A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Study to Evaluate the Safety and Efficacy of EMB-001 in Subjects with Moderate-to-Severe Cocaine Use Disorder

Protocol: ERL-003

Version 5.0, Amendment 4

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Sponsor: Embera NeuroTherapeutics, Inc.

[redacted]

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SPONSOR INFORMATION

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TABLE OF CONTENTS

APPROVAL FOR PROTOCOL ERL-003 2
SPONSOR INFORMATION 3
INVESTIGATOR AGREEMENT 4
LIST OF TABLES 8
LIST OF ABBREVIATIONS 9
1. Introduction 11
2. Objectives 14
2.1 Primary 14
2.2 Secondary 14
3. Study Design 14
3.1 Overall Study Design and Plan 14
3.2 Endpoints 20
3.2.1 Efficacy Endpoints 20
3.2.2 Safety Endpoints 20
3.3 Number of Subjects 20
3.4 Discussion of Design 21
3.5 Dose Rationale 21
3.6 SARS-CoV-2 Contingencies 22
3.6.1 SARS-CoV-2 Mitigation Procedures 22
3.6.2 Limited Access to Investigative Site 22
3.6.3 Insufficient Site Staff Capacity to Monitor Subjects 23
3.6.4 Remote Monitoring of the Study 23
4. Selection and Withdrawal of Subjects 23
4.1 Inclusion Criteria 23
4.2 Exclusion Criteria 25
4.3 Withdrawal Criteria 27
4.3.1 Withdrawal after Randomization 27
4.3.2 Reasons for Withdrawal from the Study Medication 27

4.3.3 Reasons for Withholding the Study Medication 28
5. Study Treatment 29
5.1 Description of Study Drug 29
5.2 Concomitant Medications 30
5.2.1 Prohibited Medications 30
5.2.2 Allowed Medications 30
5.3 Meals and Subject Recommendations 30
5.4 Treatment Compliance 30
5.5 Randomization and Blinding 31
5.5.1 Randomization 31
5.5.2 Blinding 31
6. Study Drug Materials and Management 32
6.1 Investigational Medicinal Product 32
6.2 Investigational Medicinal Product Packaging and Labeling 32
6.3 Investigational Medicinal Product Storage 33
6.3.1 Investigational Medicinal Product Storage at Clinical Sites 33
6.3.2 Investigational Medicinal Product Storage by Subjects 33
6.4 Study Drug Administration 33
6.5 Drug Accountability 33
6.6 Investigational Medicinal Product Handling and Disposal 34
7. Baseline Assessments 34
8. Assessment of Efficacy 35
8.1 Primary Efficacy Parameter 35
8.2 Secondary Efficacy Parameters 35
8.2.1 Weekly Cocaine Non-Use Days 35
8.2.2 Quantitative Measurements of Urine BE 35
8.2.3 Use of Other Drugs 35
8.2.4 Cocaine Craving Questionnaire-Brief 35
8.2.5 Pittsburgh Sleep Quality Index 36

8.2.6 Hospital Anxiety and Depression Scale 36
8.2.7 Sheehan Disability Scale 36
9. Assessment of Safety 36
9.1 Adverse Events and Serious Adverse Events 36
9.1.1 Definition of an Adverse Event 37
9.1.2 Definition of a Serious Adverse Event 38
9.1.3 Pregnancy 39
9.1.4 Laboratory and Other Safety Assessment Abnormalities 39
9.1.5 Time Period and Frequency of Detecting Adverse Events and Serious Adverse Events 39
9.1.6 Procedures for Reporting Adverse Events 40
9.1.7 Regulatory Reporting Requirements for SAEs 42
9.2 Physical Examination 42
9.3 Vital Sign Measurements 42
9.4 Clinical Laboratory Assessments 42
9.4.1 Blood Assessments 42
9.4.2 Serology 44
9.4.3 Steroid Panel 44
9.4.4 Urine Assessments 45
9.4.5 Drug Screening 45
9.4.6 Stored Samples 45
9.5 Adrenal Insufficiency Safety Monitoring Plan 46
9.5.1 ACTH Stimulation Testing 46
9.5.2 Glucocorticoid Insufficiency Review Checklist 48
9.5.3 Patient Education 48
9.6 Electrocardiograms 49
9.7 Emergency Procedures 49
9.8 Sheehan-Suicidality Tracking Scale 50
10. Statistical Assessment 50

10.1 Analysis Populations 50
10.2 Sample-Size Determination 50
10.3 Data Analysis Considerations 51
10.4 Demographic Data and Baseline Characteristics 51
10.4.1 Efficacy Analyses 52
10.4.2 Safety Analyses 52
11. Data Management 52
12. Direct Access to Source Data/Documents 53
12.1 Study Monitoring 53
12.2 Audits and Inspections 53
13. Ethics 54
13.1 Ethical Conduct of the Study 54
13.2 Written Informed Consent 54
13.3 Study and Site Closure 54
14. Data Handling and Recordkeeping 55
14.1 Inspection of Records 55
14.2 Retention of Records 55
15. References 57
16. Appendix 59
16.1 Monitoring for Potential Glucocorticoid or Other Adrenal Insufficiency 59
16.2 Glucocorticoid Insufficiency Review Checklist 61
16.3 Protocol Amendment Summary of Changes 62

LIST OF TABLES

Table 1: Schedule of Assessments 16
Table 2: Reporting Requirements for SAEs 41
Table 3: Actions to be Taken Based on ACTH Stimulation Test Results 47

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE	Adverse Childhood Experiences Questionnaire
ACTH	adrenocorticotropic hormone
AE(s)	adverse event(s)
AI	adrenal insufficiency
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BE	Benzoylecgonine
BID	*bis in die* (twice daily)
BMI	body mass index
BSL	Baseline
BUN	blood urea nitrogen
CBC	complete blood count
CBT	cognitive behavioral therapy
CCQ-B	Cocaine Craving Questionnaire-Brief
CTQ	Childhood Trauma Questionnaire
CUD	cocaine use disorder
DHEA-S	dehydroepiandrosterone sulfate
DSM-5	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECG(s)	electrocardiogram(s)
eCRF	electronic case report form
EMB-001	metyrapone/oxazepam combination
Embera	Embera NeuroTherapeutics, Inc.
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
FU/ET	follow-up/early termination visit
GCP	Good Clinical Practice
GERD	gastrointestinal reflux disease
GIRC	Glucocorticoid Insufficiency Review Checklist

Abbreviation	Definition
HADS	Hospital Anxiety and Depression Scale
HIV	human immunodeficiency virus
HPA	hypothalamic-pituitary-adrenal
IBS	irritable bowel syndrome
IM	Intramuscular
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
mITT	modified intent-to-treat
PK	pharmacokinetic(s)
PP	per protocol
PPE	personal protective equipment
PSQI	Pittsburgh Sleep Quality Index
QTcF	QT interval corrected using Fridericia's formula
RNA	ribonucleic acid
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SD	standard deviation
SDS	Sheehan Disability Scale
Sponsor	Embera NeuroTherapeutics, Inc.
S-SHSQ	Sheehan Suicidality/Homicidality Screening
S-STS	Sheehan-Suicidality Tracking Scale
TLFB	timeline follow-back
TSH	thyroid-stimulating hormone
TUD	tobacco use disorder
ULN	upper limit of normal
URI	upper respiratory infection
US	United States
WBC	white blood cell (count)

1. INTRODUCTION

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 (Hildebrandt 2013; Koob 2008; Koob 2014). Metyrapone and oxazepam are pharmacologically distinct stress modulators, and when administered individually are effective in an animal model of cocaine use disorder (CUD; Goeders 2008). 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 (Goeders 2008; Goeders 2012; Keller 2013).

[redacted]

[redacted]

Clinical Study ECA-001 was an exploratory, double-blind, placebo-controlled study, which randomized 45 treatment-seeking subjects with cocaine dependence as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV; American Psychiatric Association 1994) on a 1:1:1 basis to receive placebo, metyrapone/oxazepam doses of 750 /10 mg BID, or metyrapone/oxazepam doses of 250 /10 mg BID, for 6 weeks (Kablinger 2012). The combination of metyrapone and oxazepam was well tolerated and tended to reduce cocaine craving and cocaine use (as determined by quantitative measurements of the cocaine metabolite benzoylecgonine [BE] in urine), with significant reductions at several time points when controlling for baseline scores.

[redacted]

[redacted]

[redacted]

This is a Phase 2, randomized, double-blind, parallel-group study in approximately 80 adult subjects with moderate-to-severe CUD. The study will compare the efficacy, safety, and tolerability of EMB-001 (720/24 mg BID) with a placebo control. For subjects experiencing tolerability issues, the investigator may consult the medical monitor to discuss possible reductions in the dosing regimen. Any changes to the planned course of treatment of 720/24 mg BID, must be properly documented in the eCRF and subject medical record (as appropriate).

2. OBJECTIVES

2.1 Primary

The primary objective of this study is to evaluate the efficacy of EMB-001 compared with placebo in treating moderate-to-severe CUD.

2.2 Secondary

The secondary objectives of this study are to evaluate the safety and tolerability of EMB-001 in subjects with moderate-to-severe CUD.

3. STUDY DESIGN

3.1 Overall Study Design and Plan

This study is a Phase 2, randomized, double-blind, placebo -controlled, parallel-group, study to compare the safety and efficacy of EMB-001 with a placebo control in approximately 80 subjects with moderate-to-severe CUD. Subjects will receive

investigational medicinal product (IMP) during a 12-week, double-blind Treatment Period (Week 2 through Week 13) and a 1-week, double-blind Taper Period (Week 14).

After undergoing study procedures during the Screening and Baseline Periods, subjects who meet inclusion and exclusion criteria will then be randomized in a 1:1 ratio (n=40/arm) to 1 of the following for the Treatment Period (weeks 2 – 13) on Study Day 8:

- EMB-001 720 mg metyrapone/24 mg oxazepam mg BID, for a total daily dose of 1440 mg metyrapone and 48 mg oxazepam (Active Group)
- Placebo BID, (Placebo Group)

During the Taper Period (week 14), subjects in the Active Group will receive EMB-001 240/8 mg BID; and the Placebo Group will continue to receive placebo. Both groups will change from taking three capsules BID (twice daily) to one capsule BID (twice daily).

There will be a follow-up visit for safety assessments at Week 18.

Safety and other baseline assessments will be performed during the Screening Period (Day -30 to -1), the Baseline Period (Day 1 to 7) and on Study Day 8, and safety and efficacy will be assessed at least twice a week during Treatment and Taper Periods, and at follow-up/early termination. Cocaine use will be evaluated by self-report and by urinary cocaine metabolite benzoylecgonine (BE), assessed twice weekly by study personnel using samples collected at the study site. Several methods will be employed to optimize and confirm adherence to IMP and protocol activities, including a medication adherence monitoring and optimization service/methodology. All subjects will receive a referral for cognitive behavior therapy (CBT) at the final study visit or at early termination.

The Screening and Baseline Periods are up to 37 days prior to initiation of treatment (Days -30 to 7). The total duration of the study will be up to 22 weeks.

The measurements and evaluations that will be conducted are presented in the schedule of assessments (Table 1).

Table 1: Schedule of Assessments

Study Period	**Screening[a]**	**Baseline**	**Treatment**																**Taper**	**FU/ET**
Study Week	**-4 to -1**	**1**	**2**	**2 and 3**		**4**		**5 and 6**		**7**		**8 and 9**		**10**		**11 and 12**		**13**		**14**	**18/ET**
Study Day	**-30 to -1**	**1, 4**	**8**	**11, 18**	**14, 21**	**25**	**28**	**32, 39**	**35, 42**	**46**	**49**	**53, 60**	**56, 63**	**67**	**70**	**74, 81**	**77, 84**	**88**	**91**	**98**	**126/ET**
Visit window (days)				±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±2	±4
Procedure																					
Written informed consent	X																				
Inclusion/exclusion criteria	X																				
Demographics, medical history, and medication history	X																				
Physical examination[b]	X																				X
FSH (females only)	X																				
TSH	X																				
Serum or urine pregnancy (females only)[n]	X								X				X						X		X
Clinical laboratory sampling[c]	X		X				X				X				X				X		X

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Study Period	**Screening[a]**	**Baseline**	**Treatment**																**Taper**	**FU/ET**
Study Week	**-4 to -1**	**1**	**2**	**2 and 3**		**4**		**5 and 6**		**7**		**8 and 9**		**10**		**11 and 12**		**13**		**14**	**18/ET**
Study Day	**-30 to -1**	**1, 4**	**8**	**11, 18**	**14, 21**	**25**	**28**	**32, 39**	**35, 42**	**46**	**49**	**53, 60**	**56, 63**	**67**	**70**	**74, 81**	**77, 84**	**88**	**91**	**98**	**126/ET**
Serology[o]	X																				
Steroid panel[k]			X																X		X
Urinalysis (with microscopy)	X		X																X		X
MINI	X																				
S-SHSQ	X[l]																				
Drug screen[d]	X	X	X		X		X		X		X		X		X		X		X	X	X
GIRC[e]	X		X		X		X		X		X		X		X		X		X	X	X
GIRC symptoms only[m]*				X		X		X		X		X		X		X		X			
ACTH stimulation testing				X[f]																	
Vital signs[g]	X	X	X		X		X		X		X		X		X		X		X	X	X
12-lead ECG	X		X								X								X		X
S-STS	X	X	X		X		X		X		X		X		X		X		X	X	X
Randomization			X[h]																		
AEs*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications*		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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Study Period	Screening[a]	Baseline	Treatment																Taper	FU/ET
Study Week	**-4 to -1**	**1**	**2**	**2 and 3**		**4**		**5 and 6**		**7**		**8 and 9**		**10**		**11 and 12**		**13**		**14**	**18/ET**
Study Day	**-30 to -1**	**1, 4**	**8**	**11, 18**	**14, 21**	**25**	**28**	**32, 39**	**35, 42**	**46**	**49**	**53, 60**	**56, 63**	**67**	**70**	**74, 81**	**77, 84**	**88**	**91**	**98**	**126/ET**
Urine BE	X[h]	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ACE			X																		
CTQ			X																		
CCQ-B			X		X		X		X		X		X		X		X		X	X	X
HADS			X		X		X		X		X		X		X		X		X	X	X
SDS			X				X				X				X				X		X
PSQI			X				X					X[i]							X		X
TLFB[j]*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medication adherence*			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Referral for CBT																					X

ACE: Adverse Childhood Experiences Questionnaire; ACTH: adrenocorticotropic hormone; AE: adverse event(s); BE: benzoylecgonine; BMI: body mass index; BSL: baseline; CBC: complete blood count; CBT: cognitive behavioral therapy; CCQ-B: Cocaine Craving Questionnaire-Brief; CTQ: Childhood Trauma Questionnaire; DHEA-S: dehydroepiandrosterone sulfate; ECG: electrocardiogram; FSH: follicle stimulating hormone; FU/ET: follow-up/early termination; GIRC: Glucocorticoid Insufficiency Review Checklist; HADS: Hospital Anxiety and Depression Scale; IMP: investigational medicinal product; MINI: Mini International Neuropsychiatric Interview; PSQI: Pittsburgh Sleep Quality Index; SDS: Sheehan Disability Scale; S-SHSQ: Sheehan Suicidality/Homicidality Screening Questions; S-STS: Sheehan-Suicidality Tracking Scale; TLFB: timeline follow-back; TSH: thyroid stimulating hormone

[a] Screening assessments may be performed during multiple site visits, as needed, during the Screening Period.

[b] To include height, weight, and BMI.

[c] Sample for CBC and chemistry evaluations, including cortisol and ACTH. Perform between 6 to 10 am and sample drawn pre-dose.

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[d] Test for alcohol, opiates, benzodiazepines, barbiturates, cocaine, amphetamine, methamphetamine, and phencyclidine. Benzodiazepine and cocaine results following initiation of dosing on Day 8 will be blinded. During Screening, a retest may be allowed at the discretion of the Investigator in consultation with the Medical Monitor.

[e] To include collection of blood sample for serum sodium analysis and measurement of orthostatic blood pressure. Any positive finding on the GIRC will trigger a serological evaluation of glucocorticoid insufficiency (see Appendix 16.1).

[f] Performed once on Day 11 during Week 2. Any positive finding on the GIRC will trigger a STAT local serum morning cortisol (if STAT test available) and then an ACTH stimulation test if this STAT cortisol result is <18 mcg/L (or if STAT test is unavailable). All ACTH stimulation tests must be administered in the early morning and at trough (pre-dose) of medication administration; if the subject has taken medication that morning it must be postponed to the next day. Actions to be taken based on results of the ACTH stimulation test are described in Table 3.

[g] To include blood pressure, pulse rate, respiratory rate, and temperature. For scheduled visits, values for HR, SBP and DBP from the GIRC orthostatic assessment will be used for the vital signs values.

[h] To be randomized, subject must have 1 positive BE result during the Screening Period.

[i] Day 60 only.

[j] TLFB will be administered by the site. Subjects will be asked to retrospectively estimate their cocaine use. During Screening, subjects will recall use for the 28 days prior to the date of the interview. At all subsequent visits, subjects will be asked to recall use since their last Visit.

[k] Steroid panel: DHEA-S, 11-deoxycortisol, 11-deoxycorticosterone, and free and total testosterone

l Only the three homicidality questions of the S-SHSQ will be used. If a subject responds YES to any of these questions, additional evaluation of the subject will be done using the homicidality module of the MINI.

[m] Symptom items of the GIRC include: significant loss of appetite, severe nausea/vomiting/diarrhea, unexplained abdominal pain and report of unexplained persistent fever.

[n] Serum pregnancy test at Screening; urine pregnancy test on Days 35, 63, 91 and 126/ET.

[o] HCV confirmatory testing (HCV RNA) will require a new blood sample

*These procedures will be performed by telemedicine, such as phone, text, or video chat, on Days 11, 18, 25, 32, 39, 46, 53, 60, 67, 74, 81 and 88.

3.2 Endpoints

3.2.1 Efficacy Endpoints

The primary endpoint will be the continuous abstinence from cocaine use over the final 3 weeks (Week 11 to Week 13) of the Treatment Period as assessed by self-reports using the timeline follow-back (TLFB) interview and confirmed by urine BE.

The following secondary efficacy endpoints will be assessed:

- Weekly cocaine non-use days by self-report
- Quantitative measurements of urine BE
- Use of other drugs assessed in drug screens
- Cocaine Craving Questionnaire-Brief (CCQ-B)
- Pittsburgh Sleep Quality Index (PSQI)
- Hospital Anxiety and Depression Scale (HADS)
- Sheehan Disability Scale (SDS)

3.2.2 Safety Endpoints

The following safety endpoints will be assessed:

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

3.3 Number of Subjects

A total of approximately 80 subjects is planned.

3.4 Discussion of Design

An active group and placebo control group are considered appropriate to adequately assess efficacy. It is also considered acceptable regarding safety, given the following:

1. Both drugs included in EMB-001 have been previously approved by FDA for (at least) single-day dosing at maximum doses much higher than those tested in this study
2. Both have been studied at the highest dose proposed for this study with repeated dosing in studies ERL-001 and ERL-002
3. There are 7 other published studies (two studies with some cortisol supplementation) in which metyrapone has been given safely at doses of 250 to 4000 mg/day for 2 to 8 weeks

3.5 Dose Rationale

Based on the results of Studies ERL-001 and ERL-002 and other published studies, the planned dose is considered to be well tolerated in this population. [redacted]. Since oxazepam has been previously approved and used for decades in chronic dosing at doses up to 120 mg/day, it was deemed prudent to assess moderately higher doses of oxazepam here than were tested in Study ECA-001, which used oxazepam doses of 20 mg/day (Kablinger 2012). Conversely, there are less data on repeated dosing of metyrapone in subjects with normal HPA axes, at higher doses than proposed for assessment in the Embera Phase 2 program, so the metyrapone dose has been capped at 1440 mg/day. Therefore, the metyrapone/oxazepam doses planned in this study are EMB-001 at 720/24 mg BID, and placebo.

For subjects experiencing tolerability issues, the investigator must consult the medical monitor to discuss possible reductions in the dosing regimen. Any changes to the planned course of treatment of 720/24 mg BID, must be properly documented in the eCRF and subject medical record (as appropriate).

3.6 SARS-CoV-2 Contingencies

3.6.1 SARS-CoV-2 Mitigation Procedures

Investigative sites will follow their institutional guidelines for SARS-CoV-2 mitigation.

3.6.2 Limited Access to Investigative Site

If investigative site staff lose or have a diminished capacity to monitor subjects at the investigative site (for example, because subjects are not permitted to enter the site facility), subjects who have completed Day 11 may continue in the study with remote assessments. For these subjects, planned study procedures will continue to be followed, but may be completed through remote assessments. Remote assessments will be completed in person by a visiting nurse or site personnel (at the subject's residence or at the subject's designated approved location such as a private office) and by site staff using available telemedicine systems. Additional local contingencies, such as reduced direct contact through increased personal protective equipment (PPE) and/or physical distancing that allow for subjects to continue to return to the investigative site are allowed.

Remote assessments can be performed for all study procedures with the exception of the ACTH stimulation test. For this reason, only subjects who have completed the steady state ACTH stimulation test on Day 11 will be eligible to convert to remote assessments. Subjects who need remote assessments but have not yet completed Day 11 study procedures will be discontinued. In addition, subjects who have a finding on the GIRC and have an abnormal next morning cortisol result will be discontinued from the study (because a remote ACTH stimulation test will not be possible).

An investigative site may deliver study drug to a subject who has completed Day 11 procedures but cannot be assessed at the investigative site due to diminished site capacity issues. Sites must use a documented transport procedure, approved in advance by the sponsor. The transport procedure must assure chain of custody of the study drug. When delivering to a subject, study drug may be transported at ambient conditions (as happens when subjects transport their own study drug to and from the investigative site).

No new subjects will be screened or randomized at a site that needs to monitor subjects remotely until the site is once again able to adequately conduct assessments at the investigative site.

3.6.3 Insufficient Site Staff Capacity to Monitor Subjects

If investigative site staff do not have sufficient capacity to monitor subjects either remotely or at the site, study activities at this study center will be suspended. Any subject receiving study drug in this context will be instructed to discontinue study medication immediately. All efforts will be made to perform study subject discontinuation procedures, including study medication taper.

3.6.4 Remote Monitoring of the Study

Embera recognizes that during the SARS-CoV-2 public health emergency, traditional on-site monitoring, as described in Section 12.1, might be not be possible for reasons such as (1) sites may not be able to accommodate monitoring visits (e.g., due to staffing limitations or site closures) or (2) monitors may not be able to travel to trial sites. In such circumstances, remote review of source documentation, as described in the study monitoring plan and agreed with investigative sites will be allowed.

Remote monitoring activities, including remote review of source documents, should be documented in the same level of detail as on-site monitoring activities. Any resulting actions identified from the remote source document review should be consistent with procedures and processes described in the study monitoring plan.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

Subjects who meet all the following criteria will be included in the study:

1. Provide written informed consent prior to any study procedures
2. Are 18 to 65 years of age and able, in the opinion of the investigator, to understand written and spoken English or Spanish
3. Have body mass index (BMI) >18.5 and <35 kg/m^2

4. Have DSM-5 diagnosis of moderate-to-severe CUD per the Mini International Neuropsychiatric Interview (MINI) and

    a. Have used cocaine 9 days or more in the prior 28 days per a TLFB performed during Screening

    b. Have a positive urine test for cocaine (urine BE ≥150 ng/mL), as assessed by BE, during the Screening Period

5. Are seeking treatment for CUD. Subjects with past rehabilitation attempts are eligible if the most recent rehabilitation attempt ended at least 30 days prior to Screening

6. Are able to take oral medications and are willing to adhere to medication regimen during the study, including being able and willing to use a medication adherence monitoring and optimization service/methodology

7. Provide evidence of a stable living residence in the last 2 months prior to randomization, have reasonable transportation arrangements to the study site, and have no plans to move within the next 18 weeks

8. 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 and a negative pregnancy test during the Screening Period

9. 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

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

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

4.2 Exclusion Criteria

Subjects who meet any of the following criteria at Screening will not be enrolled in the study:

1. Any significant current medical conditions (neurological, cardiovascular, endocrine, thyroid, renal, liver), seizures, delirium or hallucinations, or other unstable medical conditions that would, in the opinion of the investigator or designee, put the subject at significantly greater clinical risk

2. Known hypersensitivity to or intolerance of oxazepam, metyrapone, or any benzodiazepine, or severe hypersensitivity reaction (e.g., angioedema) to any drug

3. Have a heightened likelihood of having adrenal insufficiency in the investigator's or designees' opinion. Subjects with a screening cortisol value of < 3 mcg/dL have the biochemical diagnosis of adrenal insufficiency (AI) and are at highest risk to become symptomatic/develop adrenal crisis during prolonged metyrapone use and should be excluded

4. Required treatment with oral, inhaled or intraarticular glucocorticoids in the last 3 months and/or topical glucocorticoids administered as a cream in the last week (except when applied to a small body surface area)

5. Have presence of clinically significant finding on medical history, physical examination, clinical laboratory tests, vital sign measurements, ECGs (including clinically significant arrhythmia, or QT prolongation (as defined as QT interval corrected by the Fridericia correction formula [QTcF] >450 msec for male subjects and >470 msec for female subjects) that contraindicate participation in the study

6. Have donated or lost ≥400 mL of blood or plasma in the 12 weeks prior to the baseline visit. Donation of blood or plasma is prohibited during the study (through the follow-up visit)

7. Have current court-mandated treatment requirement for a substance-use disorder

8. Current DSM-5 moderate-to-severe substance use disorder, other than CUD, tobacco or caffeine

9. 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, in the opinion of the investigator or designee

10. Have a history of clinically serious overdose on drugs and/or alcohol

11. Have a positive test result at Screening for opioids, benzodiazepines, phencyclidine, barbiturates, amphetamines, or alcohol

12. 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)

13. Currently suicidal or homicidal

14. In the opinion of the investigator, evidence of current severe mental illness that may interfere with subject safety or data integrity

15. Lifetime history of schizophrenia or bipolar disorder or current psychotic disorder

16. Current use of any medications (including herbal remedies or supplements, etc.) with central nervous system activity in the last 30 days. Selective serotonin reuptake inhibitor/serotonin–norepinephrine reuptake inhibitor antidepressants are allowed if they have been administered at a stable dose for at least 3 months

17. Have a history of any illness, condition, or use of medications that, in the opinion of the investigator or designee, might confound the results of the study or pose additional risk in administering the investigational agents to the subject or preclude successful completion of the study

18. Have positive serology test results at screening for human immunodeficiency virus (HIV)-1/HIV-2 antibodies, hepatitis B surface antigen, or hepatitis C antibody. If a subject is hepatitis C antibody positive and RNA negative OR their liver function tests are <2 times the upper limit of normal (ULN) range, and they have been treated for hepatitis C, the investigator may include the subject with the approval of the Medical Monitor

4.3 Withdrawal Criteria

4.3.1 Withdrawal after Randomization

If a subject is withdrawn from study medication at any time after randomization, the assessments and procedures for the follow-up/early termination visit (Table 1) must be completed. Additional safety assessments may be performed if clinically indicated. Information pertaining to subject withdrawal will be recorded in the electronic case report form (eCRF).

Subjects withdrawn from the study after randomization may be replaced after consultation and agreement with the Sponsor.

4.3.2 Reasons for Withdrawal from the Study Medication

Subjects with peak stimulated cortisol <12 µg/dL following an ACTH stimulation test, or who are symptomatic for glucocorticoid insufficiency, will be discontinued from the study.

Subjects who are known to have active SARS-CoV-2 infection through testing (e.g. via nucleic acid amplification test or other future FDA-approved test) during the study will be discontinued from the study.

Every effort should be made to keep subjects in the study. However, a subject may be discontinued prior to completion of the study for the following reasons:

- AE
- Protocol deviation
- Investigator discretion
- Subject withdrew consent
- Active SARS-CoV-2 infection
- Sponsor/FDA decision to stop study

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 Sponsor clinical staff and endocrinology consultants.

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.

4.3.3 Reasons for Withholding the Study Medication

Subjects with a positive finding on the GIRC may be symptomatic for adrenal insufficiency and investigators should withhold study drug until the ACTH Stimulation test (or STAT cortisol test, if available, and normal) results are available. Additionally, investigators may contact the covering endocrinologist to discuss appropriate treatment course for any patient 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.

5. STUDY TREATMENT

Subjects will receive twice-daily dosing from Week 2 through the Week 13 visit. Study drug will be tapered during the Taper Period (Week 14) or as indicated in the context of an early discontinuation.

The Screening and Baseline Periods are up to 37 days prior to initiation of treatment. The follow-up visit is planned for Day 126. Subjects who complete the study will be on study for up to 22 weeks.

5.1 Description of Study Drug

EMB-001 is provided as capsules that contain metyrapone and [redacted]

At each EMB-001 720 mg metyrapone/24 mg oxazepam dose, subjects will receive 3 capsules, each of which will contain 240 mg metyrapone/8 mg of oxazepam.

At each EMB-001 240 mg metyrapone/8 mg oxazepam dose (taper Week 14), subjects will receive 1 capsule, which will contain 240 mg metyrapone/8 mg of oxazepam.

Placebo capsules contain placebo [redacted]

At each placebo dose, subjects will receive 3 capsules, each of which will contain placebo. At each placebo dose during taper Week 14, subjects will receive 1 capsule, which will contain placebo.

5.2 Concomitant Medications

5.2.1 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, except as specified under the allowed medications (Section 5.2.2).

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.

5.2.2 Allowed Medications

Selective serotonin reuptake inhibitor/serotonin–norepinephrine reuptake inhibitor antidepressants will be allowed if they have been at a stable dose for at least 3 months prior to screening and remain at that dose through the study.

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.

5.3 Meals and Subject Recommendations

All doses of IMP are to be taken with milk, with yogurt, or after a meal, to minimize nausea and vomiting, which can lead to impaired absorption.

Subjects will be encouraged not to take recreational drugs or consume alcohol during the study.

5.4 Treatment Compliance

This study will employ a medication adherence monitoring and optimization service/methodology. Details on use of the service/methodology will be provided to the sites in a manual.

5.5 Randomization and Blinding

5.5.1 Randomization

A total of approximately 80 subjects will be randomized to treatment, 40 subjects to each of the following treatment groups:

- Placebo BID
- EMB-001 720/24 mg BID, for a total daily dose of 1440/48 mg

Randomization will be stratified by cocaine use at screening, in order to ensure adequate representation of subjects with different cocaine use levels. Enrollment for less frequent use (<15 days in the prior 28 days) will be capped at around 30%. Once around 30% of less-frequent use have been randomized, subsequent enrollment will only be allowed for subjects in the relatively more frequent use category.

The randomization schedule will be generated by [redacted] prior to the start of the study, using validated software.

Although 10% to 20% of the subject population is expected to be female, balanced randomization with respect to gender may not be achieved, especially considering the restriction of enrollment to women of non-childbearing potential.

5.5.2 Blinding

The sponsor will provide the investigator with sufficient supplies of blinded IMP to complete the study. To maintain the study blind, placebo capsules are identical in appearance to capsules of the active medication. Administration schedules for active medication and placebo capsules are identical. The blinded IMPs that will be provided for each subject are EMB-001 or matching placebo capsules packaged in bottles.

Subject randomization codes and treatment designation (EMB-001 or placebo) will be provided to study personnel by [redacted] and must be maintained by study personnel in a manner to prevent disclosure of the subjects' treatment allocations to clinical personnel.

Breaking of the blind is expressly forbidden, except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the subject. In the

event of such an emergency, the investigator is to make every effort to contact the study monitor or designee prior to breaking the blind.

If the treatment blind is broken for any subject, that subject is to be withdrawn from the study and the investigator is to notify the [redacted] medical monitor immediately. The reason for discontinuation (the event or condition that led to the unblinding) will be recorded as the primary reason for discontinuation.

6. STUDY DRUG MATERIALS AND MANAGEMENT

6.1 Investigational Medicinal Product

The primary investigator and clinical site personnel will be blinded to which IMP (EMB-001 720/24 mg BID or placebo) each subject is receiving.

Subjects will receive blinded IMP from Week 2 through Week 13 and during the Taper Period (Week 14) in accordance with their randomization. During the Taper Period (Week 14), subjects in the EMB-001 Active Group will receive EMB-001 240/8 mg BID (one capsule per dose) and the placebo group will continue to receive placebo (one capsule per dose).

Subjects who experience tolerability issues that require a dose lower than 720/24mg BID will decrease to one capsule per dose (or remain on one capsule per dose) during the Taper period (Week 14).

6.2 Investigational Medicinal Product Packaging and Labeling

The Sponsor will provide EMB-001 and the placebo in capsules which will be packaged in bottles with 48 capsules per bottle.

Labeling and packaging of the IMP will meet applicable regulatory requirements as specified by state and federal law. The bottle labels will ensure that the label will protect the blinding of the study.

6.3 Investigational Medicinal Product Storage

6.3.1 Investigational Medicinal Product Storage at Clinical Sites

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

All capsules must be stored in a secure area. Access to and administration of these IMPs must be limited to the investigator and authorized site staff. The IMP must be administered only to subjects enrolled in the study and in accordance with the protocol.

Under normal conditions of handling and administration, IMP is not expected to pose significant safety risks to site staff.

6.3.2 Investigational Medicinal Product Storage by Subjects

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

6.4 Study Drug Administration

Subjects should be instructed to take the capsules with milk, with yogurt, or after a meal, to minimize nausea and vomiting, which can lead to impaired absorption.

The IMP will be administered twice daily from Week 2 through Week 14.

For subjects experiencing tolerability issues, the investigator must 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.

6.5 Drug Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of IMP dispensed and/or administered to study subjects and the amount received from and returned to the Sponsor or its representative. Product accountability records must be maintained throughout the course of the study.

6.6 Investigational Medicinal Product Handling and Disposal

After the study monitor has confirmed the accountability records, all remaining/leftover IMP will be destroyed locally by the pharmacy according to the pharmacy policy and procedures or returned to the sponsor/designee as agreed.

7. BASELINE ASSESSMENTS

After informed consent has been obtained, subjects will undergo screening evaluations as detailed in Table 1.

Demographic data will include date of birth, age, race, ethnicity, cocaine use status, and sex for all subjects screened, and reproductive status for women (to confirm that subject is of non-childbearing potential).

Baseline characteristics will include concomitant medical conditions and medications, alcohol and cocaine use, medical history, and a comprehensive physical examination, and review of body systems to determine eligibility. Particular attention should be paid to the following:

- Thorough review of all body systems, including any previous or current conditions
- Axis 1 disorders assessment
- Cocaine use history: form of cocaine (e.g., crack, powder) and route of administration (e.g., internasal, smoked) and frequency (TLFB)
- Pharmacotherapy, chronic use of any medication (prescribed and over the counter)
- History of allergies or idiosyncratic reactions to drugs
- Cortisol, ACTH, and related hormones
- For women, evidence of non-childbearing potential such as 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 FSH level >40 mIU/mL during the Screening Period.

- For women, serum or urine pregnancy test

Additional baseline assessments include urinalysis with microscopy, the Adverse Childhood Experiences Questionnaire (ACE), the Childhood Trauma Questionnaire (CTQ) and the MINI.

8. ASSESSMENT OF EFFICACY

The efficacy procedures and their timing are detailed in Table 1.

8.1 Primary Efficacy Parameter

The primary efficacy parameter will be the continuous abstinence from cocaine use over the final 3 weeks of the Treatment Period (Week 11 to Week 13) as assessed by self-reports using the TLFB interview and confirmed by urine BE.

8.2 Secondary Efficacy Parameters

8.2.1 Weekly Cocaine Non-Use Days

The number of weekly non-use days will be determined from subject self-reporting on the TLFB.

8.2.2 Quantitative Measurements of Urine BE

Urine BE levels will be used to determine cocaine use.

8.2.3 Use of Other Drugs

Use of other drugs will be determined from the drug screens for drugs of abuse, which include tests for alcohol and opiates, benzodiazepines, cocaine, amphetamine, methamphetamine, and phencyclidine.

8.2.4 Cocaine Craving Questionnaire-Brief

The CCQ-Brief consists of 10 statements on respondent's feelings and thoughts about using cocaine as he or she is completing the questionnaire (i.e., right now). This

instrument allows investigators to obtain a reflection of the respondent's general cocaine craving. Each item is scored on a scale ranging from 1 for "strongly disagree" to 7 for "strongly agree."

8.2.5 Pittsburgh Sleep Quality Index

The PSQI is a self-report questionnaire that assesses sleep quality over a 1-month time interval. The measure consists of 19 individual items, each weighted on a 0 to 3 interval scale. The global PSQI score is then calculated by totaling the 7 component scores, providing an overall score ranging from 0 to 21, where lower scores denote a healthier sleep quality.

8.2.6 Hospital Anxiety and Depression Scale

Anxiety and depression will be measured by the HADS. This is a 14-item questionnaire (7 items each that assess depression and anxiety) in which the response to each item is ranked from 0 to 3.

8.2.7 Sheehan Disability Scale

The SDS is a brief, 5-item self-report tool that assesses functional impairment in work/school, social life, and family life. Total score ranges from 0 to 30 (0=unimpaired, 30=highly impaired).

9. ASSESSMENT OF SAFETY

The safety procedures and their timing are detailed in Table 1. Safety measures include AEs including SAEs, laboratory investigations, ACTH stimulation testing, the GIRC, physical examinations, vital sign measurements, ECGs, and the S-STS. Assessments performed on Study Day 8 will serve as baseline for laboratory investigations, vital signs, and ECG. Physical examination performed during screening will serve as the baseline physical exam.

9.1 Adverse Events and Serious Adverse Events

The investigator or site staff will be responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

9.1.1 Definition of an 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 the following:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- A 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 the following:

- 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 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose, results in the following:

1. Results in death
2. 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.

3. Requires 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

4. Results in 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.

5. Is a congenital anomaly/birth defect
6. 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 Pregnancy

Women of childbearing potential are excluded from enrollment in this study.

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 clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs.

9.1.5 Time Period and Frequency of Detecting Adverse Events and Serious Adverse Events

The investigator or the site staff is responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

Adverse events will be collected from the time of randomization to (and including) the follow-up contact.

SAEs will be collected from the time the informed consent is signed to (and including) the follow-up contact. All SAEs must be reported to [redacted] within 24 hours.

9.1.6 Procedures for Reporting Adverse Events

It is the responsibility of the investigator to document all AEs that occur during the study. AEs will be elicited by asking the subject nonleading questions, for example, "Have you experienced any new or changed symptoms since we last asked/since your last visit?" All AEs, including those that are ongoing at the end of the follow up visit, will be followed to resolution unless, in the investigator's opinion, the condition is unlikely to resolve and is stable.

All AEs and their outcomes must be reported to the Institutional Review Board (IRB) as required by the IRB, federal, state or local regulations, and governing health authorities.

All AEs will be recorded in the subjects' charts and will then be transcribed into the provided eCRFs and in the subject medical record (as appropriate). 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.

9.1.6.1 Severity Assessment

Severity will be assessed using the following guidelines by a qualified and designated investigator:

- Grade 1: Mild. Easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities
- Grade 2: Moderate. Sufficiently discomforting to interfere with normal everyday activities; intervention may be needed
- Grade 3: Severe. Prevents normal everyday activities; treatment or other intervention usually needed
- Grade 4: Life threatening or disabling
- Grade 5: Death

9.1.6.2 Relationship (Causality)

Relationship to IMP will be assessed using the categories presented below by a qualified and designated investigator:

- Unrelated: Clinical event with an incompatible time relationship to IMP administration and that could be explained by underlying disease or other drugs or chemicals
- Related: Clinical event with a reasonable time relationship to IMP administration and is unlikely to be attributed to concurrent disease or other drugs or chemicals.

9.1.6.3 Reporting a Suspected Unexpected Adverse Reaction

All AE/SAEs that are suspected of having a causal relationship to IMP and "unexpected" are to be reported to [redacted], and the IRB as required by the IRB, federal, state or local regulations, and governing health authorities.

9.1.6.4 Reporting a Serious Adverse Events

All SAEs must be reported promptly to [redacted] as described in Table 2.

Table 2: Reporting Requirements for SAEs

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 [redacted] any SAEs, regardless of relationship to IMP, including those listed in the protocol or the Investigator's Brochure, and must include an assessment of whether there is a reasonable possibility that the IMP 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 [redacted] 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 [redacted] on behalf of the Sponsor in addition to that information reported on the eCRF. All subjects experiencing an SAE must be followed up and the outcome reported.

9.1.7 Regulatory Reporting Requirements for SAEs

Prompt reporting of SAEs by the investigator to [redacted] is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met by the Sponsor.

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

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

9.2 Physical Examination

A comprehensive physical examination and review of body systems will be performed at screening and at follow up/early termination. The physical examination will include measurements of height and weight and calculation of BMI.

9.3 Vital Sign Measurements

Vital sign measurements include the following:

- Blood pressure, pulse rate, respiratory rate, and temperature at each visit
- Weight and height at screening and follow-up/early termination

9.4 Clinical Laboratory Assessments

Investigators or medically qualified site staff will obtain blood and urine specimens and send them to the clinic laboratory. Details pertaining to specimen collection, processing, storage, and shipping procedures will be provided in an investigator laboratory manual.

9.4.1 Blood Assessments

Blood samples will be collected as detailed in Table 1.

9.4.1.1 Hematology

Hematology assessments will include the following analytes:

- Red blood cell count
- White blood cell (WBC) count
- WBC differential
- Hemoglobin
- Hematocrit
- Mean corpuscular hemoglobin
- Mean corpuscular hemoglobin concentration
- Red cell distribution width
- Mean corpuscular volume
- Platelet count

9.4.1.2 Serum Chemistry

Chemistry assessments will include the following analytes:

- Total protein
- Albumin
- Calcium
- Sodium
- Phosphorus (inorganic)
- Cholesterol
- Triglycerides
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Electrolytes (sodium, potassium, magnesium, chloride)

- Bicarbonate
- Blood urea nitrogen (BUN)
- Blood glucose
- Uric acid
- Total and direct bilirubin
- Alkaline phosphatase (ALP)
- Lactate dehydrogenase
- Gamma glutamyl transpeptidase
- Creatine phosphokinase
- Serum creatinine

At screening only, FSH must be measured to confirm postmenopausal status of female subjects. Thyroid stimulating hormone (TSH) must be measured to rule out thyroid dysfunction.

Information on ACTH, cortisol, and related hormone assessments is provided in Section 9.5 and in the Appendix (Section 16.1). At screening, cortisol must be measured to confirm values greater than 3 mcg/dL for inclusion in the study.

9.4.2 Serology

Serological assessments will include the following analytes:

- Human immunodeficiency virus (HIV)-1/HIV-2 antibodies
- Hepatitis B surface antigen
- Hepatitis C antibody (hepatitis C RNA if confirmatory testing needed)

9.4.3 Steroid Panel

Steroid panel assessments will include the following analytes:

- DHEA-S
- 11-deoxycortisol

- 11-deoxycorticosterone
- Free testosterone
- Total testosterone

9.4.4 Urine Assessments

Urinalysis (with microscopy) will be done at screening.

9.4.5 Drug Screening

Samples will be sent to the central laboratory for testing for the following:

- Alcohol
- Opiates
- Benzodiazepines
- Barbiturates
- Cocaine
- Amphetamine
- Methamphetamine
- Phencyclidine

Results for benzodiazepines and cocaine following initiation of dosing on Day 8 will be blinded. Use of opiates or alcohol in combination with benzodiazepines such as the oxazepam in EMB-001 may put subjects at risk of respiratory suppression so this is considered a safety laboratory assessment. Subjects' drug use prior to and during the screening period will be used in enrollment and randomization decisions.

9.4.6 Stored Samples

Following the completion of the study and analysis of the data, blood samples may be stored for further investigations. The further investigations will be performed only to address any specific efficacy, safety, or tolerability question(s) that arise from the results of this study.

All samples will be retained for a maximum of 1 year after the last subject completes the study.

9.5 Adrenal Insufficiency Safety Monitoring Plan

As noted in the introduction above, administration of metyrapone to patients with normal HPA axis function for multiple days (i.e., repeated dosing) has the potential to cause adrenal insufficiency, which can be clinically significant. Clinical studies with >200 subjects treated with metyrapone for 1 to 8 weeks at doses of 250 to 4000 mg/day have been conducted without any cases of clinically significant adrenal insufficiency, so the risk should be modest at most in this study. However, prudence dictates careful monitoring for this potentially clinically significant risk and therefore a comprehensive plan for monitoring adrenal function has been designed into this trial.

9.5.1 ACTH Stimulation Testing

An ACTH stimulation test will be performed when each subject has reached steady-state concentrations of EMB-001 or placebo on Day 11 (Day 4 of drug administration) and is therefore at the greatest risk of adrenal suppression. It will also be triggered by positive results on the GIRC (Section 9.5.2 and in the Appendix [Section 16.1]).

The ACTH stimulation test must be performed in the early morning due to diurnal variation in cortisol and must be performed at trough drug concentration (i.e., just before the morning dose is taken). If these criteria are not met, the subject must return the next day for the test to be performed.

Actions to be taken based on ACTH stimulation test results are provided in Table 3.

Table 3: 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 (<12 µg/dL)	The subject must be withdrawn from the study.		
Intermediate (≥12 µg/dL but <18 µg/dL)	The subject must return to the clinic 2 times per week and be evaluated once by telemedicine per week for the following 4 weeks. At the additional visit each week the subject should be assessed for vital signs, AEs, concomitant medications, GIRC, clinically significant symptoms, and suicidality.		
	ACTH stimulation test 1 week after initial ACTH stimulation test	Normal cortisol (≥18 µg/dL)	The subject can return to the regular visit schedule (1 in-person visit and 1 telemedicine interaction per week) and discontinue further ACTH stimulation tests.
		Abnormal cortisol (<12 µg/dL)	The subject must be withdrawn from the study.
		Intermediate cortisol (≥12 µg/dL but <18 µg/dL)	The subject must continue the 3 interactions (2 in-person visits, 1 telemedicine) per week schedule and return in 1 more week for another ACTH stimulation test.
	If intermediate results were obtained in the 1-week ACTH stimulation test, 1 week later another ACTH stimulation test is performed.	Normal cortisol (≥18 µg/dL)	The subject can return to the regular visit schedule (1 in-person visit and 1 telemedicine interaction per week) and discontinue further ACTH stimulation tests.
		Abnormal cortisol (<12 µg/dL)	The subject must be withdrawn from the study.
		Intermediate cortisol (≥12 µg/dL but <18 µg/dL)	The subject must continue the 3 interactions (2 in-person, 1 telemedicine interaction) per week schedule and return in 2 more weeks for another ACTH stimulation test.
	If intermediate results were obtained in the 2-week ACTH stimulation test, 2 weeks later another ACTH stimulation test is performed	Normal cortisol (≥18 µg/dL) or intermediate (≥12 µg/dL but <18 µg/dL)	The subject can return to the regular visit schedule (1 in-person visit and 1 telemedicine interaction per week) and discontinue further ACTH stimulation tests.
		Abnormal cortisol (<12 µg/dL)	The subject must be withdrawn from the study.

9.5.2 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 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. The GIRC is located in the Appendix (Section 16.2).

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, unless the baseline (prior to infusion of ACTH) cortisol assay results are ≥ 18 mcg/dL. In this case no ACTH stimulation test will be performed, the subject will continue in the study and the GIRC symptom will be monitored. If the cortisol results are < 18 mcg/dL or unavailable in the morning at the time the subject returns to the clinic, the ACTH test will be administered. Based on the cortisol results from the ACTH stimulation test, subjects may continue on study, be withdrawn, or continue on study with ACTH monitoring for 4 weeks or until normalization of the ACTH stimulation test result (see Table 3 and the Appendix [Section 16.1] for details).

9.5.3 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

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.”

All subjects with adrenal/glucocorticoid crisis will be discontinued from the study and emergently referred for appropriate assessment and further treatment, including hydrocortisone replacement and/or other action as clinically indicated. All subjects discontinued from dosing and the study for the above reasons will be referred for appropriate assessment and further treatment and will be monitored regularly until resolution.

There will also be an endocrinologist available by telephone 24/7 for the sites to consult with as needed.

9.6 Electrocardiograms

At the times detailed in Table 1, full 12-lead ECGs will be recorded using a standardized ECG machine that automatically calculates the heart rate and measures the PR, QRS, QT, and QTcF. All 12-lead ECGs will be read locally by the investigator or his/her designate.

Abnormal findings on the screening ECG should be carefully considered and any subject excluded who, in the judgment of the investigator, may not safely complete treatment in this study.

9.7 Emergency Procedures

In case of an emergency that occurs while the subject is outside of the unit, each subject will be provided with a wallet card identifying the potential risk for adrenal insufficiency as a result of participation this study and will be instructed to carry the card with them at all times. This 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 will also be provided with a MedicAlert necklace or bracelet, which includes the specific instruction, “In emergency, give hydrocortisone 100 mg IV or IM.”

9.8 Sheehan-Suicidality Tracking Scale

The S-STS is a prospective, subject self-report or clinician-administered rating scale that tracks both treatment-emergent suicidal ideation and behaviors. It will be performed at every study visit.

10. STATISTICAL ASSESSMENT

This section covers the statistical considerations and data analysis to address the objectives of the study.

A more technical and detailed elaboration of the statistical analyses to be used will be provided in the statistical analysis plan (SAP).

10.1 Analysis Populations

Study populations are defined as follows, and include, but may not be limited to, the following:

- Safety population: The safety population will include all randomized subjects who receive study treatment
- Modified intent-to-treat (mITT) population: The mITT population will include all randomized subjects who receive study treatment and return for at least 1 post-baseline efficacy visit
- Per-protocol (PP) population: The PP population will include all randomized subjects who complete the study with no major protocol deviations

All safety analyses will be performed on the safety population and all efficacy analyses will be performed on the mITT and PP populations.

10.2 Sample-Size Determination

Sample-size calculations were based on a comparison between EMB-001 and placebo. In a one-sided test for two-sample, independent proportions, at the significance level of 5%, 25 completers per group will provide at least 80% power to detect a difference in abstinence rates of 10% in the placebo arm and 40% in the active arm. Including a

dropout rate of approximately of 37.5%, randomization of 80 subjects (approximately 40 subjects in each group) will provide ample power to meet study objectives.

Assumptions for abstinence rates for sample size determination are based upon treatment response in current standard of care, limited published data from studies detecting active-placebo difference in cocaine use disorder and based upon considerations for Phase 2 efficacy and safety studies. The current standard of care for cocaine use disorder, psychosocial treatments, is associated with an abstinence rate of 31.7% (Dutra 2008). One prior drug treatment study with similar design to the current study reported 3-week abstinence rate of 33.3% for the active treatment and 16.7% for placebo (Mariani 2012). Finally, Phase 2 studies should be powered to detect substantial treatment effects because subsequent studies, allowing more heterogeneous populations evaluated at more investigative sites, tend to observe smaller active-placebo differences. For these reasons, a sample size calculation assuming 10% placebo response and 40% active response is appropriate for this Phase 2 study.

Phase 2 studies, by their nature, represent initial investigations of efficacy. Hypothesis tests structured using one-sided alpha are consistent with a narrow interest to determine whether an active treatment has better efficacy than placebo.

10.3 Data Analysis Considerations

All data will be summarized and analyzed according to treatment group.

Continuous variables will be summarized using descriptive summary statistics (number of observations, mean, standard deviation [SD], median, minimum, and maximum, etc.) as applicable. Categorical values will be summarized using frequencies and percentages.

SAS Version 9.4 or higher will be used for efficacy and safety analysis.

10.4 Demographic Data and Baseline Characteristics

Baseline and demographic data will be listed and summarized by treatment group using descriptive statistics.

10.4.1 Efficacy Analyses

Efficacy data will be listed and summarized by treatment group. This will include descriptive summary statistics (mean, median, SD, maximum, minimum) for continuous variables and frequencies of events for categorical data.

The primary outcome measure will be continuous abstinence from cocaine use over the final 3 weeks (Week 11 through Week 13) of the Treatment Period as assessed by self-reports using the TLFB interview and confirmed by urine BE. A urine will be considered negative for cocaine use when the urine BE result is < 150 ng/mL in the primary analysis.

Secondary efficacy endpoints will be weekly cocaine non-use days (as self-reported and as confirmed by urine BE levels), quantitative measurements of urine BE, the CCQ-B, the PSQI, the HADS, and the SDS. All efficacy parameters will be evaluated statistically as appropriate.

10.4.2 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.

Safety variables will not be statistically analyzed except for AE data.

11. DATA MANAGEMENT

For this study, subject data will be entered into the Sponsor-defined eCRFs, subject medical record, and transmitted electronically from the clinical site to [redacted].

Management of clinical data will be performed in accordance with applicable [redacted] standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). An appropriate medical dictionary that covers all approved drugs in the region will be referenced. eCRFs (including queries and

audit trails) will be retained by [redacted], and copies will be sent to the investigator to maintain as the investigator copy. In all cases, subjects' initials will not be collected by or transmitted to [redacted] or to the Sponsor.

12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

12.1 Study Monitoring

In accordance with applicable regulations, Good Clinical Practice (GCP), and Sponsor's (or designee) clinical procedures, clinical monitors will contact the site prior to the start of the study to review, with the site staff, the protocol, the study requirements, and their responsibilities to satisfy regulatory, ethical, and Sponsor (or designee) clinical requirements. A detailed monitoring plan will describe the frequency and methods for on-going review of Investigator compliance with the protocol, applicable regulations and GCP.

When reviewing data-collection procedures, the discussion will include identification, agreement, and documentation of data items for which the eCRF will serve as the source document.

The Sponsor (or designee) will monitor the study to ensure the following:

- That data are authentic, accurate, and complete
- That the safety and rights of subjects are being protected
- That the study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements

The investigator and the head of the medical institution (where applicable) agree to allow the monitor direct access to all relevant documents.

12.2 Audits and Inspections

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an audit or inspection, the investigator (and institution) must agree to grant

the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.

13. ETHICS

13.1 Ethical Conduct of the Study

The study will be conducted in accordance with all applicable regulatory requirements, including a US IND.

The study will be conducted in accordance with GCP, all applicable subject privacy requirements, and the guiding principles of the Declaration of Helsinki, including, but not limited to the following:

- IRB review and approval of study protocol and any subsequent amendments
- Subject informed consent
- Investigator reporting requirements

13.2 Written Informed Consent

Written informed consent must be obtained from each subject prior to participation in the study.

13.3 Study and Site Closure

Upon completion or termination of the study, the [redacted] monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and [redacted] standard operating procedures.

The Sponsor reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe noncompliance. If the Sponsor determines that such action is required, the Sponsor will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, the Sponsor will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for safety reasons, the Sponsor will promptly inform the investigator. The Sponsor will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB promptly and provide the reason(s) for the suspension/termination.

14. DATA HANDLING AND RECORDKEEPING

14.1 Inspection of Records

The investigator and the head of the medical institution (where applicable) agree to allow the monitor direct access to all relevant documents.

14.2 Retention of Records

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a Sponsor audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable backup of the reproductions exists and that there is an acceptable quality-control procedure in place for creating the reproductions.

The Sponsor will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, Sponsor standard operating procedures, and/or institutional requirements.

The investigator must notify the Sponsor of any changes in the archival arrangements including, but not limited to, archive of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

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