper diary.

10.3.3 Electronic Case Report Forms

Safety and all smoking behavioral and self-report measures will be captured using Medrio. All information collected within Medrio is compliant with 21 CFR 11 requirements.

10.4 MISSING DATA

Missing data will remain as missing, i.e., no attempt will be made to impute missing values and only observed values will be used in data summarizations and analysis.

10.5 DATA HANDLING

Data of all participants enrolled including screening failures and AE/SAEs during the study (from the time of informed consent to the end of the study of the participant) will be captured in the source documents.

10.6 DATA VALIDATION

Data that are entered will be verified and edit checked to ensure accuracy. Inconsistencies that arise from these checks will be resolved and documented by study staff.

10.7 DATABASE LOCK

Upon completion of the trial, after data entry is complete, the data has been cleaned, and the sponsor has reviewed and provided approval, the database will be locked, and final write access will be removed.

11 PLANNED STATISTICAL METHODS

All data measures (e.g., withdrawal symptoms questionnaires, smoking history, smoking diaries, etc.) are captured initially using paper or an electronic data capture system. Verified data files will be analyzed using Statview or SAS (Statview, SAS Institute, Cary NC). Data will be inspected for outliers and if sufficiently extreme (Chauvenet's criterion, after verifying normality of distributions) will be censored from the data analysis or appropriate transformation or non-parametric analyses will be utilized. Details of these analyses will be presented in the Statistical Analysis Plan.

Summary statistics will be calculated including means, medians and standard deviations for continuous variables (including questionnaire rating scales), and frequency tables will be constructed for categorical outcomes. Confidence intervals will be calculated for abstinence outcomes and other measures of interest.

This is an exploratory study and no formal hypothesis testing will be performed.

The planned sample size, of up to 50 subjects, is supported by a comparison to historical control rates and the evaluation of a meaningful treatment effect in an exploratory study such as this one. In early Phase 2 studies of varenicline in smoking cessation, smoking cessation rates with placebo were 12% and ranged between 40% and 51% for varenicline (23). A sample size of 52 achieves 90% power to detect a difference (active minus historical control rate) of 18% using a two-sided Z-test variance estimate based on the historical control rate and a 5% type I error (alpha). These results assume that the control rate under the null hypothesis is 12%.

11.1 ABSTINENCE OUTCOMES

Abstinence at each time point will be defined by a self-report of no cigarette smoking (not even a puff) since the prior session, confirmed by an expired air CO reading of less than 5 ppm. The primary abstinence outcome will be abstinence during study weeks 9-12. A secondary smoking abstinence outcome will be abstinence during the 6 months after the start of Week 9 in participants who have not relapsed prior to week 12. The main goal of the 6-month follow-up is to assess the persistence of therapeutic effects for those who do achieve abstinence. Evaluation of 6-month follow-up will be limited to data collected at the Rose Research Center.

11.2 SAFETY ANALYSES

Safety variables will be listed and summarized with descriptive statistics as appropriate.

Continuous variables will be summarized by treatment group using descriptive summary statistics (number of observations, mean, SD, median, minimum, and maximum, etc.) as applicable. Categorical values will be summarized by treatment group using frequencies and percentages. In addition, individual data for vital sign measurements, ECG intervals, and laboratory tests will be flagged to detect any potentially clinically important changes for each subject.

12 ETHICS AND REGULATIONS

12.1 IRB APPROVAL

The protocol, informed consent document and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. In addition, any participant recruitment materials must be approved by the IRB prior to being used.

Any change to the protocol must be submitted to the IRB for review and approval before implementation. A protocol change intended to eliminate an apparent immediate hazard to participants may be implemented immediately provided the reviewing IRB are notified within 10 working days.

12.2 INVESTIGATIONAL NEW DRUG APPLICATION

An Investigational New Drug (IND) application has been granted (IND 075799) for the use of EMB-001 as a treatment for CUD. The FDA has agreed that an initial TUD study can be conducted under this IND application.

12.3 GCP AND REGULATORY REQUIREMENTS

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and applicable regulatory requirements. The study must be conducted in accordance with the regulations of the United States Food and Drug Administration (FDA) as described in 21 CFR 50, 56 and 312, applicable laws and the IRB requirements.

12.4 PARTICIPANT INFORMATION AND CONSENT

It is the responsibility of the Investigator to provide each participant with full and adequate verbal and written information using the IRB-approved informed consent form (ICF), including the objective and procedures of the study and the possible risks involved before inclusion in the study. Informed consent must be obtained prior to performing any study-related procedures.

The signed and personally dated original and completed ICF(s) must be kept by the Investigator and filed in the Investigator study file at the site or with the participant's files and a copy must be given to the participant. The participant will be informed that if they discontinue from the study, the data collected until the point of discontinuation will be maintained as part of the study data and the samples collected prior to discontinuation will be analyzed, unless they refuse in writing.

12.5 AMENDMENT TO INFORMED CONSENT FORM

If a protocol amendment is required, an amendment may be required to the ICF. If revision of the ICF is necessary, the Investigator or designee will ensure that the documents have been reviewed and approved by the IRB before participants are informed and sign the amended ICF (including date and time).

13 ADMINISTRATIVE CONSIDERATIONS

13.1 PARTICIPANT CONFIDENTIALITY

All information obtained during the conduct of the study with respect to the participants' state of health will be regarded as confidential. A statement to this effect will be written in the information provided to the participant. An agreement to disclose any such information will be obtained from the participant in writing and signed by the participant, in compliance with all local and national data protection and privacy legislation.

13.2 RECORD RETENTION

All records of data, in any form, will be maintained by investigational sites as required by ICH/GCPs. Essential documents will be retained for at least 15 years after completion of the study. Appropriate measures will be taken to prevent accidental or premature destruction of these documents.

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APPENDIX 4 – RESEARCH PARTICIPANT PAYMENT VERIFICATION FORM

Each site is responsible for subject remuneration consistent with the informed consent.

APPENDIX 6 – SESSION PAYMENT FORM

Each site is responsible for subject remuneration consistent with the informed consent.