STATISTICAL ANALYSIS PLAN

TITLE OF CLINICAL TRIAL:

A Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled Clinical Trial of PH94B Nasal Spray for the Acute Treatment of Anxiety Induced by a Public Speaking Challenge in Adult Subjects with Social Anxiety Disorder (PALISADE-1)

Clinical Trial Protocol PH94B-CL026 v2.0 03 January 2022

NCT04754802

Version number: 2.0

Date of issue: 09 May 2022

Sponsor: VistaGen Therapeutics, Inc.
343 Allerton Avenue
South San Francisco, CA 94080

Approval Signature Page

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
C-SSRS	Columbia Suicidality Severity Rating Scale
CGI-I	Clinical Global Impression Scale of Improvement
CS	Clinically Significant
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
GCP	Good Clinical Practice
i.n.	Intranasal
ICE	Intercurrent Event
ICF	Informed Consent Form
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent to Treat
LLN	Lower Limit of Normal
LSAS	Liebowitz Social Anxiety Scale
MedDRA	Medical Dictionary for Medical Affairs
MINI	Mini International Neuropsychiatric Interview
n	Sample Size
N	Population Size
NCS	Not Clinically Significant
PCS	Potentially Clinically Significant
PGI-C	Patient Global Impression of Change
PH94B	PH94B Nasal Spray
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
QTcF	QT Corrected with Fridericia Formula
SAD	Social Anxiety Disorder
SAE	Serious Adverse Event
SD	Standard Deviation
SI	International System
SOC	System Organ Class
SUDS	Subjective Units of Distress Scale
TEAE	Treatment-Emergent Adverse Event
UDS	Urine Drug Screen
ULN	Upper Limit of Normal
VistaGen	VistaGen Therapeutics, Inc.
WHO	World Health Organization
WHO DD	WHO Drug Dictionary

1 INTRODUCTION

The statistical analysis plan (SAP) details the planned statistical analysis methods required to address the study objectives as described in PH94B-CL026: A Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled Clinical Trial of PH94B Nasal Spray for the Acute Treatment of Anxiety Induced by a Public Speaking Challenge in Adult Subjects with Social Anxiety Disorder (PALISADE-1).

This SAP should be read in conjunction with the study protocol and case report form (CRF). The version of this SAP is based on the protocol PH94B-CL026 version 2.0 dated 03-Jan-2022 and the CRF dated 23-Dec-2021.Changes to these documents may result in subsequent changes to the SAP. The final, sponsor-approved version of the SAP must occur prior to database lock. Analysis programming activities will initiate upon SAP approval.

1.1 Modification History

SAP Revision Chronology:	Date:	Details:
v1.0 to v2.0	09-May-2022	[redacted]

1.2 Changes to the Planned Analysis

There are no changes to the planned analysis from the Protocol. Any deviations from the original statistical analysis plan will be described and justified in the final clinical study report.

2 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Efficacy	
Primary	
To evaluate whether the efficacy of PH94B to relieve acute anxiety induced during a public speaking challenge in adult subjects with SAD is greater than that for placebo as measured by the Subjective Units of Distress Scale (SUDS).	The difference in average SUDS score during a 5-minute public speaking challenge after treatment with PH94B or placebo at Visit 3 (Treatment) and the average SUDS score during a similar 5-minute public speaking challenge after treatment with placebo at Visit 2 (Baseline).
Secondary	
The comparison of PH94B-treated subjects with placebo-treated subject with regard to clinician-observed change in subject's response to an anxiety-provoking situation between Visit 2 and Visit 3 as measured by Clinical Global Impression Scale of Improvement (CGI-I).	The proportion of Clinical Global Impression Scale of Improvement (CGI-I) scores of 1 [redacted] or 2 [redacted] recorded at the end of Visit 3.
[redacted]	
[redacted]	[redacted]
Safety	
The determination of safety and tolerability of PH94B compared to placebo in adult subjects with SAD.	• AEs, suicidal ideation (C-SSRS), and level of depression (HAM-D)

Objectives	Endpoints
	• Changes from Screening in laboratory parameters, vital signs, ECGs, and physical examinations.

3 STUDY DESIGN

3.1 General Description

The Study is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel design group trial of the efficacy and safety of PH94B in the acute treatment of anxiety in adult subjects diagnosed with SAD as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition and confirmed by the Mini International Neuropsychiatric Interview (MINI).

Subject participation in the study will last a total of 3 to 7 weeks, depending on the duration of the screening period and intervals between visits. Upon signing an informed consent, all subjects will complete Visit 1 (Screening) and enter a screening period [redacted]. If subjects meet all eligibility criteria at the end of the screening period, subjects will complete Visit 2 (Baseline) and participate in a 5-minute public speaking challenge [redacted]. At Visit 3 (Treatment), the subject will be randomized. The subject will self-administer randomized investigational product (IP) and will then undergo a 5-minute public speaking challenge with SUDS scores being collected [redacted] by the same trained observer who was present for that subject during the Visit 2 public speaking challenge. At the end of the Visit 3 public speaking challenge, the subject will complete the [redacted], and the site personnel will complete the Clinical Global Impression Scale of Improvement (CGI-I) assessment. One week (± 2 days) after the completion of Visit 3, subject will come back for Visit 4 (Follow-up) that will involve a repeat of the safety psychiatric assessments conducted at Screening [redacted]

3.2 Study Population

Eligibility for participation in the study will be determined from demographic information, medical and psychiatric history, physical and psychiatric examination, electrocardiogram (ECG), clinical laboratory findings, and clinical rating scale assessments performed at the Screening Visit. Subjects may be recruited from the Investigator or sub-Investigator clinical practices, center's existing database, referring physicians, or direct advertisement or other lead generation source.

3.3 Randomization and Blinding

Randomization will be stratified within study site with a ratio of 1:1.

Each study site will be provided with a supply of blinded IP, each vial individually numbered with a unique alpha-numeric identification code. For Visit 2 and Visit 3, the interactive system

will provide a unique vial identification code indicating the medication vial to be dispensed to the subject. The vial identification codes will be recorded in the drug dispensing record and the electronic case report form (eCRF).

The vial number can be used to break the blind if deemed medically necessary by the medical monitor. Contact information will be provided to the study site.

3.4 Sample Size

Sample size considerations are based on the similarly designed Phase 2 randomized, double-blind, placebo-controlled clinical study of PH94B with the primary outcome variable being average subjective anxiety based on the SUDS scores. [redacted]

4 ANALYSIS POPULATIONS

4.1 All Subjects Population

All Subjects Population: The All Subjects Population will include all subjects who sign an informed consent, have a Screening Visit performed, and are entered into the eCRF for the study. The All Subjects Population will be used for summaries of subject disposition and protocol deviations.

4.2 Intent-to-Treat Population

Intent-to-Treat (ITT) Population: The ITT Population will include all subjects who are randomized. Subjects in this population will be analyzed according to the randomized treatment assignment, regardless of treatment received.

4.3 Safety Population

Safety Population: The Safety Population will include all subjects who receive IP. AEs will be classified by time of occurrence and Visit 3 group assignment to identify more clearly those arising after exposure to [redacted] only and those arising after exposure to [redacted]. Subjects will be analyzed according to the treatment received, regardless of the randomized treatment assignment.

5 GENERAL CONSIDERATIONS

5.1 General Data Handling

All analyses will be conducted based on SAS 9.4 or higher.

In general, analysis tables will be presented by Visit 3 treatment group using the following groupings of subjects:

- PH94B
- Placebo
- Overall

Data will be presented in by-subject data listings. Subject ID will be four digits consisting of the site ID (first two digits) and subject number (last two digits). Unless otherwise stated, all listings will be sorted by treatment group, subject ID, and assessment date (and time, if available).

Unless stated otherwise, continuous data will be summarized by Visit 3 treatment group based on n, mean, median, standard deviation (SD), minimum value, and maximum value.

Unless stated otherwise, categorical data will be summarized by Visit 3 treatment group using n and percentage based on the number of non-missing values.

The precision level used for descriptive statistics will be based on the following:

- Minimum and Maximum: same number of significant digits as the raw data.
- Mean, Median, Q1, and Q3 (as applicable): one additional decimal place to that reported for Minimum and Maximum
- SD: two additional decimal places than the Minimum and Maximum
- Percentages <100% will be reported to one decimal place and percentages of 100% will be reported with no decimal place.
- P-values will be reported to four decimal places. If the value is below 0.0001 it will be noted as < 0.0001; if the value above 0.9999 it will be noted as > 0.9999.

Unless otherwise noted, statistical inference will be based on a 5% significance level (i.e., 95% confidence intervals will be produced).

5.2 Reference Dates and Definitions

The reference dates for this study are as follows:

- Informed consent date is defined as the eCRF-provided date on which a subject signed the informed consent form.
- Randomization date is defined as the date on which the subject is randomized to study treatment.
- Treatment start date is defined as the date of first dose of IP including dosing of [redacted] at Visit 2.

- Treatment end date is defined as the date of last dose of IP.
- The calculation of age will use the informed consent date as its reference date.
- Safety Population data, such as AEs and laboratory assessments, will use the treatment start date as a reference date. In this study, because first dose of PH94B will not occur until Visit 3, AEs will be reported for both prior to Visit 3 IP administration and post.
- Study day will be based on treatment start date as a reference date.

Variable	Definition
Baseline Value	Baseline may refer to the last non-missing value [redacted]
Post-Baseline Value	Defined as values collected after IP administration.
Change from Baseline	Defined as: Post-Baseline Value – Baseline Value
Percent Change from Baseline	Defined as: (Value at Post-baseline Visit – Value at Baseline)/Value at Baseline x 100. Note: To compute percent change from baseline, the baseline value cannot be equal to zero.
Temperature (in °C)	= (temperature (in °F) - 32) * 5/9
Height (in cm)	= height (in inches) * 2.54
Weight (in kg)	= weight (in lbs) * 0.4536

5.3 Study Day and Duration Variables

Reference date calculations will generally be defined as the following, assuming non-missing dates:

- date of interest – reference date + 1 when the date of interest >= reference date;
- otherwise, date of interest – reference date.

If either date is missing, reference date calculations will not be performed.

Study day, based on the treatment start date as the reference, would either have a negative value if collected before dosing or a positive value if collected on or after the day of dosing; there will be no study day zero.

Duration of time is dependent on reference dates and will be calculated in a manner similar to that of the reference date calculation, assuming that dates of interest will strictly follow reference dates (e.g., no negative values). For example, duration on study is defined as the end of study date – treatment start date + 1. Duration of treatment is defined as treatment end date – treatment start date + 1, where treatment end date is the date of last dose of IP.

5.4 Visit Windows

The basis of summarization and analysis will be by visit as recorded in the database. Visit windows will not be applied unless missing dates lead to ambiguity.

5.5 Assigned and Actual Treatment

Once the Investigator deems a subject to be eligible for the study based on inclusion/exclusion criteria, the subject will be randomly assigned at Visit 3 in a blinded manner to either PH94B nasal spray or placebo in a 1:1 ratio.

At the end of the study, assigned treatment will be determined based on randomization number and the unblinded randomization list. Actual treatment will be determined based on batch ID data provided with the final unblinded data.

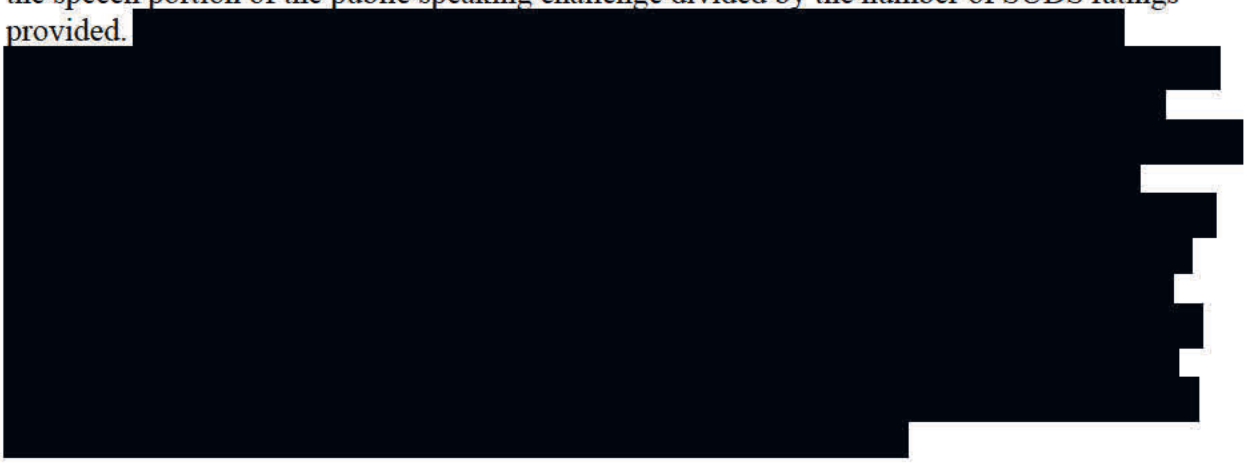
Intent to Treat (ITT) Population analyses will be conducted based on the randomized (assigned) treatment. Safety Population analyses will be conducted on the basis of the actual treatment received.

5.6 Missing Data

All attempts will be made to ensure completeness of data. Missing safety data will not be imputed and will be presented as collected in the study database. Missing primary efficacy data will be imputed for purpose of analysis, as described below. Missing efficacy data in analyses other than the primary efficacy analysis will not be imputed.

5.6.1 Multiple Imputation for Primary Endpoint

It is expected that all study subjects who are randomized at Visit 3 will complete the Visit 3 public speaking challenge immediately after randomization and will be included in the primary efficacy analysis. Average Visit 3 SUDS is defined as the sum of SUDS ratings provided during the speech portion of the public speaking challenge divided by the number of SUDS ratings provided.



5.6.2 Missing Date Imputation

In cases where adverse event (AE) or medication dates are missing, the following methods will be used to determine flags for treatment-emergent adverse events (TEAEs), prior medications, and concomitant medications.

5.6.2.1 Adverse Event Flags

If the AE start date is completely missing, or if the patient was not treated, no imputation will be conducted. If the AE start date is missing day and month, use the following guidelines to impute dates for purposes of determining treatment-emergent flags:

- If the treatment start date is missing or the AE start year does not fall in the same year as that of the treatment start date or if the AE record contains information to indicate that the event ended before the treatment start date (e.g. the AE end date month and year are earlier than the treatment start date or the full AE end date is known and occurs earlier than the treatment start date), then set the AE start month and day to January 1st.
- Otherwise, set the AE start date to the treatment start date.

If only the AE start day is missing, do the following:

- If the study treatment start date is missing or the AE start month and year does not fall in the same month and year as that of the treatment start date or if the AE contains information to indicate that the event ended before the treatment start date, then set the AE start day to the 1st day of the month of the AE start date.
- Otherwise, set the AE start date to the treatment start date.

AE end dates will not be imputed.

5.6.2.2 Prior and Concomitant Medication Flags

If medications have missing start or stop dates, appropriate programming logic will be applied to designate the medications as prior or concomitant and, if concomitant, as before or after Visit 3 dosing. If a missing date part leads to uncertainty as to whether a medication is concomitant, the medication will be considered concomitant. If a missing date part leads to uncertainty as to whether a concomitant medication was taken after Visit 3 dosing, the medication will be considered to be taken after Visit 3 dosing.

For example, if the medication start year or end year is after treatment start year, a medication will be considered concomitant even if the month and/or day are missing from the start date or

end date. Likewise, if the medication start occurs in the same year as treatment start, and the medication start month or end month is after the treatment start month, then the medication will be considered concomitant even if the medication start or end day is missing. Similar logic will be applied to other cases of partially missing dates for all designations of prior, concomitant, before Visit 3 dosing, and after Visit 3 dosing.

5.7 Multiplicity

Testing of the secondary endpoint will proceed once the primary endpoint achieves statistical significance. In this way, Type I error is well controlled.

6 STUDY SUBJECT DATA

6.1 Subject Disposition

All subjects who provide informed consent will be accounted for in this study. The number of subjects randomized, completed, and discontinued from the study, as well as reasons for discontinuation, will be summarized by treatment group and overall. Additionally, the number of subjects in each analysis population will be displayed. Data will also be presented in a by-subject listing.

6.2 Protocol Deviations

Protocol deviations will be identified via the eCRFs and classified as major or minor deviations before the database is locked. Protocol deviations will be summarized for the All Subjects Population by treatment group (including "not randomized") and overall. Data will also be presented in a by-subject listing.

6.3 Demographic and Baseline Characteristics

Demographic and baseline characteristic data will include age (based on date of informed consent), age group (18-35 years, 36-55 years, 56-65 years), sex, race, ethnicity, height, and weight. Age will be calculated as an integer in years as the difference between the subject's date of informed consent and the date of birth.

Demographic and baseline characteristic data will be summarized for all subjects in the ITT and Safety populations by treatment group and overall. Data will also be presented in a by-subject listing.

6.4 Medical History

Medical and psychiatric history will be collected at screening. All medical and psychiatric history terms will be coded by using Medical Dictionary for Regulatory Activities (MedDRA), version 24.0 – Mar 2021. A table will be generated to summarize medical history by system organ class (SOC) and preferred term (PT). Data will be summarized for all subjects in the Safety Population by treatment group and overall. A subject will be counted only once at each level of reporting. Data will also be presented in a by-subject listing, which will include system SOC, PT, and the verbatim term.

6.5 Reproductive System

Reproductive system information will be collected for applicable subjects during screening. The data will be provided in a by-subject listing.

[redacted]

[redacted]

6.7 Mini International Neuropsychiatric Interview (MINI)

The MINI will be completed during screening for all subjects. The data will be provided in a by-subject listing.

6.8 Prior and Concomitant Medication

Prior medications are those which have been identified to have been discontinued prior to the first dose of study medication. Concomitant medications are those which have been identified to have been taken at any point during the study after the first dose of study medication, including medications which started prior to first dose of study drug that are ongoing at first dose. The medications will be coded using B3 WHO Drug Global – Mar 2021.

Partial dates will be imputed according to Section 5.7 for the determination of prior, concomitant, and subsequent medications.

The incidence of prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) Level 2 classification and preferred term for all subjects in the Safety Population by treatment group and overall. Concomitant medications will be categorized according to whether they were taken before Visit 3 dosing, during or after Visit 3 dosing, or both. Medications categorized as "Before Visit 3 Dosing" will be those concomitant medications that were taken prior to dosing at Visit 3. Medications categorized as "During or After Visit 3 Dosing" will be those that were taken at any point after dosing at Visit 3. Medications that are ongoing or have an end date that matches the date of Visit 3 dosing will be categorized as "During or After Visit 3 Dosing". A medication may be counted as both "Before Visit 3 Dosing" and "During or After Visit 3 Dosing" if taken during both time periods.

Finally, all prior and concomitant medication data will be presented in a by-subject listing. The listing will include ATC Level 2 classification, preferred term, and verbatim term.

6.9 Concomitant Therapies and Procedures

Concomitant therapies and procedures will be collected and coded using MedDRA v24.0 - Mar 2021. Concomitant therapies and procedures will be summarized similarly to concomitant medications and presented in a by-subject listing. The listing will include SOC, PT, and verbatim term and will indicate whether the therapy or procedure occurred before or after Visit 3 dosing.

6.10 Previous Psychotropic Drug Treatment

Previous psychotropic drug treatments taken more than one month prior to screening will be documented separately from prior and comcomitant medications. These previous psychotropic

drugs will be coded and summarized using B3 WHO Drug Global – Mar 2021. The data will also be presented in a by-subject listing.

6.11 Previous Non-Drug Mental Health Treatment

Previous non-drug mental health treatments will be documented separately from concomitat therapies and procedures. These previous non-drug mental health treatments will be coded and summarized using MedDRA v24.0 - Mar 2021. The data will also be presented in a by-subject listing.

6.12 Investigational Product Exposure and Compliance

[redacted] Site personnel will instruct the subject to self-administer the IP by one spray into each nostril (right and left nasal passages), for two total sprays per dose; thus, one dose equals 2 sprays, or 3.2 µg.

All vials dispensed at Visit 2 will contain [redacted].

The total number of doses of placebo and PH94B will be summarized by treatment group.

Data will also be presented in a by-subject listing.

7 EFFICACY

All efficacy analysis reporting will be based on the ITT Population.

7.1 Primary Efficacy: Estimand, Endpoint and Analyses

7.1.1 Primary Estimand

Attribute	Definition
Treatment	The treatment of interest is PH94B, 3.2 µg administered as an intranasal (i.n.) solution (a 1.6 µg spray to each nostril per dose).
Population	The population of interest is adult subjects with SAD as defined by the protocol inclusion / exclusion criteria.
Endpoint	The endpoint to be measured is the change from baseline (Visit 2) to Visit 3 in average SUDS score during a 5-minute public speaking challenge.
Intercurrent Events (ICEs)	ICEs are expected to be rare. Any ICE that does occur will be handled using the treatment policy strategy, i.e., included in the treatment regimen under evaluation. See Section 5.6.
Population Summary	The difference of means from Visit 2 to Visit 3 in SUDS score will be estimated for each treatment group. PH94B will be compared to placebo using differences in group means.

7.1.2 Primary Endpoint and Analysis – Average SUDS Scores

The primary efficacy endpoint of the study is the difference in average SUDS score during a 5-minute public speaking challenge after treatment with PH94B or placebo at Visit 3 and the average SUDS score during a similar 5-minute public speaking challenge after treatment with placebo at Baseline (Visit 2).

The SUDS, used at Visit 2 and Visit 3 as part of each public speaking challenge, is scored 0–100. It is a standard instrument for rating social and performance anxiety in patients with SAD during role playing situations. Appendices A and B in the study protocol provide further detail on the public speaking challenge and SUDS scores.

An ANCOVA model will be used to test the null hypothesis that there is no difference in change from baseline average SUDS scores between PH94B- and placebo-treated subjects. Treatment group and analysis site will be included as factors and baseline average SUDS score as a covariate. [redacted]

[redacted]

[redacted]

[redacted]

It is expected that all subjects who are randomized at Visit 3 will complete the Visit 3 public speaking challenge immediately after randomization and be included in the primary efficacy analysis. [redacted] The effects of the missing data will be evaluated through the results of the planned sensitivity analyses described in Section 6.2.1.3.

7.1.2.1 Sensitivity Analyses

Sensitivity analyses will be performed for the primary efficacy outcome. If imputation of missing data is required, a complete case sensitivity analysis will be implemented.

Additional sensitivity analyses may include imputation using treatment group mean SUDS change scores and imputation of zero change from baseline.

In order to satisfy requirements of a CAPA, an additional sensitivity analysis will be done by performing the primary analysis with Subjects 0101, 0103, and 0104 removed. If removal of these subjects results in an analysis site with too few patients for parameter estimation, then the model will be run without analysis site, both with and without the three subjects.

7.2 Secondary Efficacy: Estimand, Endpoint and Analysis

7.2.1 Secondary Estimand

Attribute	Definition
Treatment	The treatment of interest is PH94B, 3.2 µg administered as an intranasal (i.n.) solution (a 1.6 µg spray to each nostril per dose).
Population	The population of interest is adult subjects with SAD as defined by the protocol inclusion / exclusion criteria.
Endpoint	The endpoint to be measured is the CGI-I score at Visit 3.
Intercurrent Events (ICEs)	ICEs are expected to be rare. Any ICE that does occur will be handled using the treatment policy strategy, i.e., included in the treatment regimen under evaluation.
Population Summary	The proportion of subjects with CGI-I scores of 1 [redacted] or 2 [redacted] for PH94B will be compared to placebo using a comparison of binomial proportions.

7.2.2 Secondary Endpoint and Analysis – CGI-I Scores

The secondary efficacy endpoint in the study is the proportions of CGI-I scores of 1 [redacted] or 2 [redacted] recorded at the end of Visit 3.

The secondary endpoint analysis will compare treatment groups using a normal approximation (Wald) test for the difference between two binomial proportions. The null hypothesis to be tested is that the population proportions of each treatment group are equal. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

[redacted]

[redacted]

[redacted]

8 SAFETY

Safety will be evaluated based on data collected for AEs, clinical laboratory data, vital signs, electrocardiogram (ECG) data, and physical examinations.

All safety analysis reporting will be based on the Safety Population. No formal statistical testing will be conducted for the safety analyses. Descriptive statistics will be used to evaluate safety data in this study. Summaries will present data by treatment group and overall. Listings will list safety data by treatment group and subject.

8.1 Adverse Events

An AE is any symptom, sign, illness, or experience that develops or worsens in intensity during the course of the study. Any newly developed illnesses or injuries should be regarded as adverse events. AEs will be assessed for severity, relationship to study drug, and seriousness. Further details about AE determination and categorization can be found in the study protocol.

Serious adverse events (SAEs) will be recorded starting at Visit 1 after signing informed consent. AEs will be recorded from the time of first IP administration through end of study. A TEAE is defined as any AE occurring on or after start of IP. All summaries of AEs will be based on TEAEs. All AEs recorded on the eCRF, whether treatment-emergent or not, will be presented in a data listing. Non-TEAEs will be flagged in the listings.

All AE data will be reported for two time periods: prior to Visit 3 dosing, and during or after Visit 3 dosing. This is due to the fact that all subjects receive [redacted] at Visit 2 and then receive randomized treatment [redacted] at Visit 3. AEs will be assigned to a time period based on AE start date. An AE that starts on the day of Visit 3 dosing will be assigned as “during or after Visit 3 dosing”. From Screening until IP administration at Visit 2, any clinically significant abnormality should be recorded as a preexisting condition in the medical history, not as an AE.

All AE terms will be coded by using MedDRA, version 24.0 – Mar 2021.

Missing and partially missing start and/or end dates will be imputed for the purpose of determining treatment-emergent flags and AE categorization, according to Section 5.7.

The incidence of TEAEs will be summarized by maximum severity and strongest relationship to IP. When calculating the incidence of TEAEs, each TEAE will be counted only once for a given subject within a MedDRA category (i.e., overall, SOC, or PT). When TEAEs are summarized within levels of another TEAE assessment (i.e., severity or relationship), TEAEs will be counted once per subject at the worst level of the assessment (i.e., greatest severity or relationship to IP). Any missing severity assessments will be assumed to be severe and missing relationship assessments will be assumed to be related.

An overview summary table of TEAEs will be produced, including counts and percentages of subjects with any incidences of: TEAEs, TEAEs by maximum severity, TEAEs by relationship to IP, TEAEs leading to study discontinuation, TEAEs leading to death, TEAEs related to IP leading

to death, serious TEAEs and serious TEAEs by maximum relationship to IP, serious TEAEs leading to study discontinuation and serious TEAEs leading to death.

In addition to the overview of TEAEs, the following summaries of TEAEs will be produced:

- TEAEs by System Organ Class and Preferred Term
- TEAEs by System Organ Class, Preferred Term and Maximum Severity
- TEAEs by System Organ Class, Preferred Term and Relationship to IP
- Severe TEAEs by System Organ Class and Preferred Term
- Serious TEAEs by System Organ Class and Preferred Term
- Serious TEAEs Related to IP by System Organ Class and Preferred Term
- TEAEs Leading to Study Discontinuation by System Organ Class and Preferred Term

Listings for SAEs, AEs leading to death, and AEs leading to study discontinuation will be produced as tables. Finally, all AE data will be presented in a by-subject data listing.

8.2 Clinical Laboratory Evaluations

Hematology, clinical chemistry, urinalysis, and thyroid laboratory tests, along with urine drug sreen and pregnancy tests, will be collected at various time points in the study. Hematology, clinical chemistry, urinalysis, and thyroid parameters are scheduled to be collected during screening and at Visit 4. Urine pregnancy and urine drug screen are scheduled to be collected at every visit. Refer to the Schedule of Time and Events in Appendix 1.

Hematology, clinical chemistry, urinalysis, and thyroid parameters will be reported based on the International System of Units (SI). The list of parameters to be collected can be found in the study protocol section 5.4.

Observed values and changes from baseline for laboratory evaluations will be summarized at each visit by treatment group and overall. Laboratory data will also be summarized in shift from baseline tables to display the number and percentage of subjects with clinical laboratory values categorized as low (below the lower limit of normal [LLN]), normal, or high (above the upper limit of normal [ULN]), at each post baseline visit by Visit 3 treatment group.

All laboratory parameters will be presented in a by-subject data listing and values that are outside normal ranges will be flagged. Per the data transfer agreement with ACM, abnormality flags in the data will be as follows: LP=Low Panic, LN=Low Normal, N=Normal, HN=High Normal, HP=High Panic, AB=Abnormal, SC=See Comment. Per ICH E3, an abnormal lab listing will be provided, showing all values for a given lab parameter for a given subject for which at least one abnormal value occurred.

Urine drug screen and pregnancy tests will not be summarized in tables, however their data will be included in a by-subject data listing.

8.3 Vital Signs and Physical Examinations

Vital signs will be collected at all visits. Physical examinations will be performed at Visit 1 and Visit 4. Refer to the Schedule of Time and Events in Appendix 1.

Vital signs collected at all visits will include temperature, heart rate, respiratory rate, systolic blood pressure, and diastolic blood pressure. Height and weight will be collected at Visit 1 and will be summarized and listed with Demographics and Baseline Characteristics data. For other vital signs parameters, observed values and changes from baseline (as applicable) will be summarized for each visit. Vital signs data will also be presented in a by-subject data listing.

Significant findings from physical examinations will be recorded with medical history or adverse events. Physical examination data will be listed.

8.4 Electrocardiograms (ECGs)

Electrocardiogram (ECG) data is scheduled to be collected at Visit 1 and Visit 4.

Collected ECG parameters include ventricular rate, RR interval, PR interval, QRS interval, QT interval, QTc interval, and an assessment for whether the ECG results were normal, abnormal not clinically significant, or abnormal clinically significant. The QT interval corrected using the Fredericia formula (QTcF) will be calculated as $QTcF = QT/RR^{1/3}$, where QT is measured in msec and RR is measured in sec. (Note that RR is collected in msec and will need to be converted to sec.) Observed values and changes from baseline for quantitatve ECG parameters will be summarized at each visit. Qualitative results will also be summarized.

All ECG data will be presented in a by-subject data listing.

8.5 Columbia Suicidality Severity Rating Scale (C-SSRS)

C-SSRS data is scheduled to be collected at the end of every visit. The C-SSRS questionnaire given at Visit 1 will ask subjects to report on ideation and behavior over the past six months. The C-SSRS questionnaire given at other visits will ask subjects to report on ideation and behavior since the last visit.

The C-SSRS will be scored in the following way:

- *suicidal ideation indicator:* if the response to any one of the five suicidal ideation questions below is "Yes", then set the suicidal ideation indicator equal to 1. Otherwise set the suicidal ideation indicator equal to 0.
    - Wish to be Dead
    - Non-specific Active Suicidal Thoughts
    - Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
    - Active Suicidal Ideation with Some Intent to Act, without Specific Plan

  - Active Suicidal Ideation with Specific Plan and Intent

- *suicidal behavior indicator:* if the response to any one of the five suicidal behavior questions below is "Yes", then set the suicidal behavior indicator equal to 1. Otherwise set the suicidal behavior indicator indicator to 0.
  - Preparatory Acts or Behavior
  - Aborted Attempt
  - Interrupted Attempt
  - Actual Attempt (nonfatal)
  - Completed Suicide

- *suicidal ideation or behavior indicator:* if the response to any one of the five suicidal ideation questions or any one of the five suicidal behavior questions above is "Yes", then set the suicidal ideation or behavior indicator equal to 1. Otherwise set the suicidal ideation or behavior indicator indicator to 0.

The number and percentage of subjects with each of the indicators and individual items above will be summarized by visit and Visit 3 treatment group. Subjects indicating self-injurious behavior without suicidal attempt will also be summarized. C-SSRS data will provided in a by-subject listing.

8.6 Hamilton Depression Scale (HAM-D)

Subjects will have their depression rated according to the HAM-D at Visit 1 and Visit 4. HAM-D total score ranges from 0 to 54, where 0 indicates no depression and 56 indicates severe depression. Total score for the HAM-D will be summarized by Visit 3 treatment group, and HAM-D results will be listed.

9 REFERENCES

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH E3 Guideline: Structure and content of clinical study reports questions & answers (R1). 2012. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_QAs_R1_Step4.pdf. Accessed 13 Jan 2016.

2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: Structure and content of clinical study reports E3. Step 4. 1995 http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf. Accessed 13 Jan 2016.

3. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH E9: Statistical principles for clinical trials. 1998. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf . Accessed 15 June 2016.

4. E9(R1) STATISTICAL PRINCIPLES FOR CLINICAL TRIALS: ADDENDUM: ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS Guidance for Industry, May 2021, Revision 1. https://www.fda.gov/media/148473/download

[redacted]