STATISTICAL ANALYSIS PLAN

A Phase 2a, Randomized, Double Blind, Placebo- and Active-Controlled Efficacy and Safety Study of EMB-001 in Subjects with Tobacco Use Disorder

Protocol No.: ERL-T002 Version 2.0

Study No.: ERL-T002

NCT NCT04933916

PREPARED FOR: *Embera NeuroTherapeutics, Inc.*

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SAP APPROVAL

Study ERL-T002 was terminated early due to business reasons. The SAP was not finalized.

By my signature, I confirm that this SAP has been reviewed by *Embera NeuroTherapeutics, Inc*, and has been approved for use on the *ERL T002* study:

Name	Title / Company	Signature	Date

Prepared by

[redacted] Biostatistician, [redacted]

Date: _____ Signature: _____

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List of Abbreviations and Definitions

Abbreviation	Description
11βHSD1	11β-hydroxysteroid dehydrogenase
11DOC	11-deoxycorticosterone
ACTH	adrenocorticotropic hormone
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	*bis in die* (twice daily)
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CO	carbon monoxide
CUD	cocaine use disorder
DHEA-S	dehydroepiandrosterone sulfate
DOC	deoxycorticosterone
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (Fourth ed.)
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (Fifth ed.)
ECG	electrocardiogram
eCRF	electronic case report form
EMB-001	metyrapone/oxazepam combination
Embera	Embera NeuroTherapeutics, Inc.
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
FTND	Fagerström Test of Nicotine Dependence
FU/ET	Follow-up/Early Termination Visit
GCP	Good Clinical Practice
GIRC	Glucocorticoid Insufficiency Review Checklist
HADS	Hospital Anxiety and Depression Scale
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HPA	hypothalamic-pituitary-adrenal
HR	heart rate
IDS	IDS Investigational Drug Service
IND	Investigational New Drug (application)
IP	investigational product
IRB	Institutional Review Board
ITT	intent-to-treat set
mCEQ	modified Cigarette Evaluation Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
MD	Medical Doctor
MDMA	Ecstasy
MNWS	Minnesota Nicotine Withdrawal Scale
MOZAT	3-(2-chlorophenyl)-5-(2-(2,4-difluoro-6-(fluoro-18F)phenoxy)propan-2-yl)-4-methyl-4H-1,2,4-triazole
MRI	magnetic resonance imaging
N/A	not applicable
PA	Physician Assistant
PCP	phencyclidine
PET	positron emission tomography
PK	pharmacokinetic(s)
PPS	per-protocol set
PSS	Perceived Stress Scale
QSU-brief	Tiffany Questionnaire of Smoking Urges-Brief
QTcF	QT interval corrected by the Fridericia correction formula
SAEs	serious adverse events
SAP	statistical analysis plan

Abbreviation	**Description**
SCQ-A	Smoking Expectancies Questionnaire
SCRN	Screening Visit
SS	Modified Intent to treat set (mITT set)
S-STS	Sheehan-Suicidality Tracking Scale
Tx	treatment
TUD	tobacco use disorder
WBC	white blood cell (count)

1. INTRODUCTION

As per ICH E9 [2], the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis.

This document describes the rules and conventions to be used in the presentation and analysis of safety and efficacy [1] and Bright Pharmaceutical Services, Inc SOPs. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

The Statistical Analysis Plan (SAP) was written based on the following documentation:

Document	**Date**	**Version**
Protocol ERL-T002	04-MAR-2021	2.0

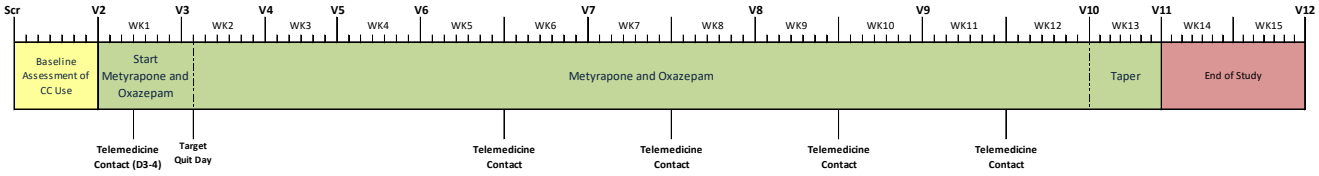
2. PROJECT OVERVIEW

2.1 Study Design

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

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



Participants will be enrolled after screening once all safety laboratory results have been received and reviewed by the medical staff (MD or PA). Study drugs will be dispensed starting at V2, and at each subsequent visit until Visit 11.

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

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

The measurements and evaluations that will be conducted are presented in Table 1 - Schedule of Events.

2.2 Objectives and Endpoints

The objectives of this study are to evaluate the safety and tolerability of EMB-001.

The exploratory objectives of this study are to evaluate the potential efficacy of EMB-001 by evaluating abstinence during study weeks 9-12, by abstinence during the 6 months after the and by smoking related questionnaires .

2.3 Sample Size

This is an exploratory study and no formal hypothesis testing will be performed. The primary abstinence outcome will be abstinence during study weeks 9-12.

The planned sample size, of up to 50 subjects, is supported by a comparison to historical abstinence 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 abstinence rates with placebo were 12% and ranged between 40% and 51% for varenicline (Ebbert J. Varenicline for smoking cessation: efficacy, safety, and treatment recommendations. Patient Prefer Adherence. 2010 Sep;355.). 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%.

2.4 Randomization and Blinding

Not applicable.

2.4.1 Randomization

Not applicable.

2.4.2 Blinding

Not applicable.

2.5 Planned Analyses

No interim analysis is planned.

2.6 Schedule of Events

Table 1: Schedule of Events

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Visit Assessments and Procedures	Screening	Study Visits														6-month F/U SMS
		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 Form	•																
Employment History		•															
Medical History/Review of Systems	•																
Glucocorticoid Insufficiency Review Checklist (GIRC) - Visit Based		•	•	•	•	•		•		•		•		•	•	•	
Glucocorticoid Insufficiency Review Checklist (GIRC) - Telephone		•					•		•		•		•				
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 (via daily SMS text)	•	•	•	•	•	•		•		•		•		•	•	•	•
Medication Compliance (via daily SMS text)		•	•	•	•	•		•		•		•		•	•	•	
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. GIRC will include only symptom and sign-based items of the GIRC (i.e. will not include assessment of orthostatic hypotension or measurement of serum sodium).

Targeted examination as needed.

^^ Also done if GIRC is positive and 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.

#

3. STATISTICAL CONSIDERATIONS

Data will be summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data) for demographic and baseline characteristics, efficacy and safety measurements.

Unless otherwise stated, the following methods will be applied:

3.1 General Considerations

Repeat/unscheduled assessments: Only values collected at scheduled study visits/time points will be presented in summary tables. However, additional exams may be scheduled as necessary to ensure the safety and well-being of subjects who experience AEs during the study. If a repeat assessment was performed, the result from the original assessment will be presented as the result at the specific visit/time point. All collected data will be included in the data listings. Moreover, unscheduled assessments will have the prefix "UNSCHEDULED" and will be sorted by the start date for clarity.

3.2 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.

3.3 Multi-center Studies

Analysis of any site effects is not planned in the Protocol.

3.4 Multiple Comparisons/ Multiplicity

No adjustment for multiplicity is planned in the Protocol.

3.5 General Statistical Principles

All the data collected during the study (data originating from the electronic case report forms [eCRFs] or electronic transfers) and required for Tables verification will be presented in the data listings. Event-based listings will be sorted by subject identifier and event start date (for example, AE start date). Assessment-based listings will be sorted by subject identifier, parameter name (alphabetically unless specifically stated otherwise), visit, and time point (if applicable).

Results of statistical analyses, descriptive summary statistics, and supportive listings will also be presented.

3.6 Key Definitions

The principles and definitions that will be applied to all tables, listings, and figures (TLF), unless otherwise specified, are described in Table 2 below.

Table 2 Principles and definitions for all tables, listings, and figures (TLF)

Principle/definition	Value
Baseline	Is defined as the last available valid, non-missing observation for each subject before the first study treatment administration at Visit 2 . Repeat and unscheduled assessments will be included in the derivation of the baseline values. Typically, the last assessment before the first administration may differ from indicated as "baseline" in the database.

Principle/definition	Value
Change from baseline	Is defined as the difference between the results collected/ derived at a post-baseline visit and baseline value. The change from baseline value at each post-baseline visit will be calculated for all continuous parameters using the following formula: *Change from Baseline Value= Result at post-Baseline visit – Baseline Value* The change from baseline value will only be calculated if the specific post-baseline visit/time point result and the baseline value for the parameter are both available and will be treated as missing otherwise. In the data listings, the change values will be set to 'N/A' (not applicable) for pre-baseline and baseline assessments.
Study Day	Is defined as the relative day of the event starting with the date of the first study treatment administration (the reference date) as Day 1 (there will be no Day 0). The study day of events occurring before the first study treatment administration will be calculated as: *Study Day = (Date of Event - Date of First Study Treatment Administration)* For events occurring on or after Day 1, the study day will be calculated as: *Study Day = (Date of Event - Date of First Study Treatment Administration) + 1* Study days will only be calculated for events with complete dates and will be undefined for events that are 'Ongoing' at the end of the study.
Significance tests	The default significant level will be 0.05 (5%); confidence intervals will be 95% and all tests will be two-sided unless otherwise specified in the description of the analyses.
Treatment group labels and order presented	EMB-001 720/24 mg BID
Display convention of Results	Results will be center-aligned in all summary tables and left-aligned in all listings. Subject identifiers, visits, and parameter labels, and comments may be left-aligned if required.
Date and Time Display Convention	Date only: YYYY-MM-DD Date and time: YYYY-MM-DD/HH:MM
Descriptive summary statistics for continuous variables	Descriptive statistics will include the number of non-missing values (n), arithmetic mean, standard deviation (SD), median, Q1, Q3, minimum and maximum values. The minimum and maximum values will be displayed to the same decimal precision as the source data; the arithmetic mean, median, values will be displayed to one more decimal than the source data. SD values will be displayed to two more decimals than the source data for each specific variable. The maximum number of decimal places in the statistical report is four. If a descriptive statistical value has more than four decimal places, this value will be rounded to four decimal places. The appropriate precision for derived variables will be determined based on the maximum precision of the data on which the derivations are based and statistics will be presented in accordance with the above-mentioned rules.
Descriptive summary statistics for categorical variables	Descriptive statistics will include frequencies and percentages per category as well as clinical evaluations (normal, abnormal and not clinically significant, abnormal and clinically significant). The denominator in all percentage calculations will be the number of subjects in the relevant analysis population with non-missing data unless specifically stated otherwise. Percentages will be rounded to one decimal place.
Include "Missing" as a category	No, n will change, unless stated otherwise.
Display for 0 percentages	0.0% (in case there is at least one another non-missing result in the line) Do not display (in case all results in the line are 0 (missing values)) , unless stated otherwise.

3.7 Windowing Conventions

Not applicable.

Table to be deleted- this is for information purposes only

Visit Assessments and Procedures	Screening	Study Visits														6-month F/U SMS
		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																	

4. ANALYSIS SETS

Agreement and authorization of subjects included/excluded from each analysis set will be conducted prior to statistical analysis stage of the study.

No formal statistical analyses will be undertaken for subjects who screen fail.

4.1 All Subjects Enrolled Set (ASE set)

The all subjects enrolled (ASE) set will contain all subjects who provide informed consent for this study.

4.2 Modified Intent-to-Treat set (mITT set): All randomized subjects.

The subjects from the ASE set who receive at least 1 dose of the study drug.

5. SUMMARY OF STUDY DATA

Subject disposition will be presented with screen failures for ASE set.

Demographic characteristics, baseline variables, medical history, prior and concomitant medications will be reported for mITT set.

5.1 Subject Disposition

Source: Table 14.1.1, Table 14.1.2, Table 14.1.3, Listing 16.2.1.1, Listing 16.2.1.2, Listing 16.2.1.3.

The following subject disposition summaries will be provided:

- A summary of the number of subjects signed the Informed Consent and the number of screen failures with reasons for premature study termination.
- A summary of the number and percentage of subjects included in each population for statistical analysis with reasons for exclusion.
- A summary of the number and percentage of subjects completed the study and prematurely discontinued from the study by major reason for discontinuation.
- Subjects who completed each study visit.
- Subjects who started the follow-up period (completed at least one follow-up visit).

Subject randomization details, visit dates and withdrawal/study completion details will be provided. A listing for subject disposition will be provided for all subjects who signed the Informed Consent. Listings for inclusion/ exclusion by analysis set with the reasons of exclusion will be provided.

5.2 Protocol Deviations

Source: Listing 16.2.2.1

Major protocol deviations that could potentially affect the efficacy results for all subjects and exclusion of subjects from statistical analysis and PP set will be considered at BDRM prior to database lock.

All protocol deviations will be tabulated by deviation category.

5.3 Demographic and Baseline Characteristics

Source: Table 14.1.4, Listing 16.2.3.1

Descriptive statistics for the following demographic and anthropometric characteristics, which are evaluated on screening, will be presented in accordance with section **Error! Reference source not found.**:

- demographic characteristics: age, gender assigned at birth, current gender identity, race; ethnicity, marital status.
- anthropometric characteristics: height, weight, body mass index (BMI).

Body mass index will be calculated as weight (kg) / [height (m)]^2.

All data will be listed.

5.4 Concurrent Illnesses and Medical Conditions

Source: Table 14.1.5, Table 14.1.6, Listing 16.2.3.2

Information on prior and concomitant medical history will be collected at screening. If registered medical history events will be coded, results will be tabulated by system organ class (SOC) and preferred term (PT), otherwise, appropriate listings will be presented only.

Medical history events marked as "Resolved" will be considered as prior diseases. Medical history events marked as "Ongoing" will be considered as concomitant diseases.

Prior and concomitant diseases will be tabulated separately.

All data will be listed.

5.5 Prior and Concurrent Medications

Source: Table 14.1.7, Table 14.1.8, Listing 16.2.3.3, Listing 16.2.3.4

Prior and concomitant medications will be analyzed based on the information from the Concomitant/Prior Medications (CM) domain.

Classification of treatment as either Prior or Concomitant will be based on start/stop dates and "ONGOING" checkbox in the appropriate eCRF form. Medications starting after the completion/withdrawal date will be listed but will not be classified or summarized.

Medications that start and stop prior to the date of first dose of study therapy will be classified as Prior medications. If a medication starts before the date of first dose of study therapy and stops on or after the date of first dose of study therapy (or "ONGOING") then the medication will be classified as Concomitant. Medications will be classified as Concomitant if they have a start date on or after the date of the first dose of study therapy.

If the information about start/end date of therapy is missing or incomplete, the rules from section 6 will be applied for classification. Medications will be assumed to be concomitant, unless there is clear evidence (through comparison of partial dates) to suggest that the medication stopped prior to the first dose of study therapy. If there is clear evidence to suggest that the medication stopped prior to the first dose of study therapy, the medication will be assumed to be Prior.

Prior and concomitant medications will be presented in separate tables. Concomitant medications started after the end of treatment period will also be tabulated separately.

By-subject listings will be provided.

6. EFFICACY AND EXPLORATORY ANALYSES

No formal hypothesis testing of efficacy will be performed.

Exploratory analysis of potential efficacy will be performed on the *Modified Intent to treat set (mITT set)*.

6.1 Exploratory Analyses

Source: Table 14.2.1.1, Table 14.2.1.2, Table 14.2.2.1, Table 14.2.3.2, Table 14.2.3.1, Table 14.2.3.2, Table 14.2.4.1, Table 14.2.4.2, Table 14.2.5.1, Table 14.2.5.2, Table 14.2.6.1, Table 14.2.6.2, Table 14.2.7.1, Table 14.2.7.2, Table 14.2.8.1, Table 14.2.8.2, Table 14.2.9.1, Table 14.2.9.2, Table 14.2.10.1, Table 14.2.10.2
Listing 16.2.4.1 , Listing 16.2.4.2 , Listing 16.2.4.3 , Listing 16.2.4.4 , Listing 16.2.4.5 , Listing 16.2.4.6 , Listing 16.2.4.7 , Listing 16.2.4.8 , Listing 16.2.4.9, Listing 16.2.4.10

Abstinence at study weeks 9-12 will be the primary exploratory outcome. 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. In addition, subjects who have 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 or equal to 10 ppm will be displayed. 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 exploratory endpoints of this study will evaluate the efficacy of EMB-002 by examining the following questionnaires:

- Sheehan Suicidality Tracking Scale (Sheehan-STS);

  The Sheehan-STS is an eight-item prospective rating scale that tracks suicidal ideation and behaviors. Each item is scored on a 5-point Likert scale ranging from 0 to 4 (0=not at all, 1=a little, 2=moderately, 3=very, and 4=extremely). This questionnaire will be administered at each study session.

  Total Score will be analyzed.

- 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.

- 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).

- 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):

  - Desire or craving to smoke
  - Anger, irritability, frustration
  - Anxiety or nervousness
  - Difficulty of concentrating
  - Impatience, restlessness
  - Hunger
  - Depression

- 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).

- 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).

- 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). Our study will utilize the PSS-10 during V2, V6, V8, V10, and V12 to evaluate self-reported perceived stress levels.

- 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.

- Employment History;

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

- Glucocorticoid Insufficiency Review Checklist;

  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.

For exploratory endpoints (questionaries) which were collected on several Visits (repeated measures):

- Continuous data with collected data for baseline:

Mean score changes from baseline over time will be analyzed using a restricted maximum likelihood based repeated measures approach (MMRM). The analysis model includes fixed (discrete) effect parameter for analysis visit, as well as continuous covariates for baseline score.

An unstructured, compound symmetry and AR(1) (co)variance structures will be examined using FIT statistics and the structure with the lowest Akaike's Information Criterion (AIC) will be used to model the within-subject errors. In case this model will not converge, only descriptive statistics with note “model did not converge” will be presented. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

PROC MIXED SAS procedure will be used for the statistical test.

- Continuous data without collected data for baseline:

Mean score changes from baseline over time will be analyzed using one-way ANOVA. The analysis model includes fixed (discrete) effect parameters for analysis visit.

PROC MIXED SAS procedure will be used for the statistical test.

- Sensitivity analysis.

Statistical analysis performed using Kruskal Wallis test will be repeated for all variables as the sensitivity analysis.

PROC NPAR1WAY SAS procedure will be used for the statistical test.

7. SAFETY ANALYSES

Safety analysis will be conducted on *Modified Intent to treat set (mITT set)*.

The following parameters will be analyzed:

- Exposure;
- Blood Samples
    - Hematology;
    - Clinical Chemistry;
    - Serology;
        - Human immunodeficiency virus (HIV 1/2 antibodies and HIV-1 p24 antigen)
        - Hepatitis B surface antigen
        - Hepatitis C virus antibody
- Steroid panel
- Serum Pregnancy Test
- Urine Samples
    - Urinalysis Assessments
        - pH
        - Red blood cell traces
        - Bilirubin
        - Protein
        - Glucose

        - Specific gravity
        - Nitrite
        - WBC Esterase
    - Drug Screening
        - Cocaine
        - THC
        - Amphetamines
        - Methamphetamines
        - Ecstasy (MDMA)
        - Phencyclidine (PCP)
        - Benzodiazepines
        - Barbiturates
        - Opiates
- Alcohol Breathalyzer
- Urine Pregnancy Test
- Expired Air CO Breath Test
- Adverse events, serious adverse events;
- ACTH Stimulation Testing
- Adrenal/Glucocorticoid Crisis
- Electrocardiogram (ECG)
- Vital Signs

7.1 Exposure

Source: Table 14.3.1.1, Table 14.3.1.2, Table 14.3.1.3 Listing 16.2.5.1

Exposure will be presented for the Modified Intent to treat set (mITT set) with descriptive statistics for:

- treatment duration, days;
- total dose;
- Treatment Compliance (%)

Treatment duration will be calculated (in days) as time between date of first injection and date of last injection (+ 1 day) for each subject.

Total dose will be calculated as sum of all administered doses during treatment duration for each subject.

Treatment Compliance (%): participants will be queried via SMS text messages whether they have been compliant with taking the study specific medications. These messages will commence after the second visit and continue through the End of Study.

7.2 Blood Samples

Source: Table 14.3.2.1.X, Table 14.3.2.2.X, Table 14.3.2.3.X, Listing 16.2.5.2.X, Listing 16.2.5.3.X, Listing 16.2.5.4.X

Clinical laboratory evaluations include the following parameters:

- Hematology;
- Clinical Chemistry;
- Serology;
  - Human immunodeficiency virus (HIV 1/2 antibodies and HIV-1 p24 antigen)
  - Hepatitis B surface antigen
  - Hepatitis C virus antibody
- ACTH Stimulation Testing
- Steroid Panel

For laboratory parameters the following tables will be presented:

- descriptive statistics of measurement values and changes from baseline;
- shift tables based on comparison with normal range if applicable (Lower/Normal/Higher);

All laboratory data will be listed.

7.3 Adverse Events

Source: Table 14.3.3.1, Table 14.3.3.2, Table 14.3.3.3, Table 14.3.3.4, Table 14.3.3.5, Table 14.3.3.6, Table 14.3.3.7, Table 14.3.3.8, Listing 16.2.5.5.X

Only treatment-emergent AEs will be analyzed.

Treatment-emergent AE is any reported adverse event that starts after initiation of the study therapy.

All registered AEs will be coded using the MedDRA version 21.0 (or further updating) and tabulated in the report with grouping by primary system organ class (SOC) and preferred term (PT).

Number (percentage) of subjects and number of AEs on treatment will be presented in the following tables:

- All AE / SAE;
- AE / SAE by relation to the study drug;
- AE / SAE related to the study drug;
- AE / SAE by severity;

Tables of AE/SAE by severity will be prepared using the following rules: each SOC / PT category will include only the AEs with the worst severity for each subject. In the Total category, all AEs of the subject will be presented. Each subject will be counted only once with the worst severity in each SOC and each PT level as well as in Total level.

All AEs and SAEs will be listed. AEs which occurred before the start date of the study therapy, will be presented in a separate listing only.

Imputed dates will not be presented in the listings.

Algorithm for Treatment Emergence of Adverse Events:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study medication start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

7.4 Physical examination

Source: Table 14.3.4.1.X, Listing 16.2.5.6

Physical examination results will be presented in:

- frequency tables for normal/abnormal assessment and clinically significant evaluation.

All physical examination data will be listed.

7.5 Vital signs

Source: Table 14.3.4.2.X, Listing 16.2.5.7

Vital signs, body weight and body height results will be presented in accordance with section

Vital signs and body weight results will be presented as the following outputs:

- descriptive statistics of measurement values and changes from baseline (vital signs, body weight, BMI);

- frequency tables for out-of-range assessment and clinically significant evaluation (vital signs).

All data will be listed.

7.6 12-lead ECG

Source: Listing 16.2.5.8

All 12-lead ECG data will be provided in a data listing.

7.7 Pregnancies

Source: Listing 16.2.5.9

Female subjects will be tested for pregnancy. The results of these tests and pregnancies will be reported in the listing.

7.8 Other Safety Measures

Source: Listing 16.2.5.10.X

Other analysis as:

- Steroid panel
- Serum Pregnancy Test
- Urine Samples
    - Urinalysis Assessments
        - pH
        - Red blood cell traces
        - Bilirubin
        - Protein
        - Glucose
        - Specific gravity
        - Nitrite
        - WBC Esterase
    - Drug Screening
        - Cocaine
        - THC
        - Amphetamines
        - Methamphetamines
        - Ecstasy (MDMA)
        - Phencyclidine (PCP)
        - Benzodiazepines
        - Barbiturates

    - Opiates
- Alcohol Breathalyzer
- Urine Pregnancy Test
- Expired Air CO Breath Test
- ACTH Stimulation Testing
- Adrenal/Glucocorticoid Crisis

will be provided in a data listing.

8. OTHER ANALYSES

Not applicable.

9. TECHNICAL DETAILS AND REPORTING CONVENTIONS.

The data analysis (datasets/outputs/codes) for the Statistical Report will be generated using SAS version 9.4 (or later). Copyright, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

10. SUMMARY OF CHANGES TO THE PROTOCOL

Questionnaires presented as Exploratory analysis instead of Safety.