PROTOCOL AMENDMENT 1

PRODUCT NAME/NUMBER:	PH94B Nasal Spray
PROTOCOL NUMBER:	PH94B-CL030
IND NUMBER:	061332
NCT:	NCT05030350
DEVELOPMENT PHASE:	3
PROTOCOL TITLE:	A Phase 3 Open-label Safety Trial of PH94B Nasal Spray in the Acute Treatment of Anxiety in Adult Subjects with Social Anxiety Disorder (SAD)
PROTOCOL DATE:	Version 1.0, 12-Aug-2021
AMENDMENT 1 DATE:	Version 2.0, 14-Mar-2022
SPONSORED BY:	VistaGen Therapeutics, Inc. 343 Allerton Avenue South San Francisco, CA 94080, USA
CONTRACT RESEARCH ORGANIZATION:	[redacted]

This study will be performed in compliance with ICH Good Clinical Practices and applicable regulatory requirements, including the archiving of essential documents. Information contained in this protocol is confidential in nature, and may not be used, divulged, published, or otherwise disclosed to others except to the extent necessary to obtain approval of the institutional review board or independent ethics committee, or as required by law. Persons to whom this information is disclosed should be informed that it is confidential and may not be further disclosed without the express permission of VistaGen Therapeutics, Inc.

1. APPROVAL SIGNATURES

PROTOCOL NUMBER:	PH94B-CL030
PROTOCOL TITLE:	A Phase 3 Open-label Safety Trial of PH94B Nasal Spray in the Acute Treatment of Anxiety in Adult Subjects with Social Anxiety Disorder (SAD)
AMENDMENT 1 DATE:	Version 2.0, 14-Mar-2022

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

SIGNATURE **DATE:**

[redacted]

14-Mar-2022 | 09:11:28 PDT

[redacted]

VistaGen Therapeutics, Inc.

[redacted]

15-Mar-2022 | 06:52:56 PDT

[redacted]

VistaGen Therapeutics, Inc.

[redacted]

15-Mar-2022 | 04:56:39 PDT

[redacted]

VistaGen Therapeutics, Inc.

Sponsor:	VistaGen Therapeutics, Inc., a Nevada corporation (VistaGen) 343 Allerton Avenue South San Francisco, CA 94080
Medical Monitor:	[redacted] Phone: +1 650-577-3647 [redacted]
Medical Director:	[redacted] VistaGen Therapeutics, Inc [redacted]

2. PROTOCOL SUMMARY

2.1. Synopsis

PRODUCT NAME/NUMBER	PH94B Nasal Spray
PROTOCOL NUMBER	PH94B-CL030
DEVELOPMENT PHASE	3
PROTOCOL TITLE	A Phase 3 Open-label Safety Trial of PH94B Nasal Spray in the Acute Treatment of Anxiety in Adult Subjects with Social Anxiety Disorder (SAD)
INDICATION	Social anxiety disorder
OBJECTIVES	Primary: The primary objective of the study is to evaluate the safety and tolerability of repeated dosing of PH94B over a period of up to 12 months as assessed by documenting adverse events (AEs), standard clinical measurements (physical examination, vital signs, clinical chemistry, hematology, suicidality, level of depression, and 12-lead electrocardiogram [ECG]), and [redacted]. [redacted] [redacted] • To assess individuals' subjective predicted anxiety and avoidance of common [redacted] • [redacted] ll severity of the subject's SAD [redacted] • [redacted] subject's SAD symptoms over the course of the study • [redacted] • [redacted] • [redacted] • [redacted]
RATIONALE	The study is designed to evaluate the safety and tolerability of the long-term administration of 3.2 µg of PH94B as needed, up to 4 times a day, in adult subjects with SAD prior to acute anxiety-provoking social situations in daily life.

STUDY DESIGN	This is a multicenter, open-label, multiple dose study in adult subjects diagnosed with SAD. Subjects diagnosed with SAD by Mini-International Neuropsychiatric Interview (MINI) and with a Liebowitz Social Anxiety Scale (LSAS) total score of ≥ 50 are to be enrolled. The study will enroll subjects who have previously participated in any PH94B SAD study (for example, PALISADE-1 [PH94B-CL026] or PALISADE-2 [PH94B-CL032]) who meet requirements of the inclusion and exclusion criteria for the present study. Procedures: Subject participation in the study will last up to approximately 12 to 13 months, depending on the duration of the screening period and intervals between visits. Upon signing the informed consent form, subjects will begin participation in the present study at Visit 1 or Visit 2, depending on when they finished participation in their antecedent study: • Subjects who finished participation in their antecedent PH94B SAD study more than 14 days before entering the present study will complete Visit 1 and enter a screening period lasting between 7 and 35 days. Subjects who meet all eligibility criteria will return to the clinic to complete Visit 2 (Baseline) • Subjects who finished participation in their antecedent PH94B SAD study within the last 14 days will enter the present study at Visit 2 (Baseline) At Visit 2 (Baseline, Day 0), all subjects will undergo baseline measurements of clinical laboratory assessments (clinical chemistry, hematology, urinalysis, pregnancy test [if female and of childbearing potential], and urine drug screening), 12-lead ECG, vital signs, physical examination, Hamilton Rating Scale for Depression (HAM-D17), Hamilton Rating Scale for Anxiety (HAM-A), LSAS, Columbia-Suicide Severity Rating Scale (C-SSRS), and Clinical Global Impression Scale of Severity (CGI-S). At Visit 2 (Baseline), subjects will be trained on how to use and store PH94B Nasal Spray, and how to use an electronic diary (eDiary) application each day to record their dosing of PH94B (including a record of days when PH94B was not used) and any health problems they experienced that day. Adverse events (AEs) and concomitant medications will be reported and recorded. The subject will receive a 1-month supply of PH94B for use (up to 4 times per day) at the subject's discretion, as needed for social anxiety. Subjects will be instructed to return to the clinic for Visit 3 after 30 days (±3 days). At Visit 3, subjects will undergo clinical laboratory assessments (clinical chemistry, hematology, urinalysis, pregnancy test, and urine drug screening), vital signs, 12-lead ECG, physical examination (limited to nasal passage and oropharynx examination unless any AEs are reported), HAM-D17, HAM-A, LSAS, C-SSRS, CGI-S, Clinical Global Impression Scale of Improvement (CGI-I), and self-evaluation by Patient Global Impression of Change (PGI-C). At Visit 3, PH94B use and any daily reports of health problems that have been recorded in the eDiary will be reviewed, and AEs and concomitant medications will be reported and recorded. Subjects will receive a 1-month supply of PH94B. Subjects will return to the clinic at monthly intervals (±7 days, Visits 4 to 13), and will repeat the same assessments as those performed at Visit 3. PH94B use and any daily reports of health problems that have been recorded in the eDiary application will be reviewed, AEs and concomitant medications will be reported and recorded. Subjects will receive a 1-month supply of PH94B at each monthly visit. At Visit 14 (12 months±2 weeks), treatment will conclude, and subjects will undergo clinical laboratory assessments (clinical chemistry, hematology, urinalysis, pregnancy test, and urine drug screening), vital signs, 12-lead ECG, physical examination, HAM-D17, HAM-A, LSAS, C-SSRS, CGI-S, CGI-I, PGI-C, and the Penn Physician Withdrawal Checklist (PWC-20). Also, PH94B use and any daily reports of health

	problems that have been recorded in the eDiary application will be reviewed and AEs and concomitant medications will be recorded and reported. Subjects will also be informed of their follow-up visit (Visit 15). Subjects will return to the clinic for a follow-up visit (Visit 15, 54 weeks ±3 days), approximately 2 weeks after the last PH94B administration, to undergo C-SSRS, PWC-20, and vital signs assessments, and record AEs. Subjects who discontinue study treatment without completing 12 months of treatment will attend an Early Termination Visit (Visit 14) as soon as possible after discontinuing treatment, and return to the clinic for a follow-up visit (Visit 15) approximately 2 weeks later. <u>Safety Considerations:</u> Safety and tolerability of PH94B (≤ 4 doses per day up to 12 months in up to 600 subjects) will be assessed and summarized through changes from Visit 2 (Baseline) to end of treatment (Visit 14) in AEs, laboratory values, 12-lead ECGs, physical examinations, suicidality, level of depression, vital sign assessments, and withdrawal symptoms following exposure to PH94B.
PLANNED NUMBER OF SUBJECTS	A sufficient number of subjects from previous PH94B SAD studies will be screened or rolled over to obtain up to 600 subjects to receive up to 12 months of PH94B treatment.
STUDY ENTRY CRITERIA	Subjects who have participated in a previous PH94B SAD study will be enrolled in the present study if they meet the following eligibility criteria. <u>INCLUSION CRITERIA</u> To be considered eligible to participate in the study, all subjects must meet the following inclusion criteria: 1. Subject must have participated in a previous PH94B SAD study. Note: Subjects who have not participated in a prior PH94B SAD study may be permitted to enroll following approval by the sponsor on a case-by-case basis. 2. Written informed consent provided prior to conducting any study-specific assessment. 3. Male and female adults, 18 through 65 years of age, inclusive. 4. Women of childbearing potential must be able to commit to the consistent and correct use of an effective method of birth control throughout the study and must also have a negative urine pregnancy test result at both Screening (Visit 1) (for subjects who attend Visit 1) and Baseline (Visit 2), prior to IP administration. Effective methods of contraception include: condoms with spermicide, diaphragm with spermicide, hormonal contraceptive agents (oral, transdermal, or injectable), or implantable contraceptive devices. 5. Current diagnosis of SAD as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, and confirmed by the Mini-International Neuropsychiatric Interview (MINI). 6. Clinician-rated HAM-D17 total score < 18 at study entry (Screening [Visit 1] or Visit 2 [Baseline] as applicable). 7. Negative COVID-19 test for subjects with COVID-19 symptoms or those who had direct exposure to someone with a positive COVID-19 test, and/or completion of quarantine period consistent with requirements at the study site as determined by the investigator.

	EXCLUSION CRITERIA To be considered eligible for entry into the study, a subject must not meet any of the following exclusion criteria at study entry. 1. Any history of bipolar disorder (I or II), schizophrenia, schizoaffective disorder, psychosis, anorexia or bulimia, premenstrual dysphoric disorder, autism-spectrum disorder, obsessive-compulsive disorder, or treatment-refractory major depressive disorder. Any other current Axis I disorder, other than SAD, which is the primary focus of treatment. Note that subjects with concurrent Generalized Anxiety Disorder are eligible for the study provided that Generalized Anxiety Disorder is not the primary diagnosis. 2. In the opinion of the Investigator, the subject has a significant risk for suicidal behavior during the course of their participation in the study, or a. At Screening (for subjects who attend Visit 1): the subject scores "yes" on items 4 or 5 in the Suicidal Ideation section of the Columbia-Suicide Severity Rating Scale (C-SSRS) with reference to a 6-month period prior to screening; or b. At Screening (for subjects who attend Visit 1): the subject has had 1 or more suicidal attempts with reference to a 2-year period prior to screening; or c. At Baseline (Visit 2): the subject scores "yes" on items 4 or 5 in the Suicidal Ideation section of the C-SSRS with reference to last visit; or d. The subject is considered to be an imminent danger to themself or others. 3. Subjects using the following psychotropic medications at enrollment or within 30 days before study entry: antidepressants (including monoamine oxidase inhibitors), anxiolytics, stimulants, anticonvulsants, mood stabilizers, antipsychotic medications, gabapentin, pregabalin, opioids, naltrexone, esketamine, and ketamine. Eszopiclone, ramelteon, melatonin, zaleplon, zolpidem, or anti-histamines prescribed for insomnia are allowed. 4. Use of benzodiazepines or unapproved treatments such as beta blockers, within 30 days before study entry and during the study. Use of beta blockers for treatment of hypertension or cardiac conditions is allowed. Subjects who have been taking benzodiazepines daily for 1 month or longer at the time of Visit 1 are not eligible to participate. 5. Use of any over-the-counter product or herbal preparation for treatment of the symptoms of anxiety or social anxiety within 30 days before study entry; concomitant use is prohibited during the study. 6. Clinically significant nasal pathology or history of significant nasal trauma, nasal surgery, total anosmia, or nasal septum perforation that may have damaged the nasal chemosensory epithelium. 7. Subjects who meet criteria for moderate or severe alcohol or substance use disorder within the 1 year prior to entry into the study. 8. Subjects with a positive urine drug screen at study entry [redacted] 9. An acute or chronic condition, including an infectious illness, uncontrolled seasonal allergies at the time of the study, or significant nasal congestion that potentially could affect drug delivery to the nasal chemosensory epithelium. 10. Any current clinically significant and/or uncontrolled medical condition, based on medical history or as evidenced in screening assessments, such as COVID-19, HIV, cancer, stroke, congestive heart failure, uncontrolled diabetes mellitus, or any other medical condition or disease that, in the clinical judgment of the Investigator, could

	place the subject at undue risk, interfere with study participation, or confound the results of the study. 11. Women who have a positive urine pregnancy test prior to IP administration. Women who are currently breastfeeding are not eligible. 12. History of cancer or malignant tumor not in remission for at least 2 years. Basal cell skin cancers are not exclusionary. 13. Subjects with clinically significant abnormalities in hematology, blood chemistry, urinalysis, 12-lead ECG, or physical examination identified at study entry or during the legacy study which, in the clinical judgment of the Investigator, could place the subject at undue risk, interfere with study participation, or confound the results of the study.
TEST PRODUCT	Name: PH94B Nasal Spray Dose, route, frequency: 3.2 µg administered as an intranasal (i.n.) solution (a 1.6-µg spray to each nostril per dose), up to 4 times a day.
CONTROL PRODUCT	Not applicable
TREATMENT REGIMENS	Treatment will be administered as needed at 3.2 µg per dose of PH94B (≤ 4 doses per day) from Visit 2 (Baseline) to Visit 14 (End of Treatment). Treatment with PH94B should be self-administered as needed approximately 15 minutes prior to or during an anxiety-provoking social situation or event. Consecutive nasal administrations of IP should be [redacted], with no more than 4 administrations per day. Treatment does not need to be administered every day.
PLANNED STUDY SITES	The study is designed as a multicenter study conducted in the USA with approximately 40 clinical study sites.
CRITERIA FOR EVALUATION	The primary outcome variable for the study is the change from Baseline (Visit 2) in AEs after the administration of PH94B prior to anxiety-provoking social situations in daily life for subjects with SAD. In addition to the primary outcome variable, the change from Baseline (Visit 2) in standard clinical measurements and behavioral assessment scores (LSAS, CGI-S, CGI-I, and PGI-C) in response to anxiety-provoking social situations in daily life after the administration of PH94B will be evaluated in subjects with SAD. Safety endpoints: • Incidence and severity of AEs, AEs leading to discontinuation, and SAEs • Changes in vital signs results • Changes in clinical laboratory evaluation (hematology, chemistry, and urinalysis) results • Changes in 12-lead ECG results • Changes in physical examination findings • Changes in HAM-D17 scores • Changes in C-SSRS scores • PWC-20 scores after termination of PH94B [redacted]: • Change in total LSAS scores over time with use of PH94B • Change in proportion of subjects with CGI-S scores >4 over time with use of PH94B

	• Change in proportion of subjects with CGI-I scores of 1 (Very much improved) or 2 (Much improved) over time with use of PH94B • Change in proportion of subjects with PGI-C scores of 1 (Very much improved) or 2 (Much improved) over time with use of PH94B • [redacted] • [redacted] • [redacted]
STATISTICAL METHODS	Analysis Populations: Safety population: All subjects who receive IP. All analyses will be performed using the Safety population. Safety Analyses: Safety and tolerability implications are best addressed by applying descriptive statistical methods to the data, supplemented by calculation of confidence intervals wherever this aids interpretation. The incidence of AEs for defined periods of exposure (e.g., 3 months, 6 months, 9 months, 12 months, and overall) will be evaluated in the form of a proportion relating number of subjects experiencing events to number of subjects at risk for AEs by organ, relatedness, severity of reported AE, and by frequency of AE. In addition, frequency-type of reported AEs (once, continuous, or adaptability to treatment) by time of occurrence after Visit 2 dispensation may be tabulated. These data will be summarized and tabulated, including confidence intervals when appropriate, for descriptive purposes, and may serve as nonparametric endpoints. Time series analysis will be used where warranted to determine whether frequency of AEs changes with increased duration of exposure. Efficacy Analyses: Exploratory endpoints address efficacy using patient- and clinician-rated scales and will be evaluated for significant changes from baseline using a generalized linear model for repeated measures.
SAMPLE SIZE DETERMINATION	Based on feedback from the FDA, the sample size for this study (up to 600 subjects) has been selected to attain a PH94B safety database per the ICH E1 Guideline.
STUDY AND TREATMENT DURATION	The sequence and maximum duration of the study periods will be as follows: 1. Screening and washout (if applicable): From 7 to 35 days 2. 12-Month treatment period: From Visit 2 (Baseline) through Visit 14 (End of Treatment) 3. Follow-up period: Follow-up visit (Visit 15) conducted approximately 2 weeks after last treatment The maximum study duration for each subject is approximately 59 weeks. The maximum treatment duration for each subject is 12 months.

2.2. Schedule of Events

Table 2-1: Schedule of Events

Assessment/Evaluation	Study Periods					
	Visit 1	**Visit 2**	**Visit 3**	**Visits 4 to 13**	**Visit 14 / ET**	**Visit 15**
	Screening	**Baseline**	**1st Month**	**Monthly**	**End of Treatment**	**Follow-up**
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Informed Consent Form	X[a]	X[a]				
Subject Demographics	X					
Urine Drug Screen	X	X	X	X	X	
Pregnancy Test[b]	X	X	X	X	X	
MINI 7.0.2	X					
Medical and Psychiatric History	X					
Record Concomitant Medication Use	X	X	X	X	X	
[redacted]	[redacted]					
LSAS	X	X	X	X	X	
HAM-D17 [redacted]	[redacted]					
C-SSRS	X	X	X	X	X	X
Physical Examination[c,d]	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X
12-Lead Electrocardiogram[e]	X	X	X	X	X	
Clinical Chemistry, Hematology, and Urinalysis	X	X	X	X	X	
Review Inclusion/Exclusion Criteria	X	X[f]				
CGI-S	X	X	X	X	X	
CGI-I			X	X	X	
PGI-C			X	X	X	
PWC-20					X	X

Assessment/Evaluation	Study Periods					
	Visit 1	**Visit 2**	**Visit 3**	**Visits 4 to 13**	**Visit 14 / ET**	**Visit 15**
	Screening	**Baseline**	**1st Month**	**Monthly**	**End of Treatment**	**Follow-up**
	Day -35 to Day -7	**Day 0**	**Day 30 ±3 days**	**±7 days**	**52 Weeks ±2 weeks**	**54 Weeks ± 3 days**
Training on Use of PH94B		X				
Storage Instructions		X	X	X		
Training on eDiary App to Record PH94B Use and Health Problems		X				
Adverse Event Recording		X	X	X	X	X
Dispense PH94B to Subject		X	X	X		
eDiary Review			X	X	X	

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale; CGI-I = Clinical Global Impression Scale of Improvement; CGI-S = Clinical Global Impression Scale of Severity; eDiary = electronic diary; ET = Early Termination; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D17 = Hamilton Rating Scale for Depression (17 items); LSAS = Liebowitz Social Anxiety Scale; MINI = Mini-International Neuropsychiatric Interview; PGI-C = Patient Global Impression of Change; PWC-20 = Penn Physician Withdrawal Checklist; SAD = social anxiety disorder

a Subjects will sign an informed consent form for the present study at either Visit 1 or Visit 2, depending on when they enter the study.

b Pregnancy tests will only be given to female subjects of childbearing potential and not post-menopausal females.

c Physical examination will include measurement of weight and an examination of the nasal passages. Height will be measured at Screening and at Visit 14. The physical examinations done at Visit 1, Visit 2 and Visit 14 will be comprehensive. The physical examinations done at Visit 3 to Visit 13 will be focused but must include examination of the nasal passages and oropharynx. Other organ systems should be examined at Visit 3 to Visit 13 if the subject reports AEs or if the investigator has specific concerns.

d [redacted].

e 12-Lead electrocardiograms will be administered in a supine position after the subject has rested for 5 minutes.

f For all subjects, a review of inclusion and exclusion criteria will be conducted at Visit 2 to confirm eligibility.

Note: Long-term C-SSRS will be administered at screening. All other C-SSRS evaluations will be "Since Last Visit."

Note: If central laboratory urine drug screen testing is positive for a subject [redacted], then the participation of the subject in the study may have to be discontinued. The Medical Monitor should be consulted on these cases. An unscheduled repeat urine drug screen may be obtained to investigate whether drug use is continuing.

3. TABLE OF CONTENTS

3.1. List of In-Text Tables

REASONS FOR AMENDMENT

1. The study entry criteria were modified such that only subjects who have participated in a previous SAD study with PH94B (e.g., PALISADE-1 or PALISADE-2) can participate.
2. The number of potential study sites was modified to 40, to more accurately reflect the number of sites that are likely to be involved based on the PALISADE-1 and PALISADE-2 studies.
3. The estimate of 800 subjects to be screened to provide 600 subjects was removed, and replaced by text stating that a sufficient number of subjects would be screened.
4. The eligibility criteria were changed such that the use of anxiolytics in the 30 days before study is now exclusionary; their use is also prohibited during the study, with the exception of buspirone.
5. The eligibility criteria were changed such that the use of stimulants in the 30 days before study is now exclusionary; their use is also prohibited during the study.
6. The eligibility criteria were changed to exclude subjects who are using low-dose antipsychotics (rather than allowing their inclusion on a case-by-case basis).
7. The eligibility criteria were changed such that the use of antidepressants in the 30 days before study is now exclusionary. Treatment with antidepressants (except MAO inhibitors and ketamine) or buspirone can be initiated during the study provided that the antidepressant has been approved for the treatment of SAD or major depressive disorder by the FDA.
8. The eligibility criteria were changed to exclude women who are currently breastfeeding since it is not yet known whether PH94B can pass to an infant through breast milk.
9. The inclusion criterion concerning COVID-19 was modified to provide additional clarification.
10. Text describing prohibited therapies was updated to explain that legitimate use of prohibited medications for a short period will not necessarily lead to exclusion, but should be discussed on a case-by-case basis with the Medical Monitor.
11. The maximum duration of the screening period was increased from 30 days to 35 days.
12. Modify the rationale to clarify that <u>acute</u> symptoms of anxiety are being investigated.
13. Language was added to indicate that subjects are to complete the eDiary even on days when they have not used any PH94B, and to record details of any health problems they experience.
14. The order in which assessments should be carried out during the screening visit was updated.
15. Physical examination updated.
16. The Penn Physician Withdrawal Checklist was added to safety assessments, to be conducted at Visit 14/ET visit and Visit 15 (Follow-up visit); relevant descriptions of the assessment and the analysis were added.
17. The analysis population definitions were simplified.
18. Removed text stating that a physician is required to see subjects at each visit, since this is not necessary.

[redacted]

20. Text was added to advise male subjects with partners of childbearing potential to use contraception throughout their participation in the study, although this is not mandatory.
21. Text was added to clarify that ECGs should be performed in a supine position after the subject has rested for 5 minutes, to ensure consistency in the way ECG is measured.
22. Information on sample retention was updated.
23. Text describing the investigational product was clarified, including the addition of a description of monthly kits that will be provided.
24. Text describing the subject identification numbers was clarified.
25. Contact details for the study medical monitor were added.
26. New appendices were added to provide investigators with the [redacted] Hamilton Depression Rating Scale, Clinical Global Impression Scale of Improvement, Clinical Global Impression Scale of Severity, Patient Global Impression of Change, and the PWC-20.

A "Summary of Amended Sections" is provided in APPENDIX J.

AMENDED PROTOCOL

The following are the amended protocol and appendices, including all revisions specified above and detailed in the "Summary of Amended Sections" (is provided in APPENDIX J).

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	EXPLANATION
AE	adverse event
C-SSRS	Columbia-Suicide Severity Rating Scale
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression Scale of Improvement
CGI-S	Clinical Global Impression Scale of Severity
CI	confidence interval
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CSR	clinical study report
EC_{50}	concentration giving half-maximal response
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
GABA	gamma aminobutyric acid
GCP	Good Clinical Practice
[redacted]	[redacted]
HAM-D17	Hamilton Depression Scale (17 items)
IB	investigator brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
i.n.	intranasal
IND	Investigational New Drug
IP	investigational product
IRB	institutional review board
LSAS	Liebowitz Social Anxiety Scale
MAO	monoamine oxidase
MINI	Mini-International Neuropsychiatric Interview
PGI-C	Patient Global Impression of Change
PWC-20	Penn Physician Withdrawal Checklist
SAD	social anxiety disorder
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation

ABBREVIATION	EXPLANATION
SUDS	Subjective Units of Distress Scale
UAE	unanticipated adverse event
UDS	urine drug screen

5. INTRODUCTION

This document is a protocol for a Phase 3 human research study. This study is to be conducted according to United States and international standards of Good Clinical Practice (GCP) (Food and Drug Administration [FDA] Title 21 part 312 and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] guidelines), applicable government regulations, and institutional research policies and procedures.

5.1. Background and Rationale

5.1.1 Social Anxiety Disorder

The essential features of social anxiety disorder (SAD) are defined as intense, marked, and persistent fear of social or performance situations, in which the subject believes embarrassment, humiliation, judgment, or rejection could occur as a consequence of exposure to unfamiliar people or possible scrutiny by others in the social or performance (e.g., public speaking) situation. The anxiety or fear resulting from the social or performance situation is profound. The avoidance, fear, or anxious anticipation of these situations interferes significantly with the person's daily routine, having a marked impact on occupational functioning and social life. The disorder has a lifetime prevalence estimated at up to 13%, with onset typically in the mid-teens or earlier, and it is diagnosed slightly more frequently in females than in males. Social anxiety tends to be a chronic disorder with periods of exacerbation, and a reported mean duration of illness of approximately 20 years.[1,2]

Two subtypes of social anxiety are described in Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: (i) social anxiety (formerly called generalized subtype) in which fear and avoidance extend to a wide range of social situations, and (ii) performance subtype only, in which the subject fears only one or a few circumscribed situations. Public speaking is by far the most prevalent of social fears.[1]

Social anxiety disorder has a lifetime comorbidity rate of approximately 81% with other psychiatric disorders (particularly affective disorders, other anxiety disorders, and substance abuse disorders), as well as being associated with increased non-psychiatric medical difficulties. People with SAD identify themselves as struggling with social impairment, inadequate social support, overall role impairment, specific impairment in education, work, and other activities, as well as interference in their efforts at self-improvement. Unfortunately, for these subjects, there is a strong consensus that SAD is one of the least commonly recognized and treated mental disorders.[1,2]

Current treatments for SAD include both psychosocial and pharmacologic measures. Psychosocial treatments include exposure therapy and cognitive behavioral therapy. Pharmacological measures vary widely and include antidepressants (monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors), benzodiazepines, beta blockers, and alpha-2-delta voltage gated calcium channel modulators.

5.1.2 Nasal Chemosensory Systems

In humans, as in other mammals, the olfactory system is a rostral projection of the telencephalon and it is the only sensory system with direct neural connections to the limbic system without a relay in the thalamus. Therefore, the limbic amygdala is the only brain structure that receives rapid afferent neural inputs from peripheral nasal chemosensory receptors.[3,4] Chemical cues acting on

nasal chemosensory neurons trigger sensory inputs that reach the limbic amygdala through a rapid (oligosynaptic) neural path.

The relevance of the olfactory system in behavior is revealed by the serious behavioral impairment that occurs after bilateral olfactory bulbectomy in laboratory animals,[5,6] and the development of anxiety and depression in humans with congenital anosmia.[7,8]

Stimulation of human olfactory chemosensory cells with primary odors produces olfactory awareness via the main olfactory neural circuits,[9,10] but in humans chemosensory cues also engage nasal chemosensory receptors and induce behavioral and neuroendocrine responses, without olfactory awareness.[11-16]

In most mammals, odorless chemosignals induce activation of accessory olfactory neural circuits.[17-22] However, some mammals including humans do not have an accessory olfactory system, and there are instead neural connections arising in nasal chemosensory neurons that connect with a subset of neurons in the main olfactory bulb. These main olfactory bulb neurons in turn project directly to the cortical and the medial amygdala and trigger an important contingent of forward inhibitory GABAergic neural circuits in the central amygdala involved in the modulation of fear and anxiety.[21-26]

These olfactory-limbic neural circuits play an important role in social behavior and emotions.[11-13,19,27,28] The independent sensory contribution of the olfactory system projections to the limbic amygdala on social behavior has been also confirmed in molecular biology/behavioral studies, in studies using knockout mouse lines with loss of function in different zones of the olfactory bulbs,[20] in human functional magnetic resonance imaging studies,[12,29] in clinical studies in human subjects with isolated congenital anosmia,[7,30] and in subjects with congenital hypogonadotropic hypogonadism.[31]

It has been suggested that olfactory receptor repertoires differ significantly across species.[32] Since these receptors have different roles in different behaviors (e.g., social behavior, fear, reproductive behavior) the rapid evolutionary divergences may have contributed to behavior differentiation and speciation. Therefore, the action of chemosignals on nasal chemosensory neurons differs significantly across species.[33-35]

Pherines are a family of synthetic neuroactive steroid molecules that engage specifically with human nasal chemosensory receptors. Pherines stimulate receptor neurons in the human nasal chemosensory epithelium[14,36] that activate olfactory bulb neurons and in turn trigger neural circuits in the limbic amygdala. This leads to activation of the anterior gyrus, hypothalamus, hippocampus and prefrontal cortex, and it is different from the brain areas activated by primary olfactory stimuli.[12,29] Pherines are odorless, and brain activation by pherines does not produce olfactory awareness[12,14] and can modulate brain autonomic and psychophysiologic response.[11,13,15,29,37-39]

5.1.3 PH94B

PH94B (3β-androsta-4,16-dien-3-ol) is a synthetic neuroactive steroid discovered and initially developed at Pherin Pharmaceuticals that targets human nasal chemosensory cells[11,36] and has been demonstrated in Phase 2 clinical studies to have benefits for the acute treatment of SAD.[40]

Pherines induce calcium ion entry in human nasal chemosensory neurons.[37,41] Pherines such as PH94B target G-protein-coupled receptor chemosensory receptors that are expressed in human nasal chemosensory neurons.[32,42]

In vitro screening studies using isolated, living, human nasal chemosensory neurons have shown that picomolar quantities of PH94B can selectively induce inward currents in a concentration-dependent and reversible fashion.[43] These membrane currents are carried by calcium ions.[41] [redacted]

[redacted] PH94B exerts its activity by stimulation of neural circuits involving the limbic amygdala, and it does not require systemic uptake and distribution to produce its anxiolytic pharmacological effects. PH94B is being investigated as a potential acute treatment for the alleviation of anxiety symptoms in adult patients with SAD. While PH94B may regulate gamma aminobutyric acid (GABA) circuits in the limbic amygdala, electrophysiological experiments in vitro show that PH94B does not directly bind to or modulate GABA receptors at concentrations of 10 µM or lower, which differentiates its mechanism of action from benzodiazepines.[44] PH94B had no significant effect on GABA potentiation at doses up to 10 µM, compared to the 300% potentiation induced by diazepam, a commonly-prescribed benzodiazepine. The concentration of PH94B that gives the half-maximal response (EC_{50}) could not be calculated for PH94B, whereas diazepam's EC_{50} was 72 nM (0.072 µM).

5.2. Clinical Experience

[redacted]

5.2.2 Phase 2 Studies

Two completed Phase 2 clinical studies had similar population and efficacy endpoints as the Phase 3 study PH94B-CL026 (PALISADE-1), currently in progress. These double-blind, randomized, placebo-controlled Phase 2 clinical studies [redacted], included a total of 91 female subjects who met criteria for SAD (generalized subtype) as defined by the Diagnostic and Statistical Manual of Mental Disorders 4th edition. PH94B (1.6 µg) was administered i.n. (in spray form) 15 minutes prior to both a performance (public speaking) challenge and a social interaction challenge simulation which took place at the clinical sites. The 2 challenges were separated by a 30-minute rest period. The primary outcome measures were the Clinical Global Impression Scale of Improvement (CGI-I) and the Subjective Units of Distress Scale (SUDS). The CGI-I rating is based on a 7-point scale in response to treatment ranging from very much improved (1), much improved (2), minimally improved (3), no change (4), minimally worse (5), much worse (6), and to very much worse (7). The SUDS scores range from 0 to 100, with higher scores indicating greater levels of anxiety. Subjects receiving PH94B were more likely to show improvement on the CGI-I following treatment than those who received placebo. In the PH94B group, 34 of 45 subjects (75.6%) were rated very much improved or much improved compared to only 17 of 46 subjects (37%) in the placebo group ($p < 0.001$).[40]

During the public speaking challenge, subjects randomized to PH94B ($n = 45$) showed an improvement of 26.7 points in the mean score on the SUDS at Visit 3 (initial treatment visit) as compared to Visit 2 (Baseline visit, at which all subjects received placebo). In comparison, subjects randomized to placebo ($n = 46$) showed an improvement of only 14.0 in the mean SUDS score across visits. The PH94B group's improvement from Visit 2 to Visit 3 significantly exceeded the placebo group's improvement from Visit 2 to Visit 3 ($t = 3.16$, $p = 0.002$) on this challenge.[40] No SAEs were reported and no subjects were terminated prematurely from the study due to AEs.

5.3. Summary of Potential Risks and Benefits

The potential benefits of study participation are that subjects with SAD may experience a reduction in their symptoms when they encounter anxiety-provoking situations in daily life as a result of treatment with PH94B. No other benefits of participation are anticipated.

Based on previous clinical studies conducted with PH94B, it is believed to be safe and well tolerated, and risks to subjects are considered minimal. Intranasal administration of PH94B may increase the risk of local site reactions including itching, burning, runny nose, sneezing and soreness inside the nose. In completed clinical studies, the most commonly reported AE was headache. None of these effects was reported in more subjects receiving PH94B than in subjects receiving placebo. In a nonclinical long-term safety study, no toxic effects were observed in rats administered repeated daily doses of PH94B for 6 months, suggesting that prolonged exposure to PH94B is safe; no toxic effects are expected with prolonged exposure in humans.

A summary of the pharmaceutical properties and known potential risks of PH94B is provided in the current version of the investigator brochure (IB). The Investigator must become familiar with all sections of the PH94B IB before the start of the study.

6. OBJECTIVES

6.1. Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of repeated dosing of PH94B over a period of up to 12 months as assessed by documenting AEs, standard clinical measurements (physical examination, vital signs, clinical chemistry, hematology, suicidality, level of depression, and 12-lead electrocardiogram [ECG]), and withdrawal symptoms.

[redacted]

- To assess individuals' sub[redacted]
- [redacted] observed level of overall severity of the subject's SAD symptoms over [redacted]
- [redacted] of the subject's SAD [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

6.3. Endpoint Mapping

Endpoints are mapped to study objectives as follows:

Objectives	Endpoints
Primary	
The primary objective of the study is to evaluate the safety and tolerability of repeated dosing of PH94B over a period of up to 12 months as assessed by documenting AEs, standard clinical measurements (physical examination, vital signs, clinical chemistry, hematology, suicidality, level of depression, and 12-lead ECG), and withdrawal symptoms	Incidence and severity of AEs, AEs leading to discontinuation, and SAEs Changes in vital signs results Changes in clinical laboratory evaluation (hematology, chemistry, and urinalysis) results Changes in 12-lead ECG results Changes in physical examination findings Changes in HAM-D17 scores Changes in C-SSRS scores PWC-20 scores after termination of PH94B
[redacted]	
[redacted]	
• To assess individuals' subjective predicted anxiety and avoidance of common SAD triggers in daily life over the course of the study	Change in total LSAS scores over time with use of PH94B
• [redacted] overall severity of the subject's SAD [redacted]	[redacted]
• [redacted]	[redacted]
• To assess changes in subject perception of change in overall severity of their SAD symptoms over the course of the study	Change in proportion of subjects with PGI-C scores of 1 (Very much improved) or 2 (Much improved) over time with use of PH94B
• [redacted]	[redacted]
• [redacted]	[redacted]

Objectives	Endpoints
• [redacted]	[redacted]

Abbreviations: AE = adverse event; C-SSRS = Columbia-Suicide Severity Rating Scale; CGI-I = Clinical Global Impression Scale of Improvement; CGI-S = Clinical Global Impression Scale of Severity; ECG = electrocardiogram; [redacted]; HAM-D17 = Hamilton Rating Scale for Depression (17 items); LSAS = Liebowitz Social Anxiety Scale; PGI-C = Patient Global Impression of Change; PWC-20 = Penn Physician Withdrawal Checklist; SAD = social anxiety disorder; SAE = serious adverse event

7. STUDY DESIGN

Prevention of missing data is central to this study design. All subjects will be counseled at enrollment on the importance of completing the study and communicating all issues and concerns to the study staff.

A sufficient number of subjects from previous PH94B SAD studies will be screened or rolled over to obtain up to 600 subjects to receive up to 12 months of PH94B treatment.

7.1. Overall Study Design and Plan

Subject participation in the study will last up to approximately 12 to 13 months, depending on the duration of the screening period and intervals between visits. Upon signing the informed consent form (ICF), subjects will begin participation in the present study at Visit 1 or Visit 2, depending on when they finished participation in their antecedent study:

- Subjects who finished participation in their antecedent PH94B SAD study more than 14 days before entering the present study will complete Visit 1 and enter a screening period lasting between 7 and 35 days. Subjects who meet all eligibility criteria will return to the clinic to complete Visit 2 (Baseline)
- Subjects who finished participation in their antecedent PH94B SAD study within the last 14 days will enter the present study at Visit 2 (Baseline)

At Visit 2 (Baseline, Day 0), all subjects will undergo baseline measurements of clinical laboratory assessments (clinical chemistry, hematology, urinalysis, pregnancy test [if female and of childbearing potential], and urine drug screening), 12-lead ECG, vital signs, physical examination, Hamilton Rating Scale for Depression (HAM-D17), [redacted] Liebowitz Social Anxiety Scale (LSAS), Columbia-Suicide Severity Rating Scale (C-SSRS), and Clinical Global Impression Scale of Severity (CGI-S). At Visit 2 (Baseline), subjects will be trained on how to use and store PH94B Nasal Spray, and how to use an electronic diary (eDiary) application each day to record their dosing of PH94B (including a record of days when PH94B was not used) and any health problems they experienced that day. Adverse events (AEs) and concomitant medications will be reported and recorded. The subject will receive a 1-month supply of PH94B for use (up to 4 times per day) at the subject's discretion, as needed for social anxiety.

Subjects will be instructed to return to the clinic for Visit 3 after 30 days (±3 days). At Visit 3, subjects will undergo clinical laboratory assessments (clinical chemistry, hematology, urinalysis, pregnancy test, and urine drug screening), vital signs, 12-lead ECG, physical examination (limited to nasal passage and oropharynx examination unless any AEs are reported), HAM-D17, [redacted] LSAS, C-SSRS, CGI-S, CGI-I, and self-evaluation by the patient-reported outcome measure, Patient Global Impression of Change (PGI-C). At Visit 3, PH94B use and any daily reports of health problems that have been recorded in the eDiary application will be reviewed and AEs and concomitant medications will be reported and recorded. Subjects will receive a 1-month supply of PH94B.

Subjects will return to the clinic at monthly intervals (±7 days, Visits 4 to 13), and will repeat the same assessments as those performed at Visit 3. PH94B use and any daily reports of health problems that have been recorded in the eDiary application will be reviewed, AEs and concomitant medications will be reported and recorded at each visit. Subjects will receive a 1-month supply of PH94B at each monthly visit.

At Visit 14 (12 months±2 weeks), treatment will conclude, and subjects will undergo clinical laboratory assessments (clinical chemistry, hematology, urinalysis, pregnancy test, and urine drug screening), vital signs, 12-lead ECG, physical examination, HAM-D17, [redacted] LSAS, C-SSRS CGI-S, CGI-I, PGI-C, and the Penn Physician Withdrawal Checklist (PWC-20). Also, PH94B use and any daily reports of health problems that have been recorded in the eDiary application will be reviewed, and AEs and concomitant medications will be recorded and reported. Subjects will also be informed of their follow-up visit (Visit 15).

Subjects will return to the clinic for a follow-up visit (Visit 15, 54 weeks ±3 days), approximately 2 weeks after the last PH94B administration, to undergo C-SSRS, PWC-20, and vital signs assessments, and record AEs.

Subjects who discontinue study treatment without completing 12 months of treatment will attend an Early Termination Visit (Visit 14) as soon as possible after discontinuing treatment, and return to the clinic for a follow-up visit (Visit 15) approximately 2 weeks later.

Safety Considerations:

Safety and tolerability of PH94B (≤ 4 doses per day up to 12 months in up to 600 subjects) will be assessed and summarized through changes from baseline (Visit 2) to end of treatment (Visit 14) in AEs, laboratory values, 12-lead ECGs, physical examinations, suicidality, level of depression, vital sign assessments, and withdrawal symptoms following exposure to PH94B.

7.2. Rationale and Discussion of Study Design

The present study has been designed to evaluate the safety and tolerability of PH94B with repeated dosing over a period of up to 12 months, in subjects who have participated in previous PH94B SAD studies. Participating subjects will use PH94B up to 4 times a day when they encounter anxiety-provoking social situations in daily life. Formal evaluation of the efficacy of PH94B is being conducted in 2 Phase 3 studies, which have been designed and powered to assess its efficacy in reducing anxiety in a public speaking challenge. In the present study, evaluation of the efficacy of PH94B over the 12-month treatment period is an exploratory objective.

Given that evaluation of long-term safety is the primary objective of this study, an open-label study with no comparator is considered to be an appropriate design.

Safety assessments in this study are standard for the evaluation of an investigational medicinal product, and include collection of AEs and SAEs, and evaluation of vital signs, safety laboratory tests, 12-lead ECGs, and physical examinations; given the use of the i.n. route of administration, the physical examination will include an examination of the nasal passages. Given that subjects are patients with a confirmed diagnosis of SAD, the C-SSRS will be used at each study visit as a precautionary measure. Withdrawal symptoms will also be assessed.

The exploratory evaluation of efficacy of PH94B with long-term use will use clinician-rated tools such as the LSAS, CGI-I and CGI-S, and a patient-reported outcome measure, the PGI-I. These are commonly used in clinical studies of psychiatric disorders, including SAD, and are considered appropriate for the present study.

7.3. Selection of Doses in the Study

PH94B is an investigational new drug that has shown statistically significant efficacy, rapid onset of effect, and an excellent safety profile in the treatment of performance anxiety and social

interaction anxiety in subjects diagnosed with SAD. A [redacted] formulation has been used i.n. in Phase 1 and Phase 2 clinical studies. The i.n. route of administration is required for the small quantities of PH94B to engage directly with nasal chemosensory neurons interspersed in the nasal olfactory epithelium.

Nonclinical and clinical studies with PH94B are summarized in the IB. Nonclinical studies on chronic exposure to PH94B and clinical Phase 2 studies have shown that PH94B is safe for use in human subjects [redacted]. PH94B could not be quantified in blood samples of human subjects administered [redacted] i.n. in a Phase 1 study. No SAEs associated with the administration of PH94B have been observed in any clinical study to date. Safety margin based no-observed-adverse-effect levels for toxicity have indicated that the proposed doses are safe. The profile of physiological and behavioral responses to PH94B was similar for males and females, but the magnitude of effect is slightly reduced for males at the 1.6-µg dose. Based on Phase 1 and Phase 2 study outcomes after a single dose of PH94B of 3.2 µg (one 1.6-µg spray per nostril) and observations made in study PH94B-CL019, this study proposes the self-administration of repeat dosing of PH94B 3.2 µg (one 1.6-µg spray per nostril), for males and females. PH94B, the investigational product (IP), will be self-administered i.n. up to 4 times per day in an open-label study. The objective of the study is to evaluate the safety and tolerability of PH94B use, and incidence of AEs in subjects with SAD over a 12-month observation period. Monthly clinic-based visits will be used to monitor subjects throughout the course of the study.

7.4. Study Sites

The study is designed as a multicenter study conducted in the USA with approximately 40 clinical study sites.

7.5. End of Study Definition

A clinical study is considered completed when the last subject's last study visit has occurred.

8. SUBJECT POPULATION

8.1. Selection of Study Population

Eligibility for participation in the study will be determined from demographic information, medical and psychiatric history, physical and psychiatric examination, 12-lead ECG, clinical laboratory findings, and clinical rating scale assessments.

Any information to be disseminated to potential subjects (handouts, brochures, etc.), as well as direct advertisements (including direct electronic or digital advertising), must be approved by VistaGen and by the appropriate IRB prior to use and implementation.

8.2. Study Entry Criteria

Subjects who do not meet all of the eligibility criteria will not be enrolled.

8.2.1 Inclusion Criteria

To be considered eligible to participate in the study, all subjects must meet the following inclusion criteria:

1. Subject must have participated in a previous PH94B SAD study.

   Note: Subjects who have not participated in a prior PH94B SAD study may be permitted to enroll following approval by the sponsor on a case-by-case basis.
2. Written informed consent provided prior to conducting any study-specific assessment.
3. Male and female adults, 18 through 65 years of age, inclusive.
4. Women of childbearing potential must be able to commit to the consistent and correct use of an effective method of birth control throughout the study and must also have a negative urine pregnancy test result at both Screening (Visit 1) (for subjects who attend Visit 1) and Baseline (Visit 2), prior to IP administration. Effective methods of contraception include: condoms with spermicide, diaphragm with spermicide, hormonal contraceptive agents (oral, transdermal, or injectable), or implantable contraceptive devices.
5. Current diagnosis of SAD as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, and confirmed by the Mini-International Neuropsychiatric Interview (MINI).
6. Clinician-rated HAM-D17 total score < 18 at study entry (Screening [Visit 1] or Visit 2 [Baseline] as applicable).
7. Negative COVID-19 test for subjects with COVID-19 symptoms or those who had direct exposure to someone with a positive COVID-19 test, and/or completion of quarantine period consistent with requirements at the study site as determined by the investigator.

8.2.2 Exclusion Criteria

To be considered eligible for entry into the study, a subject must not meet any of the following exclusion criteria at study entry.

1. Any history of bipolar disorder (I or II), schizophrenia, schizoaffective disorder, psychosis, anorexia or bulimia, premenstrual dysphoric disorder, autism-spectrum disorder, obsessive-compulsive disorder, or treatment-refractory major depressive disorder.

Any other current Axis I disorder, other than SAD, which is the primary focus of treatment. Note that subjects with concurrent Generalized Anxiety Disorder are eligible for the study provided that Generalized Anxiety Disorder is not the primary diagnosis.

2. In the opinion of the Investigator, the subject has a significant risk for suicidal behavior during the course of their participation in the study, or
    a. At Screening (for subjects who attend Visit 1): the subject scores "yes" on items 4 or 5 in the Suicidal Ideation section of the Columbia-Suicide Severity Rating Scale (C-SSRS) with reference to a 6-month period prior to screening; or
    b. At Screening (for subjects who attend Visit 1): the subject has had 1 or more suicidal attempts with reference to a 2-year period prior to screening; or
    c. At Baseline (Visit 2): the subject scores "yes" on items 4 or 5 in the Suicidal Ideation section of the C-SSRS with reference to last visit; or
    d. The subject is considered to be an imminent danger to themself or others.
3. Subjects using the following psychotropic medications at enrollment or within 30 days before study entry: antidepressants (including monoamine oxidase [MAO] inhibitors), anxiolytics, stimulants, anticonvulsants, mood stabilizers, antipsychotic medications, gabapentin, pregabalin, opioids, naltrexone, esketamine, and ketamine. Eszopiclone, ramelteon, melatonin, zaleplon, zolpidem, or anti-histamines prescribed for insomnia are allowed.
4. Use of benzodiazepines or unapproved treatments such as beta blockers, within 30 days before study entry and during the study. Use of beta blockers for treatment of hypertension or cardiac conditions is allowed. Subjects who have been taking benzodiazepines daily for 1 month or longer at the time of Visit 1 are not eligible to participate.
5. Use of any over-the-counter product or herbal preparation for treatment of the symptoms of anxiety or social anxiety within 30 days before study entry; concomitant use is prohibited during the study.
6. Clinically significant nasal pathology or history of significant nasal trauma, nasal surgery, total anosmia, or nasal septum perforation that may have damaged the nasal chemosensory epithelium.
7. Subjects who meet criteria for moderate or severe alcohol or substance use disorder within the 1 year prior to entry into the study.
8. Subjects with a positive urine drug screen at study entry [redacted].
9. An acute or chronic condition, including an infectious illness, uncontrolled seasonal allergies at the time of the study, or significant nasal congestion that potentially could affect drug delivery to the nasal chemosensory epithelium.
10. Any current clinically significant and/or uncontrolled medical condition, based on medical history or as evidenced in screening assessments, such as COVID-19, HIV, cancer, stroke, congestive heart failure, uncontrolled diabetes mellitus, or any other medical condition or disease that, in the clinical judgment of the Investigator, could place the subject at undue risk, interfere with study participation, or confound the results of the study.

11. Women who have a positive urine pregnancy test prior to IP administration. Women who are currently breastfeeding are not eligible.
12. History of cancer or malignant tumor not in remission for at least 2 years. Basal cell skin cancers are not exclusionary.
13. Subjects with clinically significant abnormalities in hematology, blood chemistry, urinalysis, 12-lead ECG, or physical examination identified at study entry or during the legacy study which, in the clinical judgment of the Investigator, could place the subject at undue risk, interfere with study participation, or confound the results of the study.

8.3. Premature Subject Withdrawal

All subjects will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. The Investigator should make every reasonable attempt to keep subjects in the study; however, subjects must be withdrawn from the study if they withdraw consent to participate. Investigators must attempt to contact subjects who fail to attend scheduled visits by telephone or other means to exclude the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 11.2.

The sponsor reserves the right to request the withdrawal of a subject due to protocol deviations or other reasons.

The Investigator also has the right to withdraw subjects from the study at any time for the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any AE, laboratory abnormality, positive pregnancy test, positive urine drug screen, any of the inclusion/exclusion criteria not met during the study or concomitant illness which, in the opinion of the Investigator, indicates that continued treatment with IP or any other aspect of the study is not in the best interest of the subject

  Note: If central laboratory urine drug screen testing is positive for a subject after enrollment, then the participation of the subject in the study may have to be discontinued. The Medical Monitor should be consulted on these cases. An unscheduled repeat urine drug screen may be obtained to investigate whether drug use is continuing.
- Disease progression that, in the Investigator's opinion, precludes the subject's continued participation in the study
- Significant noncompliance with the requirements of the protocol or treatment
- Two consecutive missing visits and failure to contact the Investigator within a period of 2 weeks (during the Screening and Baseline visits) or 1 month (during treatment) with no reason for missing visit
- The subject requires use of a medication prohibited by the protocol. The Investigator should discuss these cases with the medical monitor before withdrawing the subject, to determine whether the subject can continue in the study or not.
- Termination of the study by VistaGen

- At the discretion of the Investigator or VistaGen
- Pregnancy

If a subject is withdrawn before completing the study, the reason for withdrawal and the date of discontinuation will be recorded on the appropriate page of the electronic case report form (eCRF).

All attempts will be made to have subjects return to the clinic to complete the assessments or procedures performed at the Early Termination visit (see Section 10.2.3) in the event of early withdrawal after Visit 2 or any visit other than Visit 14 after IP administration. All attempts to contact the subject, including phone or email, must be recorded in the source documents. Data will be collected from subjects on treatment only.

8.4. Subject Replacement Criteria

Withdrawn subjects will not be replaced. If a substantial number of subjects are withdrawn from the study, the sponsor will evaluate the need for developing replacement criteria. Rescreening will be permitted on a case-by-case basis after discussion with the medical monitor.

The subject number for a withdrawn subject will not be reassigned to another subject.

9. TREATMENTS

All IP should be refrigerated prior to use but administered only at room temperature.

Site personnel will instruct the subject to self-administer the IP by 1 spray into each nostril (right and left nasal passages), for 2 total sprays per dose.

9.1. Identification of Investigational Product

The IP (PH94B Nasal Spray) is supplied in a 10-mL amber glass vial with a spray actuator. The spray actuator has a clear protective cover.

PH94B is odorless and contains propylene glycol, ethyl alcohol, polysorbate 80, water (q.s. to 100%), and benzalkonium chloride as a preservative, in a phosphate buffer.

PH94B will be supplied in monthly kits consisting of a sufficient number of 10-mL amber glass vials, where each vial contains 8 mL of PH94B. Each metered dose spray delivers 1.6 µg per 100 µL spray. There is sufficient volume in each vial to deliver at least 60 sprays of PH94B.

Use of the i.n. route is essential given the site of action of PH94B on nasal sensory chemoreceptors (see Section 5.1).

PH94B will be supplied by [redacted]

New vials should be allowed to come to room temperature for 30 minutes and primed before use according to the instructions provided.

9.2. Selection of Timing of Dose for Each Subject

The IP will be administered once in each nostril. Men and women will be treated with the same 3.2-µg dose of PH94B. Each nasal spray delivers 100 µL containing 1.6 µg PH94B. [redacted]

Treatment with PH94B should be self-administered approximately 15 minutes prior to or during an anxiety-provoking social situation or event. Consecutive nasal administrations of IP should be at least 1 hour apart, with no more than 4 administrations per day.

Site personnel will instruct the subject to self-administer the IP by 1 spray into each nostril (right and left nasal passages), for 2 total sprays per dosing event.

Subjects are instructed to record all PH94B administrations in the provided eDiary, even if they have not used PH94B that day (see Section 9.4.1).

9.3. Dose Adjustment Criteria

Dose adjustment is not allowed in this study.

9.4. Treatment Compliance

Study personnel will weigh each vial of IP prior to dispensing to subjects and upon return of used or unused vials of IP from subjects to the study personnel. Vial weights will be documented in the eCRF. Subjects will record their use of the IP in an eDiary during the study (see Section 9.4.1).

Subjects will self-administer the IP up to 4 times per day between visits. The study personnel will be responsible for reviewing the self-administration of the IP in the eDiary.

9.4.1 eDiary

Subjects participating in the study will be instructed to record their use of PH94B in an eDiary application. The eDiary will be made available to subjects as an "application" to be downloaded and used on their smartphone or a similar device.

Subjects will be instructed to complete the eDiary at the end of each day even if zero doses are taken that day. They will be instructed to provide information on the number of doses they self-administered that day and the approximate time of each dose.

After the subject has completed the dosing section, the eDiary will prompt the subject to answer if they have experienced any health problems that day. If they answer yes, the subject is asked to write a brief summary text in the eDiary. The Investigator or a delegate will review these summary texts at each visit and determine whether they are to be recorded in the EDC system as AEs, with their severity, duration, and relationship to the study drug.

A nominal payment will be made to subjects for each day that they complete the eDiary. This will be made available to the subject at the end of the study.

At each study visit from Visit 3 through Visit 14, study staff will review the subject's eDiary entries. Additional training on the use of the eDiary may be administered if necessary (see Section 9.4).

9.5. Method of Assigning Subjects to Treatment Groups

In this open-label, single-treatment study, all subjects will receive the same treatment.

Subject numbers will be allocated by the IRT. Subjects will be sequentially assigned 6-digit numbers as shown below. The subject number will include the site number. Instructions on subject number assignments will be included in the IRT manual.

Source[a]	Site Number	Subject ID	Example
New Subjects[b]	001	Starting with 001	001-001 001-002
PALISADE-1 Study (Completers)	001	Starting with 101	001-101 001-102
PALISADE-2 Study (Completers)	001	Starting with 501	001-501 001-502

a Participants from other antecedent studies will follow a similar systematic numbering convention.

b Subjects who have not participated in a prior PH94B SAD study may be permitted to enroll following approval by the sponsor on a case-by-case basis.

9.6. Blinding and Unblinding Treatment Assignment

Not applicable – this is an open-label study with all subjects receiving PH94B.

9.7. Permitted and Prohibited Therapies

All medications taken by or administered to the subject during the month prior to Screening (Visit 1) should be recorded in the eCRF. All concomitant medication taken during the study will be recorded on appropriate pages of the eCRF.

In order to ensure that appropriate concomitant therapy is administered, it is essential that subjects be instructed not to take any medication (either self-administered non-prescription drugs or prescription therapy prescribed by another physician) without prior consultation with the Investigator. The Investigator should examine the acceptability of all concomitant medications not explicitly prohibited. Sites should contact the Medical Monitor when uncertain about the acceptability of concomitant medications. All concomitant medication taken during the study will be recorded on appropriate pages of the eCRF.

9.7.1 Permitted Therapies

With the exception of those noted in Section 9.7.2, all medications (prescription or over-the-counter) that were started prior to Screening may be continued during the course of the study. During the course of the study, subjects should stay on stable doses of their usual allowable medication regimens. Medications for treatment of minor concurrent illnesses that arise after Screening may be allowed at the discretion of the Investigator, with the exception of the prohibited therapies specified in Section 9.7.2.

The use of eszopiclone, ramelteon, melatonin, zaleplon, zolpidem, or anti-histamines as concomitant medications for the treatment of insomnia is permitted.

[redacted]

Investigators may allow concomitant use of over-the-counter nasal decongestants as needed for seasonal allergies. Subjects may self-administer over-the-counter nasal decongestants at a minimum of 15 minutes prior to the use of IP during the study.

In general, starting treatment with antidepressants and buspirone during the study is allowed but the investigator should inform the Medical Monitor of this decision; for antidepressants, initiating treatment is permitted provided that the antidepressant has been approved for the treatment of SAD or major depressive disorder by the FDA. However, while subjects may begin treatment with antidepressants, use of MAO inhibitors or ketamine is not permitted.

9.7.2 Prohibited Therapies

At Screening (Visit 1), the Investigator may consider checking the local Prescription Drug Monitoring Database to confirm that subjects are not using scheduled central nervous system active drugs, such as benzodiazepines, if appropriate.

For subjects who use a prohibited medication (see below) during the study, Investigators should discuss the subject with the Medical Monitor. Such treatment might not be a cause for discontinuing the subject from the study. In particular, one-time use or very short-term use ($\leq$ 3 days) of prohibited medications, e.g., in cases of legitimate medical requirement such as minor surgeries or procedures, will not necessarily lead to exclusion from the study. These subjects should be discussed on a case-by-case basis with the Medical Monitor.

Prohibited medications are as follows:

- Prior use of PH94B is not permitted, except for subjects who have participated in a PH94B SAD study.

- Use of the following psychotropic medications is prohibited: anxiolytics, anticonvulsants, mood stabilizers, antipsychotic medications, stimulants, gabapentin, pregabalin, opioids, naltrexone, esketamine, and ketamine.
    - Use of antidepressants is prohibited at enrollment or within 30 days before the study. However, treatment with antidepressants or buspirone can be initiated during the study (see Section 9.7.1).

      Note: Treatment with MAO inhibitors or ketamine is prohibited at all times.
- Use of benzodiazepines and unapproved anxiety treatments such as beta blockers is not permitted within 30 days before study entry (Visit 2), or during the study.
    - Subjects requiring daily treatment with benzodiazepines are excluded from the study. If a subject develops the need to use benzodiazepines for management of anxiety, their participation in the study will be discontinued and the subject will be excluded from the study.
    - Use of beta blockers for treatment of hypertension or cardiac conditions is allowed.
- Use of any over-the-counter product or herbal preparation for treatment of the symptoms of anxiety or social anxiety is not permitted within 30 days before study entry, or during the study.

Where washout of prohibited medications is required before Visit 2 (Baseline), tapering rates are at the discretion of the Investigator and are to be determined on an individual basis, with consideration to subject state, dose, and known pharmacokinetics of the medication being discontinued. The subject must be consented before any tapering is started.

9.8. Treatment After End of Study

After the end of the study, each subject will be treated according to standard clinical practice.

9.9. Dispensing and Storage

The IP supplied by [redacted] is to be used exclusively in the clinical study according to the instructions of this protocol. The Investigator is responsible for dispensing the IP according to the dosage scheme and for ensuring proper storage of the IP.

The Investigator must confirm the receipt of the IP.

9.9.1 Dispensing

At each visit from Visit 2 (Baseline) through the final monthly visit (Visit 13), subjects will be dispensed a monthly kit containing a sufficient number of PH94B Nasal Spray vials from the respective clinical site. Each study site will be provided with an appropriate supply of IP, and each vial will be individually numbered with a unique identification code.

Prior to the subject receiving the IP at each in-clinic visit, the Investigator or study staff will use a vial from their assigned kit to instruct the subject on how to ensure the IP is primed before use according to instruction. At least 1 vial of the IP will be primed at each clinic visit following Visit 2 (Baseline) as needed. The IP will be weighed prior to priming, and again when returned to study staff. Once primed the IP must be stored at room temperature.

Subjects should use a fresh vial at the start of each week. Subjects will be instructed to remove the new vial from their home refrigerator, bring it to room temperature and prime the spray actuator before use as needed. The clinic will dispense a kit of vials with unique serialized vial identification codes at each visit.

If the IP supply is lost or depleted prior to next in-clinic visit, subjects may notify the study site through the provided study site phone number to secure additional supply of IP.

9.9.2 Storage

All IP supplied to each site by the sponsor will be maintained in a safe and secure (locked) area, stored upright in a refrigerator between 2°C (36°F) and 8°C (46°F), until dispensed, and away from direct sunlight and ultraviolet light. Access should be restricted to the designated responsible member(s) of the Investigator's staff and to the clinical monitor. The Investigator agrees that neither he/she nor any of the study staff will supply IP to any person other than subjects enrolled in the study.

Secure access to the storage area is the responsibility of the Investigator and designated staff.

New (unused) IP should be stored in the refrigerator. The spray actuator of the IP should be primed before use according to the instructions provided.

9.10. Drug Accountability

Upon receipt of each IP shipment, an inventory must be performed, and a drug receipt log filled out and signed by the person accepting the shipment. The IP will be provided with each vial assembled individually to its spray actuator. It is important that the designated study staff count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable IP in each shipment (active drug) will be documented in the study files.

Current and accurate inventory and dispensing records will be kept for all IP. Upon study completion a final inventory of all clinical supplies will be compiled. The Investigator or an assistant will instruct subjects to return spray vials to the clinical site, whether empty or containing unused IP, at study visits prior to subjects receiving additional supplies of IP. A copy of the Drug Receipt Form and the Drug Accountability Form will be retained in the Investigator's files.

If the subject reports the IP as being lost or stolen this will be recorded in the eCRF.

9.11. Labeling and Packaging

Labeling and packaging of the IP will be performed by [redacted]

9.11.1 Labeling

The vials will have a label affixed that meets the applicable regulatory requirements and may include the following: IP name, dosage strength, lot number, protocol number, specified volume of contents, caution statement ("New Drug – Limited by United States Law to Investigational Use" and "Keep out of reach of children"), storage information, vial identification code, and the sponsor's name.

The vial identification codes will be recorded in the drug dispensing record and the eCRF.

Investigators must save all empty packaging or packaging containing unused vials for final disposition by the sponsor or contract pharmacy.

9.11.2 Packaging

PH94B will be supplied in subject kits containing a sufficient number of individual PH94B Nasal Spray dosage units.

PH94B Nasal Spray dosage units are not childproof and should be stored out of reach of children.

10. STUDY PROCEDURES

Subjects must provide written informed consent for the present study before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

The required safety and tolerability endpoints for subject evaluation are outlined in Section 13.1.4, with a comprehensive schedule of events in Table 2-1. Every effort should be made to complete all required procedures and evaluations at the designated visits. A trained designated rater must see the subject at every visit. If available, the rater should be the same for a subject for each visit from Visit 2 (Baseline) to Visit 14, however, all raters will be trained for consistency.

Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the schedule of events for each subject. If a subject misses a study visit for any reason, the visit should be rescheduled as soon as possible.

Subjects who have participated in a previous PH94B SAD study will be enrolled in this study and attend Visit 1 or Visit 2 depending on the interval since they finished participation in their antecedent study, as follows:

>14 Days Since Antecedent Study: Subjects who finished participation in their antecedent PH94B SAD study more than 14 days before entering the present study will attend Visit 1 of the long-term safety study and complete all necessary screening assessments as shown in the schedule of events (Table 2-1).

For the purposes of enrollment, these subjects are referred to as "New Subjects".

≤14 Days Since Antecedent Study: Subjects who enter the present study within 14 days after finishing participation in their antecedent PH94B SAD study without meeting any of the exclusion criteria of this long-term safety study will enter the present study at Visit 2 (see Table 2-1).

For the purposes of enrollment, these subjects are referred to as "Completers".

- While these subjects enter the long-term safety study at Visit 2, Investigators must transcribe the following screening data (Visit 1) from the antecedent study to the present long-term safety study: demographics, the MINI, medical and psychiatric history, and the SAD Diagnostic Criteria checklist. If there have been any changes, these details should be updated. This data from the antecedent study must be re-entered into the Visit 1 eCRF for the present study. All other assessments scheduled for Visit 2 must be performed as indicated in the schedule of events (see Table 2-1).
- If the subject enters the present study on the same day as the last visit of their antecedent study, results from the assessments on that day may be used to enter data into the eCRFs for the antecedent study and for Visit 2 of the present study without repeating them.
    - For example, [redacted] assessment completed for the last visit of the antecedent study may be transcribed for this long-term safety study provided that the last visit occurred on the same day as Visit 2 for the present study. Details on preparing a certified copy of the results will be provided in the eCRF completion guidelines.

- For clinical laboratory assessments, 2 sets of blood and urine samples should be obtained and sent to the lab for analysis: one for the antecedent study and one for the long-term study. Note that these can be collected at the same time to avoid unnecessary needlesticks.

Subjects who have not participated in a prior PH94B SAD study may be permitted to enroll following approval by the sponsor on a case-by-case basis. For the purposes of enrollment, these subjects are referred to as "New Subjects".

10.1. Study Duration

The study comprises a 7- to 35-day screening period and a treatment period of up to 12 months, and a follow-up visit at 2 weeks after the last visit.

10.2. Study Periods and Visits

A comprehensive schedule of study assessments is presented in Table 2-1 and described in the following sections. Every effort should be made to complete all required procedures and evaluations at the designated visits. A window of ±3 days is permitted for Visit 3 and the follow-up visit (Visit 15), with a window of ±7 days permitted for Visits 4 through 13, and ±2 weeks for Visit 14.

10.2.1 Screening and Washout

10.2.1.1 Screening (Visit 1)

Screening begins after written informed consent has been obtained. The purpose of the screening phase is to:

- Ensure that appropriate subjects are entered into the study
- Determine that the subject meets all eligibility criteria
    - Subjects who enter this study more than 14 days after finishing participation in their antecedent study must undergo all the screening procedures at Visit 1 to ensure they meet eligibility
- Collect demographic and medical data permitting characterization of the subject

To meet these objectives, the duration of screening must be tailored to the individual subject and may last from a minimum of 7 to a maximum of 35 days. Subjects continuing to meet all eligibility requirements at Visit 2 (Baseline) will undergo treatment with IP (PH94B) up to Visit 14.

Generally, subjects who have participated in an antecedent PH94B SAD study will be informed about the study, the IP, required visits and scheduling, and asked whether they wish to participate. All subjects agreeing to participate must give written informed consent using the IRB-approved ICF before any study-related procedures are performed (including tapering of prohibited medications, see Section 9.7.2). The ICF will be signed and dated by the subject and Investigator or other appropriate site staff, and a copy of the signed ICF will be given to the subject. The informed consent process will be documented in the source records for each subject.

After the informed consent process is complete, the signed ICF will be obtained, and the Screening visit (Visit 1) occurs.

The following numbered procedures should be performed in a block fashion as per the order indicated. Assessments within a block, except for the first block, may be conducted in any order as per clinical judgement at Screening, which is to occur at least 7 days, but no more than 35 days prior to Visit 2:

1. ICF will be reviewed and completed before any other assessments. Collect demographic information; and assign subject number.
2. Urine sample for drug screen and pregnancy test (if appropriate) will be collected early in the screening visit to determine eligibility and to guide diagnostic interviews, especially with regards to substance use assessment. The urine sampling is to include:
    a. Obtain urine sample for urine drug screen (UDS): Instant Exam to be performed on site, with results thoroughly documented in the source; urine sample to be sent to central laboratory for confirmation if on-site UDS is positive [redacted].
    b. For females of child-bearing potential, obtain urine sample and complete on-site urine pregnancy test.
3. Medical and psychiatric history and diagnosis (usually starting with MINI) to include:
    a. Administer MINI (7.0.2).
    b. Obtain medical history (including nicotine, alcohol use, and menstrual information on women of childbearing potential) and psychiatric history.
    c. Record prior and concomitant treatment and medication use (medication name, dose, and frequency).
    d. Complete SAD diagnostic criteria checklist.
4. Standardized assessments (usually starting with LSAS but per investigator judgement based on the MINI) to include:
    a. Administer LSAS.
    b. Administer HAM-D17.
    c. [redacted]
    d. Administer C-SSRS (Baseline).
    e. Complete CGI-S with a recall period of 1 week (by the trained clinician).

5. Physical assessments (recommend blood draw last to avoid any potential impact on vitals and ECG assessment) to include:

    a. Perform physical examination, including height (inches) and body weight (pounds). The physical examination includes a review of the nasal passages. If total anosmia is suspected, Quick Olfactory Test (QOT) is to be administered.

    b. Measure vital signs after the subject has rested for 5 minutes: seated systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (°F).

    c. Obtain 12-lead ECG in supine position after the subject has rested for 5 minutes.

    d. Obtain blood and urine samples for evaluation by the central clinical laboratory, including hematology, chemistry, thyroid functioning, and urinalysis (refer to Section 10.3.1.1.1 for complete list).

6. After these assessments are complete, review all inclusion and exclusion criteria.

Procedures for rescreening subjects who initially fail to meet study entry criteria are described in Section 14.3.

10.2.1.2 Washout Period

In accordance with the study entry criteria (Section 8.2), the use of certain psychotropic medications, anxiolytics, or other preparations for the treatment of anxiety or social anxiety is prohibited within 30 days before study entry (considered as Visit 2, Baseline).

Where washout of prohibited medications (see Section 9.7.2) is required before Visit 2 (Baseline), tapering rates are at the discretion of the Investigator and are to be determined on an individual basis, with consideration to subject state, dose, and known pharmacokinetics of the medication being discontinued. The subject must be consented before any tapering is started.

10.2.2 Treatment Period

10.2.2.1 Visit 2 (Baseline)

Subjects entering the study within 14 days of their antecedent PH94B SAD study will enter this study at Visit 2. These subjects will sign an ICF for the present study at this visit and complete all Visit 2 assessments as noted in the schedule of events (Table 2-1) and detailed in this section.

All subjects will complete the following Visit 2 assessments:

- Obtain urine sample for urine drug screen: Instant Exam to be performed on site, with results thoroughly documented in the source; urine samples will be sent to the central laboratory for confirmation as needed if on-site urine drug screen is positive. If the central laboratory urine drug screen result is positive [redacted]

[redacted], the subject may have to be excluded from the study; the Medical Monitor should be consulted on these cases

- For females of childbearing potential, obtain urine sample and complete on-site urine pregnancy test
- Record concomitant medication use
- Perform physical examination, including body weight (pounds). The physical examination includes a review of the nasal passages
- Measure vital signs after the subject has rested for 5 minutes: seated systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (°F)
- Obtain 12-lead ECG in supine position after the subject has rested for 5 minutes
- Obtain blood and urine samples for evaluation by the central clinical laboratory, including hematology, chemistry, thyroid functioning, and urinalysis
- Review all inclusion and exclusion criteria

For subjects meeting all study inclusion criteria and no study exclusion criteria, the following Visit 2 procedures will be performed:

- Administer the LSAS
- Administer the HAM-D17
- [redacted]
- Administer the C-SSRS (Since Last Visit)
- Complete the CGI-S with a recall period of 1 week (by the trained clinician)
- Train subjects on the use, dosing, and storage of IP. The subject will be given instructions on:
    - how to position the actuator nozzle in the nasal passages and self-administer IP
    - the number of sprays per nostril per dose (1 per nostril)
    - how to store the nasal spray
    - Treatment with PH94B should be self-administered approximately 15 minutes prior to or during an anxiety-provoking social situation or event. [redacted], with no more than 4 administrations per day. Treatment does not need to be administered every day.
- Train subjects on how to record study drug use on the eDiary application (see Study Procedures Manual for training on the eDiary application)
- Record any AEs

  All prior, ongoing, or resolved AEs reported by subjects at the time of study entry will be considered as medical history during this study. Adverse events that become aggravated, accelerated, or exacerbated will be reported and considered as new AEs. Adverse events that recur will be considered as new AEs during this study.

- Dispense IP to subjects (1-month supply)

Subjects will be instructed to call a designated phone number provided by the study site to report any unusual or severe AEs or hospitalizations that may occur in between in-clinic visits.

Visit 3 will be scheduled 30 days (±3 days) from Baseline (Visit 2) for subjects.

10.2.2.2 Visit 3 (First Month in Clinic, ±3 Days)

At Visit 3, subjects should return to the study site and the following assessments will be completed:

- Conduct urine drug screen (Instant Exam, to be performed on site, with results documented in the source. If urine drug screen result is positive [redacted], then urine sample will be sent to central laboratory for confirmation as needed). If the urine drug screen is confirmed as positive, a repeat unscheduled urine drug screen may be obtained to investigate whether drug use is continuing. The Medical Monitor should be consulted regarding these cases.
- For females of childbearing potential, obtain urine sample and complete on-site urine pregnancy test
- Record concomitant medication use
- Administer the LSAS
- Administer the HAM-D17
- [redacted]
- Administer the C-SSRS (Since Last Visit)
- Perform focused physical examination, including body weight (pounds). The physical examination includes a review of the nasal passages and oropharynx but other organ systems should be examined only if the subject has symptoms or the investigator is concerned.
- Measure vital signs after the subject has rested for 5 minutes: seated systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (°F)
- Obtain 12-lead ECG in supine position after the subject has rested for 5 minutes
- Obtain blood and urine samples for evaluation by the central clinical laboratory, including hematology, chemistry, thyroid functioning, and urinalysis (refer to Section 10.3.1.1.1 for complete list)
- Complete the CGI-S with a recall period of 1 week (by the trained clinician)
- Complete the CGI-I as compared to baseline visit (Visit 2), with a recall period of 1 week (by the trained clinician)
- Complete the PGI-C as compared to baseline visit (Visit 2), with a recall period of 1 week (by the subject)
- Dispense study medication and provide the subject with the storage instructions of the IP (1-month supply of IP)

- Review and record AEs
- Review the use of IP and any health problems they experienced as reported in the eDiary (by study staff)

10.2.2.3 Visit 4 Through Visit 13 (Monthly Visits, ±7 Days)

At Visit 4 through Visit 13, study assessments will be the same as those conducted at Visit 3 (see Section 10.2.2.2). Visits 4 through 13 will be conducted on a monthly basis, with a ±7-day window.

10.2.3 Visit 14 End of Treatment (or Early Termination) Visit

At Visit 14, subjects should return to the study site for an End of Treatment visit, and undergo the assessments shown in the schedule of events.

In addition, subjects who discontinue from the study early (for any reason other than loss to follow-up) should return to the study site for an Early Termination Visit. Similarly, if the subject is attending a scheduled visit when the decision to discontinue is made, the investigator should perform the assessments indicated for Visit 14/Early Termination Visit in the schedule of events (Table 2-1).

The following assessments will be completed at Visit 14/Early Termination:

- Record concomitant medication use
- Obtain blood and urine samples for evaluation by the central clinical laboratory, including hematology, chemistry, thyroid functioning, and urinalysis (refer to Section 10.3.1.1.1 for complete list)
- Conduct urine drug screen (Instant Exam, to be performed on site, with results documented in the source. If urine drug screen result is positive [redacted], then then urine sample will be sent to central laboratory for confirmation as needed).
- For females of childbearing potential, obtain urine sample and complete on-site urine pregnancy test
- Obtain 12-lead ECG in supine position after the subject has rested for 5 minutes
- Perform physical examination, including height (inches) and body weight (pounds). Also includes an examination of the nasal passages
- Measure vital signs after the subject has rested for 5 minutes: seated systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (°F)
- Administer the LSAS
- Administer the HAM-D17
- [redacted]
- Administer the C-SSRS (Since Last Visit)
- Complete the CGI-S with a recall period of 1 week (by the trained clinician)

- Complete the CGI-I as compared to baseline visit (Visit 2), with a recall period of 1 week (by the trained clinician)
- Complete the PGI-C as compared to baseline visit (Visit 2), with a recall period of 1 week (by the subject)
- Complete PWC-20
- Review the use of IP and any health problems they experienced as reported in the eDiary (by the trained clinician)
- Review and record AEs (by the trained clinician)

10.2.4 Visit 15 (Follow-up, 54 weeks ±3 Days)

At Visit 15, subjects should return to the study site and the following assessments will be completed:

- Measure vital signs after the subject has rested for 5 minutes: seated systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (°F)
- Administer C-SSRS (Since Last Visit)
- Complete PWC-20
- Review and record AEs

10.3. Assessments

10.3.1 Safety Variables

Safety assessments will include the evaluation of AEs, clinical laboratory assessments, vital signs, 12-lead ECGs, physical examinations, HAM-D17, C-SSRS evaluations, and the PWC-20.

10.3.1.1 Clinical Laboratory Safety Assessments

10.3.1.1.1 Clinical Laboratory Tests to be Performed

Samples for the following laboratory tests will be collected at the time points specified in the schedule of events (Table 2-1).

The following laboratory tests will be performed on site during the study:

- Urine pregnancy test (for all female subjects of childbearing potential)
- Urine drug screen

The following laboratory tests will be performed by the central laboratory during the study:

Hematology Panel:	hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular concentration, mean corpuscular volume, platelets, red blood cell count, white blood cell count with differential, red blood cell morphology
Hematology Differential Panel:	basophils, eosinophils, lymphocytes, monocytes, neutrophils

Serum Chemistry Panel:	alanine aminotransferase, aspartate aminotransferase, albumin, calcium, chloride, alkaline phosphatase, bicarbonate, cholesterol, creatine kinase, creatinine, direct bilirubin, lactate dehydrogenase, magnesium, globulin, glucose, gamma-glutamyl transferase, indirect bilirubin, phosphorous, potassium, sodium, total bilirubin, total protein, triglycerides, urea nitrogen, uric acid
Urinalysis Macroscopic Panel:	bilirubin, blood, clarity, color, glucose, ketones, leucocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen
Urine Drug Screen:	If on-site urine drug screen is positive, urine sample will be submitted to central laboratory for confirmatory urine drug screen to be performed: opiates, cocaine, amphetamines, barbiturates, benzodiazepines, cannabinoids, methadone, phencyclidine, propoxyphene, methamphetamine, buprenorphine, ecstasy, and oxycodone [redacted]
Other:	thyroid stimulating hormone free thyroxine (T4) will automatically be performed if thyroid stimulating hormone level is above the upper or below the lower normal limits

The central laboratory should be used for any unscheduled and follow-up labs, if needed. Additional urine and blood samples may be collected for further evaluation of safety as warranted by the Investigator's judgment.

Results and reports from the central laboratory should be filed with the source documents for each subject. The central laboratory will provide laboratory results to the study site as soon as they are available; results will also be provided to the sponsor or designated data manager within agreed upon timelines.

Any laboratory value outside the normal range will be flagged for the attention of the Investigator, who must indicate whether or not the value is of clinical significance. If the result of any laboratory test performed during Screening is clinically significant, the subject should not be advanced to Visit 2 (Baseline) before discussing with the Medical Monitor. However, any abnormal result may be repeated to confirm the finding before excluding the subject from potential inclusion in the study. In addition, subjects should be excluded if they have any other abnormal laboratory test at Screening that, in the Investigator's judgment, is medically significant in that it would impact the safety of the subject, the conduct of the study, or the interpretation of the study results.

Follow-up/unscheduled laboratory tests may be performed on clinically significant abnormalities as indicated by the Investigator. Unscheduled laboratory tests may be repeated at any time at the discretion of the Investigator for appropriate medical care.

10.3.1.1.2 Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be

employed by all study personnel involved in the collection of blood and handling of specimens in both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of subject samples, specific regulations exist regarding the shipment of biologic/etiologic samples. Procedures and regulations for the packaging and shipping of infectious samples are outlined in the study laboratory manual or other appropriate reference. The Investigator is responsible for ensuring that all study samples that are to be transported to another location are packed and shipped appropriately according to the applicable regulations.

10.3.1.1.3 Evaluation of Clinical Laboratory Values

The normal ranges of values for the clinical laboratory assessments in this study will be provided by the responsible laboratory and submitted to VistaGen Therapeutics, Inc. prior to the beginning of the study. They will be regarded as the reference ranges on which decisions will be made.

If a laboratory value is out of the reference range, it is not necessarily clinically relevant. The Investigator must evaluate the out-of-range values and record his or her assessment of the clinical relevance in the appropriate eCRF.

All clinical laboratory values that in the Investigator's opinion show clinically relevant or pathological changes during or after termination of treatment must be reported as AEs and followed, as described in Section 11.2.5.

All measurements described in this section are recognized standard methods.

10.3.1.2 Clinical Examinations

10.3.1.2.1 Vital Signs

Vital signs, including heart rate, respiratory rate, and seated systolic and diastolic blood pressure will be measured after the subject has been in a seated position for 5 minutes. Temperature will also be measured.

10.3.1.2.2 Twelve-lead Electrocardiogram

A standard 12-lead ECG will be performed in a supine position after the subject has rested for 5 minutes. All ECG recordings will be identified with the subject number, initials, date, and time of the recording.

All abnormal ECGs will be submitted for a secondary evaluation by a physician with expertise in clinical pharmacology and ECG interpretation. The expert's interpretation will be captured in the EDC system. The external expert will follow-up with the site as needed. Teleconferences can be arranged between the external expert and the site to discuss difficult cases and reach a consensus.

10.3.1.2.3 Physical Examination

A complete physical examination (excluding the genitourinary examination) will be performed as indicated in the schedule of events (Table 2-1). The physical examination will include measurement of weight and height, and an examination of the nasal passages.

A focused physical examination will be performed at certain visits as per the schedule of events, but must include examination of the nasal passages and oropharynx; other organ systems should be examined if the subject has symptoms or if the investigator has specific concerns.

10.3.1.2.4 Columbia-Suicide Severity Rating Scale

The C-SSRS is a semi-structured interview that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The interview includes definitions and suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior has occurred. The C-SSRS has a "baseline" version which will be completed at Screening and a "Since Last Visit" version that will be completed at all subsequent visits. There are a maximum of 19 items to be completed: 7 that are required, 10 potential additional items if there is a positive response to a required item, and 2 items for suicide/suicide behavior present during the interview. The C-SSRS uses dichotomous scales (i.e., yes or no), Likert scales, and text or narrative to further describe the thoughts or behaviors.

10.3.1.2.5 Penn Physician Withdrawal Checklist

The PWC-20 is a 20-item simple instrument for assessing anxiolytic discontinuation symptoms. It should be administered by a suitably qualified physician or advanced practice provider.

The PWC-20 consists of 20 questions related to withdrawal from benzodiazepines or other anti-anxiety compounds (see APPENDIX H). The symptoms measured are based on those that are potentially related to anxiolytic withdrawal: gastrointestinal, mood, sleep, motor, somatic, perception, and cognition. The questions will cover any symptoms that might occur during the week following discontinuation of PH94B.

10.3.1.3 Adverse Events

The definitions and management of AEs, and any special considerations for AEs, are provided in Section 11.

10.3.2 Efficacy Variables

10.3.2.1 Liebowitz Social Anxiety Scale

The LSAS is a clinician-rated scale that has been shown to be sensitive to treatment-related change in social anxiety symptoms. The time frame for rating symptomatology is the past week. The scale consists of 24 items. Each item is given 2 ratings: fear or anxiety on scale of 0 to 3 and avoidance on a scale of 0 to 3, with a total maximum overall score of 144 (see APPENDIX A). The items in the scale can be divided into performance and social interaction items, and corresponding subscores can be derived.

10.3.2.2 [redacted]

[redacted]

[redacted]

10.3.2.3 Hamilton Rating Scale for Depression (17 Items)

The HAM-D17 scale is a 17-item clinician-rated scale to measure the severity of depression, addressing symptoms experienced in the past week, with the total score ranging from 0 to 68 (see APPENDIX D). A score of 0 to 7 is considered to be within the normal range, while a score of 20 or more indicates at least moderate depression. The time frame for rating symptomatology is the past week.

10.3.2.4 Clinical Global Impression Scales

The Clinical Global Impression Scale (CGI) is a clinician-rated scale assessment of the clinician's view of the subject's global health prior to and after participation in a clinical study. The scale assesses the clinician's knowledge of the subject's history, psychosocial circumstances, symptoms, behavior and the effect of these parameters on the subject's capability to function since the last visit with the subject. The CGI consists of 2 components, severity (CGI-S) and improvement (CGI-I). A recall period of 1 week is used.

The severity component (CGI-S) consists of 1 question that assesses the disease severity of the patient population and is on a scale of 1 to 7 ranging from normal (1) to extremely ill (7).

The improvement component (CGI-I) evaluates the change of the subject's condition from the Baseline and is on a scale of 1 to 7 ranging from very much improved (1) to very much worse (7).

In this study the disease severity refers to the severity of SAD. The scale scoring is anchored with reference to the severity of symptoms and functional impairment caused by SAD.

10.3.2.5 Patient Global Impression of Change

The Patient Global Impression of Change (PGI-C) is a self-administered instrument that measures change in subjects' overall improvement with treatment on a scale where 1 = "very much improved" and 7 = "very much worse" (see APPENDIX G). The time frame for rating is compared to the baseline visit (Visit 2).

Very Much Improved	1
Much Improved	2
Minimally Improved	3
No Change	4
Minimally Worse	5
Much Worse	6
Very Much Worse	7

11. ADVERSE EVENTS

It is the responsibility of the Investigator at the site to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of SAEs as noted below. Medical monitoring will include a regular assessment of the number and type of SAEs.

The Investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 14 days after the last day of study participation.

11.1. Definitions

11.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. (Worsening of a preexisting condition is considered an AE.) A pre-existing condition is one that is present at the start of the study. A pre-existing condition should be recorded as an AE if the frequency, intensity, or the character of the condition worsens during the study period (after signing the ICF up to Visit 14 and Visit 15/Follow-up).

For subjects who enter the present study within 14 days of their antecedent PH94B SAD study, AEs ongoing at the time of enrollment into the present study will be recorded in the medical history section of the present study.

Abnormal results of diagnostic procedures are considered to be AEs if the abnormality:

- results in study withdrawal and is associated with an SAE
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the Investigator to be of clinical significance

In addition, a clinical laboratory abnormality must be documented as an AE if any 1 of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management, e.g., change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Pregnancy is not considered an AE, but it is an important medical event, which must be followed up as described in Section 11.3.1.

11.1.2 Unexpected Adverse Event

An expected AE is one for which the nature or severity is consistent with the known AE profile of the product. For a pre-approval test product, the known information is contained in the IB. For a marketed product, the known information is contained in the current package insert for the product.

An unexpected adverse event (UAE) is one for which the nature or severity of which is not consistent with the applicable product information (e.g., IB for an unapproved investigational product or package insert/summary of product characteristics for an approved product). For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected events. Examples would be (a) acute renal failure as an expected adverse reaction with a subsequent new occurrence of interstitial nephritis (interstitial nephritis would be unexpected) and (b) hepatitis with a first occurrence of fulminant hepatitis (fulminant hepatitis would be unexpected.)

11.1.3 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization
  An elective hospital admission to treat a condition present before exposure to the IP, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE
- results in persistent or significant disability/incapacity
- is a congenital anomaly
  NOTE: A congenital anomaly in an infant born to a mother who was exposed to the IP during pregnancy is an SAE. However, a newly diagnosed pregnancy in a subject that has received an IP is not considered an SAE unless it is suspected that the IP(s) interacted with a contraceptive method and led to the pregnancy.
- is an important medical event
  NOTE: Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, 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 intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, development of drug dependency, or drug abuse.

11.1.4 Significant Adverse Events

Other significant AEs are defined as marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug, dose reduction, or significant additional concomitant therapy.

11.1.5 Treatment-emergent Adverse Events

Treatment-emergent AEs are defined as:

- AEs with onset at the time of or following the start of treatment with IP through the Follow-up Visit, or
- AEs starting prior to the start of treatment but increasing in severity or relationship at the time of, or following, the start of treatment with IP through the Follow-up Visit

11.2. Event Assessment and Follow-up of Adverse Events

The Investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 14 days after the last day of study participation. At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

11.2.1 Assessment

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. At each visit, the subject will be allowed time to spontaneously report any issues since the last visit or evaluation. The Investigator will then monitor and/or ask about or evaluate AEs using nonleading questions, such as

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made during the visit will also be considered AEs.

In addition, the Investigator will review the eDiary summary text for health problems and determine whether they are to be recorded in the EDC system as AEs.

11.2.2 Evaluation

11.2.2.1 Severity of Adverse Events

The clinical severity of an AE will be classified as:

Mild	An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities
Moderate	An event that is sufficiently discomforting to the extent of interfering with normal everyday activities
Severe	An event that prevents the subject from performing normal everyday activities

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in Section 11.1.3.

11.2.2.2 Seriousness

The Investigator is to evaluate whether the AE meets serious criteria, as described in Section 11.1.3.

11.2.2.3 Actions Taken

Actions taken may consist of:

Dose not changed	An indication that a medication schedule was maintained.
Drug withdrawn	An indication that a medication schedule was modified through termination of a prescribed regimen of medication.
Not applicable	Determination of a value is not relevant in the current context.
Unknown	Not known, not observed, not recorded, or refused.

11.2.2.4 Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as:

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved

- Fatal*
- Unknown

*Investigators should only select fatal as an outcome when the AE results in death. If more than one AE is judged to be possibly related to the subject's death, the outcome of death should be indicated for each such AE. Although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

11.2.2.5 Adverse Event Relationship to Investigational Product

The Investigator must make an assessment of each AE's relationship to the IP. The categories for classifying the Investigator's opinion of the relationship are as follows:

Related	A reasonable possibility exists of a relationship between the AE and IP.
Not related	No reasonable possibility exists of a relationship between the AE and IP.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, relevant medical history, and confounding factors such as co-medication or concurrent diseases.

11.2.3 Documentation

All AEs that occur within the period of observation for the study must be documented in the eCRF with the following information, where appropriate. (The period of observation for the study is described in Section 11.2).

- AE name or term
- When the AE first occurred (start date and time)
- When the AE stopped (stop date and time or an indication of "ongoing")
- Severity of the AE
- Seriousness (hospitalization, death, etc.)
- Actions taken
- Outcome
- Investigator opinion regarding the AE relationship to the IP

11.2.4 Treatment of Adverse Events

Adverse events that occur during the study will be treated, if necessary, by established standards of care. If such treatment constitutes a deviation from the protocol, the subject should be withdrawn from the study and the reason must be documented in the eCRF. The decision about whether the subject may continue in the study will be made by the sponsor after consultation with the Investigator and/or Medical Monitor.

If AEs occur in a subject that are not tolerable, the Investigator must decide whether to stop the subject's involvement in the study and/or treat the subject. Special procedures may be

recommended for the specific IP, such as the collection of a serum sample for determining blood concentrations of IP, specific tapering procedures, or treatment regimens, as appropriate.

11.2.5 Follow-up

Any AE will be followed up to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause(s) (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the eCRF page.

11.2.6 Reporting

11.2.6.1 Serious Adverse Events

The Investigator or designee must report all SAEs promptly to [redacted] within 24 hours of first becoming aware of the event by completing, signing, and dating the Serious Adverse Event Report Form, verifying the accuracy of the information recorded in the form with the source documents and eCRF, and sending the SAE Report Form to [redacted] by one of the following methods:

email: [redacted]

Fax number (back-up): [redacted]

This written report should be submitted on the SAE form provided for this purpose. At the time of first notification, the Investigator or designee should provide the following information, if available:

- Protocol number
- Reporter (study site and Investigator)
- Subject's study number
- Subject's date of birth
- Subject's gender
- Date of first dose of IP
- Date of last dose of IP, if applicable
- Adverse event term
- Date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria(on) that were met
- Concomitant medication at onset of the event
- Relevant medical history information

- Relevant laboratory test findings
- Investigator's opinion of the relationship to IP ("Is there a reasonable possibility that the IP caused the SAE? Yes or No?")
- Whether and when the Investigator was unblinded as to the subject's treatment assignment

Any missing or additional relevant follow-up information concerning the SAE should be sent to the sponsor/sponsor representative via the same contact details above as soon as possible, and within 7 days, on a follow-up SAE Report Form, together with the following minimal information (initial report, AE, date of occurrence, subject identification [ID], study ID, IP, and site number); this will allow the follow-up information to be linked to the initial SAE report.

Specific information may be requested by the [redacted] Pharmacovigilance Department using a follow-up request form sent via email communication.

The Investigator is required to comply with applicable regulations (including local laws and guidances) regarding the notification of his or her health authorities, IRB, principal and coordinating investigators, study investigators, and institutions. Each investigator is obligated to learn about the reporting requirements for investigators in his/her country. The study monitor may be able to assist with this.

11.2.6.2 Nonserious Adverse Events

Nonserious AEs will be recorded in the eCRF and reported by [redacted] to the sponsor in accordance with the study-specific safety management plan.

11.3. Special Considerations

11.3.1 Pregnancy

All women of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation. Women should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted prior to administration of the IP on every woman of childbearing potential. A woman who is found to be pregnant at the Screening visit will be excluded from the study and considered to be a screening failure.

A woman who becomes pregnant during IP treatment or within 14 days of discontinuing the IP will be immediately discontinued from study participation. The Investigator must report the pregnancy within 48 hours of learning of the pregnancy, to [redacted] Pharmacovigilance using the Pregnancy Data Collection Form via the same fax number and/or email address as for SAE reporting (see Section 11.2.6.1). The Investigator should contact the designated individual(s) who receive SAE notification and record information related to the pregnancy on an Exposure in Utero form provided by the sponsor or its designee.

Early Termination Visit assessments are required as soon as possible after learning of the pregnancy. The Investigator is also responsible for following the pregnancy until delivery or termination. These findings must be reported on the Exposure in Utero form and forwarded to the

designated individual(s). The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly.

Male subjects with partners of childbearing potential should be advised to use contraception throughout their participation in the study. If the partner of a male subject becomes pregnant during his IP treatment or within 14 days of his discontinuing the IP, the Investigator must report the pregnancy within 48 hours of learning of the pregnancy, to [redacted] Pharmacovigilance, as described above.

12. DATA SAFETY MONITORING BOARD

A data safety monitoring board will not be used in this study.

13. STATISTICS

An interim safety analysis will be performed when approximately 100 subjects have completed 12 months of PH94B dosing up to 4 times per day and approximately 300 subjects have completed 6 months of PH94B dosing up to 4 times per day. All subjects who have received at least 1 dose of PH94B at this point will be included in this analysis. A final analysis will be performed after the last subject has completed or discontinued from the study.

13.1. Statistical Analysis

This section presents a summary of the planned statistical analyses.

Safety, tolerability, and efficacy variables will be summarized using descriptive statistics. Descriptive summaries for categorical variables will include count and percentage. Descriptive summaries for continuous variables will include number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. Where appropriate, 95% confidence intervals (CIs) may be reported. Summaries will be presented by time point. All CIs will be 95%, unless stated otherwise.

Unless specified otherwise, all data recorded, will be listed by subject. A comprehensive description of planned analyses and statistical considerations will be described in the statistical analysis plan (SAP).

Summary statistics will be reported based upon observed data. Should a determination of treatment period be required for an AE or concomitant medication when the corresponding date is missing, or is a partial date, the event/medication will be considered as "on-treatment" unless the portions of the date that are available indicate that this is not possible.

Details of the planned analyses, including strategies if needed to assess and address consequences of the COVID-19 pandemic on study conduct and study data, will be provided in the SAP that will be finalized before the database is locked.

13.1.1 Analysis Populations

A single analysis population is planned for this study:

- Safety population: All subjects who receive IP.

All analyses will be performed using the Safety population.

Primary and exploratory endpoints may be summarized by subgroups of interest including age, sex, concomitant medications, and SAD severity. Analysis of subgroups not pre-defined in the final SAP will be labeled as such in the clinical study report (CSR).

13.1.2 Study Subjects and Demographics

13.1.2.1 Disposition and Withdrawals

The numbers of subjects randomized, completing, and withdrawing, along with reasons for withdrawal, will be tabulated. Details on the number of subjects participating in the individual antecedent PH94B SAD studies will also be provided.

13.1.2.2 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol or ICH GCP requirements. The noncompliance may be either on the part of the subject, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

Documentation of the deviations and corrective actions will be included in the data quality assessment during review.

It is the responsibility of the site Investigator to use continuous vigilance to identify and report deviations within 2 working days of identification of the protocol deviation, or within 2 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents and reported to the sponsor. Protocol deviations must be sent to the reviewing IRB per their policies. The site Investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the protocol deviation guidance plan.

13.1.2.3 Demographics and Other Baseline Characteristics

For all participating subjects, baseline is defined as Visit 2. For subjects who enter the present study within 14 days of their antecedent PH94B SAD study, Visit 2 assessments should be conducted as described in the schedule of events (Table 2-1). Demographics, medical and psychiatric history, MINI findings, SAD Diagnostic Criteria Checklists, and baseline characteristics such as gender, age, race, weight, height and baseline physical examination reports, and vital signs will be carried over.

Demographic variables will include age, sex, height, and weight. Information on race and ethnicity will be collected for any eventual analysis of differences in response to the IPs, in accordance with local regulatory requirements. Baseline subject characteristics will include medical and psychiatric history, MINI findings, and physical examination findings.

Prior and concomitant medications will be summarized, by the number and percentage of subjects taking each medication, classified using World Health Organization Drug Dictionary (WHO-DD) Anatomical Therapeutic Chemical (ATC) classes and preferred terms.

13.1.3 Exposure and Compliance

Investigational product administration will be summarized in terms of total number of doses received and average number of daily doses.

Descriptive statistics will be provided overall and for each 3-month period of exposure (0-3 months, 4-6 months, 7-9 months, and 10-12 months).

13.1.4 Safety and Tolerability Analyses

Safety analyses will be conducted using data from the safety population (as defined in Section 13.1.1). Safety variables include treatment-emergent AEs, clinical laboratory values, vital signs, changes in suicidality (C-SSRS), level of depression (HAM-D17), PWC-20 results, ECG readings, and physical examination results. No formal inferential analyses will be conducted for safety variables, unless otherwise noted.

The incidence of AEs for defined periods of exposure (e.g., 3 months, 6 months, 9 months, 12 months, and overall) will be evaluated in the form of a proportion relating number of subjects experiencing events to number of subjects at risk for AEs by organ, relatedness, severity of reported AE, and by frequency of AE. In addition, frequency-type of reported AEs (once, continuous, or adaptability to treatment) by time of occurrence after Visit 2 dispensation may be tabulated. These data will be summarized and tabulated, including CIs when appropriate, for descriptive purposes. Abnormal laboratory values, vital signs, 12-lead ECGs and findings from physical evaluations that are logged as AEs are included.

For each AE category (organ, relatedness, severity, frequency, etc.) the number of subjects reporting 1 or more AEs during the specified time period divided by the number of subjects exposed to the IP during that time period may serve as a nonparametric endpoint, and be subject to evaluation using time series analysis to investigate whether frequency of AEs changes with increased duration of exposure.

Descriptive statistics will be used to portray safety and tolerability of PH94B as measured by reports of AEs and SAEs, changes in laboratory values, 12-lead ECGs, physical examination, vital signs, and withdrawal symptoms.

Safety endpoints are as follows:

- Incidence and severity of AEs, AEs leading to discontinuation, and SAEs
- Changes in vital signs results
- Changes in clinical laboratory evaluation (hematology, chemistry, and urinalysis) results
- Changes in 12-lead ECG results
- Changes in physical examination findings
- Changes in HAM-D17 scores
- Changes in C-SSRS scores
- PWC-20 scores after termination of PH94B

13.1.4.1 Adverse Events

All AEs will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent AEs are defined as:

- AEs with onset at the time of or following the start of treatment with IP through the Follow-up Visit or Early Termination Visit, whichever occurs first, or
- AEs starting prior to the start of treatment but increasing in severity or relationship at the time of, or following, the start of treatment with IP through the Follow-up Visit or Early Termination Visit, whichever occurs first.

The number and percentage of subjects with AEs will be displayed by system organ class and preferred term. Summaries of AEs by severity and relationship to IP will also be provided. Serious adverse events and AEs resulting in discontinuation of IP will be summarized separately in a

similar manner. Subject listings of AEs, SAEs, and AEs causing discontinuation of IP will be produced.

13.1.4.2 Clinical Laboratory Evaluations

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual (absolute) values and changes from baseline values will be presented for clinical laboratory values for each time point.

The number of subjects with clinical laboratory values categorized as below, within, or above normal ranges will be tabulated showing change from baseline (shift tables) for each clinical laboratory analyte by study visit.

Laboratory values that are outside the normal range will also be flagged in the data listings and presented with the corresponding normal ranges. Any out-of-range values that are identified by the Investigator as being clinically significant will also be shown in a data listing.

13.1.4.3 Vital Signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline will be calculated for systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and body temperature.

The number of subjects with vital signs values categorized as below, within, or above normal ranges will be tabulated showing change from baseline (shift tables) for each parameter by study visit. Pre- and post-treatment values may also be presented with an analysis of mean changes from baseline.

13.1.4.4 Twelve-lead Electrocardiograms

The number and percentage of subjects with normal and abnormal ECG findings will be summarized for each time point. Abnormal results will be grouped as clinically significant and not clinically significant. A comparison of QT results will be presented. Summary statistics, for baseline values at Screening and each subsequent evaluation, will be displayed by treatment group for QT and the QT interval corrected for heart rate (QTc). In addition, the number and percent of subjects who experienced a change >30 ms or a change >60 ms will be presented.

Descriptive summaries (mean, SD, median, minimum, and maximum) will be presented for ECG measures of PR interval, QRS interval, QT interval, QTcF interval, and heart rate for each time point.

13.1.4.5 Penn Physician Withdrawal Checklist

Descriptive summaries (mean, SD, median, minimum, and maximum) will be presented for scores from the PWC-20 checklist, completed at Visits 14 and 15.

13.1.4.6 Physical Examination Findings

The number and percentage of subjects with normal and abnormal findings in the complete physical examination, including nasal passages examination, will be displayed.

13.1.5 Efficacy Analysis

Efficacy variables will be summarized and analyzed using the safety population.

13.1.5.1 Exploratory Endpoints

Overall subject improvement as assessed by the clinician's rating on LSAS, CGI-S, CGI-I, and the subject's rating of the PGI-C from Screening (Visit 1) through Follow-up (Visit 15) will be summarized, including changes from baseline where appropriate. The change in LSAS, CGI-I, and PGI-C scores from Baseline to Visit 14 may also be explored using generalized linear model for repeated measures.

In addition, overall change in the pattern in the frequency of PH94B use (frequent users; 3 or 4 times a day and less frequent users; ≤ 2 times a day), change in medication use as documented by the clinician and the subject between Screening (Visit 1) and Follow-up (Visit 15) will be summarized.

Full details on this exploratory analysis will be provided in the SAP.

The exploratory endpoints are as follows:

- Change in total LSAS scores over time with use of PH94B
- Change in proportion of subjects with CGI-S scores >4 over time with use of PH94B
- Change in proportion of subjects with CGI-I scores of 1 (Very much improved) or 2 (Much improved) over time with use of PH94B
- Change in proportion of subjects with PGI-C scores of 1 (Very much improved) or 2 (Much improved) over time with use of PH94B
- [redacted]
- [redacted]
- [redacted]

13.1.6 Interim Analysis

Data cuts for interim data summaries are planned to support regulatory filings. An interim safety analysis will be performed when approximately 100 subjects have completed 12 months of PH94B dosing up to 4 times per day and approximately 300 subjects have completed 6 months of PH94B dosing up to 4 times per day. The study will remain ongoing until the last subject has been discontinued from the study and the database has been locked.

13.2. Sample Size Determination

Based on feedback from the FDA, the sample size for this study (up to 600 subjects) has been selected to attain a PH94B safety database per the ICH E1 Guideline.[45]

14. STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the Investigator and associated personnel before the study, periodic monitoring visits, and meticulous data management.

14.1. Sponsor and Investigator Responsibilities

14.1.1 Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 16). The sponsor reserves the right to withdraw a subject from the study (Section 8.3), to terminate participation of a study site at any time (Section 14.7), and/or to discontinue the study (Section 14.6).

VistaGen Therapeutics, Inc. agrees to provide the Investigator with sufficient material and support to permit the Investigator to conduct the study according to the study protocol.

14.1.2 Investigator Responsibilities

By signing the Investigator's Agreement (Section 18.1), the Investigator indicates that he or she has read the protocol carefully, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The study will be conducted in accordance with ICH GCP and applicable United States Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, funding agency and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the study subjects. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP training.

Investigators should ensure that all persons who are delegated study-related responsibilities are adequately qualified and informed about the protocol, the IP(s), and their specific duties within the context of the study. Investigators are responsible for providing VistaGen Therapeutics, Inc. with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study may be audited by an independent person. The Investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

14.1.3 Confidentiality and Privacy

Subject confidentiality and privacy are strictly held in trust by the participating investigators, their staff, and the sponsor and their staff. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies, or pharmaceutical company supplying study product may inspect all

documents and records required to be maintained by the Investigator, including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at [redacted] This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by [redacted] staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at [redacted]

14.2. Site Initiation

Study personnel may not screen or enroll subjects into the study until after receiving notification from the sponsor or its designee that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

1. The study site has received the appropriate IRB approval for the protocol and the appropriate ICF.
2. All regulatory documents have been submitted to and approved by the sponsor or its designee.
3. The study site has a Clinical Trial Agreement in place.
4. Study site personnel, including the Investigator, have participated in a study initiation meeting.

14.3. Screen Failures

Subjects who fail inclusion and/or exclusion criteria may be rescreened for the study on a case-by-case basis after discussion with the medical monitor. Subjects may only be rescreened once 30 days or more after the original Screening visit. If a subject is eligible to enter the study after having previously failed screening, the subject will be assigned a new subject identification number.

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

14.4. Study Documents

All documentation and material provided by VistaGen Therapeutics, Inc. for this study is to be retained in a secure location and treated as confidential material.

14.4.1 Informed Consent

Informed consent forms describing in detail the study intervention, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study intervention.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB approved and the subject will be asked to read and review the document. The Investigator will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Subjects will have the opportunity to carefully review the written ICF and ask questions prior to signing. The subject should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent document prior to any procedures being done specifically for the study. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the ICF will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date) and the ICF signed before the subject undergoes any study-specific procedures. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

14.4.2 Investigator's Regulatory Documents

The regulatory documents are listed in the [redacted] study plans.

The regulatory documents must be received from the Investigator and reviewed and approved by VistaGen Therapeutics, Inc. or its designee before the study site can initiate the study and before VistaGen Therapeutics, Inc. will authorize shipment of IP to the study site. Copies of the Investigator's regulatory documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the PH94B IB, eCRF completion guidelines, copies of regulatory references, copies of IRB correspondence, and IP accountability records should also be retained as part of the Investigator's regulatory documents. It is the Investigator's responsibility to ensure that copies of all required regulatory documents are organized, current, and available for inspection.

14.4.3 Case Report Forms

Electronic case report forms (eCRFs) will be designed to capture all relevant background information as well as objective reasons for early discontinuation when it cannot be prevented.

By signing the Investigator's Agreement (Section 18.1), the Investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all subjects who sign an ICF.

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the EDC system according to the completion guidelines provided by the sponsor or its designee.

The eCRFs must be signed by the Investigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

14.4.4 Source Documents

Information recorded in the EDC system should be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, a record of obtaining informed consent, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

14.5. Data Quality Control

VistaGen Therapeutics, Inc. and its designees will perform quality control checks on this clinical study.

14.5.1 Monitoring Procedures

VistaGen Therapeutics, Inc. and/or its designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) (CRA[s]) will visit the Investigator and study site at periodic intervals and maintain periodic communication. The Investigator agrees to allow the CRA(s) and other authorized VistaGen Therapeutics, Inc. personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff. While on site, the CRA(s) will review

- regulatory documents, directly comparing entries in the EDC system with the source documents
- consenting procedures
- AE procedures
- storage and accountability of IP and study materials

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRFs are described in the [redacted] study plans. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 18.1), the Investigator agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed; to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the Investigator agrees to allow VistaGen Therapeutics, Inc. or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

Additional details on monitoring will be described in the clinical monitoring plan.

14.5.2 Data Management

VistaGen Therapeutics, Inc. or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and [redacted] standard operating procedures. A comprehensive data management plan will be developed, including a data management overview, description of database contents, annotated eCRF, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The Investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the [redacted] study plans.

14.5.3 Quality Assurance/Audit

This study will be subject to audit by VistaGen Therapeutics, Inc., or its designee. Audits may be performed to check compliance with GCP guidelines and can include:

- site audits
- Trial Master File audits
- database audits
- document audits (e.g., protocol and/or CSR)

VistaGen Therapeutics, Inc. or its designee may conduct additional audits on a selection of study sites, requiring access to subject notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB or regulatory authorities according to GCP guidelines. The Investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with eCRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the Investigator that it intends to conduct an inspection, the Investigator shall notify VistaGen Therapeutics, Inc. immediately.

14.6. Study Termination

The study may be terminated at VistaGen Therapeutics, Inc.'s discretion at any time and for any reason.

14.6.1 Premature Study Termination

The study may be temporarily suspended or terminated prematurely if there is sufficient reasonable cause at any time by VistaGen Therapeutics, Inc., IRBs, or regulatory authorities.

Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study subjects, Principal Investigators, the IND sponsor, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator will promptly inform study subjects and the IRB; the sponsor will provide the reasons for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB, and/or FDA.

In the case of study termination, study sites may be asked to have all subjects currently participating in the study complete all of the assessments for Visit 14/Early Termination.

14.7. Study Site Closure

At the end of the study, all study sites will be closed. VistaGen Therapeutics, Inc. may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines
- Inadequate subject enrollment

14.7.1 Record Retention

The Investigator shall retain and preserve one copy of all data generated in the course of the study, specifically including, but not limited to, those defined by GCP as essential until:

- Notified by VistaGen Therapeutics, Inc. that records no longer need to be retained
- At least 2 years following the date a marketing application for the IP has been approved in this indication (SAD), or the sponsor has discontinued its research with the IP, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of the IP

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the Investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor has 30 days to respond to the Investigator's notice, and the sponsor has further opportunity to retain such materials at the sponsor's expense.

14.7.2 Sample Retention

Samples may be used for purposes related to this research. The samples will be destroyed after testing is complete. In addition, identifiable samples can be destroyed at any time at the request of the subject.

14.8. Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of VistaGen Therapeutics, Inc. The protocol amendment must be signed by the Investigator and approved by the IRB before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

14.9. Use of Information and Publication

All information concerning PH94B, PH94B's operations, patent applications, formula, manufacturing processes, basic scientific data, and formulation information supplied by VistaGen Therapeutics, Inc. or its designee to the Investigator, and not previously published, is considered confidential and remains the sole property of VistaGen Therapeutics, Inc. Case report forms also remain the property of VistaGen Therapeutics, Inc. The Investigator agrees to use this information for purposes of study execution through finalization.

The information developed in this study will be used by VistaGen Therapeutics, Inc. in connection with the continued development of PH94B and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of VistaGen Therapeutics, Inc. Publication or other public presentation of PH94B data resulting from this study requires prior review and written approval of VistaGen Therapeutics, Inc. Abstracts, manuscripts, and presentation materials should be provided to VistaGen Therapeutics, Inc. for review at least 30 days prior to the relevant submission deadline.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition, or publication by the Investigator until VistaGen Therapeutics, Inc. has reviewed and commented on such a presentation or manuscript for publication. If applicable, this study will be registered at ClinicalTrials.gov, and results information from this study will be submitted to ClinicalTrials.gov.

15. FINAL CLINICAL STUDY REPORT

VistaGen Therapeutics, Inc. will retain ownership of the data.

The final CSR will be written within 1 year of completion of the clinical part of the study. This report will include a summary of the study results based on a statistical evaluation and clinical assessment of the protocol-defined endpoints.

The final CSR may be submitted to the regulatory authorities.

16. ETHICAL AND LEGAL CONSIDERATIONS

16.1. Good Clinical Practice

This study will be conducted in compliance with the April 1996 ICH Guidance for Industry GCP E6 (including archiving of essential study documents), the Integrated Addendum to ICH E6 (R2) of November 2016, and the applicable regulations of the country(ies) in which the study is conducted.

16.2. Subject Information and Informed Consent

A properly constituted, valid IRB must review and approve the protocol, the Investigator's ICF, and related subject information and recruitment materials before the start of the study.

It is the responsibility of the Investigator to ensure that written informed consent is obtained from the subject before any activity or procedure is undertaken that is not part of routine care.

16.3. Approval by Institutional Review Board

For IND studies, the minimum standards of conduct and requirements for informed consent are defined in the FDA regulations.

A valid IRB must review and approve this protocol before study initiation. Written notification of approval is to be provided by the Investigator to the study's project manager or designee before shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature. This written approval must consist of a completed [redacted] form, IRB Approval Form, or written documentation from the IRB containing the same information.

Until written approval by the IRB has been received by the Investigator, no subject may undergo any procedure not part of routine care for the subject's condition.

Protocol amendments must also be reviewed and approved by the IRB. Written approval from the IRB, or a designee, must be received by VistaGen Therapeutics, Inc. before implementation. This written approval will consist of a completed Approval form or written documentation from the IRB containing the same information.

16.4. Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the Investigator and the sponsor.

17. REFERENCES

1. Lang AJ, Stein MB. Social phobia: prevalence and diagnostic threshold. J Clin Psychiatry. 2001;62(Suppl 1):5-10.
2. Katzelnick DJ, Greist JH. Social anxiety disorder: an unrecognized problem in primary care. J Clin Psychiatry. 2001;62 (Suppl 1):11-15.
3. Papez JW. A proposed mechanism of emotion. Arch Neurol Psychiatry. 1937;38(4):725-743.
4. Maclean PD. The limbic system ("visceral brain") and emotional behavior. AMA Arch Neurol Psychiatry. 1955;73(2):130-134.
5. Cairncross. Olfactory bulbectomy as a model for depression. N.W. Bond ed. In: Animal models in psychophysiology. New York. Academic Press, 1976:99-128.
6. Song C, Leonard B. Effects of olfactory bulbectomy in the rat, alone or in combination with antidepressants and endogenous factor, an immune function. Hum Psychopharmacol Clin Exp. 1995;10(1):7-18.
7. Croy I, Nordin S, Hummel T. Olfactory disorders and quality of life-an updated review. Chem Senses. 2014;39(3):185-194.
8. Croy I, Negoias S, Novakova L, Landis BN, Hummel T. Learning about the Functions of the Olfactory System from People without a Sense of Smell. 2012. Plos One.
9. Kevetter GA, Winans SS. Connections of the corticomedial amygdala in the golden hamster. II. Efferents of the "olfactory amygdala". J Comp Neurol. 1981;197(1):99-111.
10. Sosulski DL, Bloom ML, Cutforth T, Axel R, Datta SR. Distinct representations of olfactory information in different cortical centres. Nature. 2011;472(7342):213-216.
11. Monti-Bloch L, Jennings-White C, Dolberg DS, Berliner DL. The human vomeronasal system. Psychoneuroendocrinology. 1994;19(5-7):673-686.
12. Sobel N, Prabhakaran V, Hartley CA, Desmond JE, Glover GH, Sullivan EV, et al. Blind smell: brain activation induced by an undetected air-borne chemical. Brain. 1999;122 (Pt 2):209-217.
13. Grosser BI, Monti-Bloch L, Jennings-White C, Berliner DL. Behavioral and electrophysiological effects of androstadienone, a human pheromone. Psychoneuroendocrinology. 2000;25(3):289-299.
14. Monti-Bloch L, Grosser BI. Effect of putative pheromones on the electrical activity of the human vomeronasal organ and olfactory epithelium. J Steroid Biochem Mol Biol. 1991;39(4B):573-582.
15. Monti-Bloch L, Diaz-Sanchez V, Jennings-White C, Berliner DL. Modulation of serum testosterone and autonomic function through stimulation of the male human vomeronasal organ (VNO) with pregna-4,20-diene-3,6-dione. J Steroid Biochem Mol Biol. 1998;65(1-6):237-242.

16. Monti L, Liebowitz M. Neural Circuits of Anxiolytic and Antidepressant Pherine Molecules. Epub ahead of print. CNS Spectrums. 2020;23:1-7.
17. Kevetter GA, Winans SS. Connections of the corticomedial amygdala in the golden hamster. I. Efferents of the "vomeronasal amygdala". J Comp Neurol. 1981;197(1):81-98.
18. Swanson LW, Petrovich GD. What is the amygdala? Trends Neurosci. 1998;21(8):323-331.
19. Dorries KM, Adkins-Regan E, Halpern BP. Sensitivity and behavioral responses to the pheromone androstenone are not mediated by the vomeronasal organ in domestic pigs. Brain Behav Evol. 1997;49(1):53-62.
20. Hagino-Yamagishi K. Diverse systems for pheromone perception: multiple receptor families in two olfactory systems. Zoolog Sci. 2008;25(12):1179-1189.
21. Kang N, Baum MJ, Cherry JA. A direct main olfactory bulb projection to the 'vomeronasal' amygdala in female mice selectively responds to volatile pheromones from males. Eur J Neurosci. 2009;29(3):624-634.
22. Pape HC, Jungling K, Seidenbecher T, Lesting J, Reinscheid RK. Neuropeptide S: a transmitter system in the brain regulating fear and anxiety. Neuropharmacology. 2010;58(1):29-34.
23. Pro-Sistiaga P, Mohedano-Moriano A, Ubeda-Banon I, Del Mar Arroyo-Jimenez M, Marcos P, Artacho-Perula E, et al. Convergence of olfactory and vomeronasal projections in the rat basal telencephalon. J Comp Neurol. 2007;504(4):346-362.
24. Mohedano-Moriano A, de la Rosa-Prieto C, Saiz-Sanchez D, Ubeda-Banon I, Pro-Sistiaga P, de Moya-Pinilla M, et al. Centrifugal telencephalic afferent connections to the main and accessory olfactory bulbs. Front Neuroanat. 2012;6:19.
25. Sokolowski K, Corbin JG. Wired for behaviors: from development to function of innate limbic system circuitry. Front Mol Neurosci. 2012;5:55.
26. Tovote P, Fadok JP, Luthi A. Neuronal circuits for fear and anxiety. Nat Rev Neurosci. 2015;16(6):317-331.
27. Schaal B, Coureaud G, Langlois D, Ginies C, Semon E, Perrier G. Chemical and behavioural characterization of the rabbit mammary pheromone. Nature. 2003;424(6944):68-72.
28. Nuss P. Anxiety disorders and GABA neurotransmission: a disturbance of modulation. Neuropsychiatr Dis Treat. 2015;11:165-175.
29. Savic I, Berglund H, Gulyas B, Roland P. Smelling of odorous sex hormone-like compounds causes sex-differentiated hypothalamic activations in humans. Neuron. 2001;31(4):661-668.
30. Smeets MAM, Veldhuizen MG, Galle S, Gouweloos J, de Haan AJA, Vernooij J, et al. Sense of smell disorder and health-related quality of life. Rehabil Psychol. 2009;54(4):404-412.
31. Aydogan U, Aydogdu A, Akbulut H, Sonmez A, Yuksel S, Basaran Y, et al. Increased frequency of anxiety, depression, quality of life and sexual life in young hypogonadotropic

hypogonadal males and impacts of testosterone replacement therapy on these conditions. Endocr J. 2012;59(12):1099-1105.

32. Rodriguez I, Greer CA, Mok MY, Mombaerts P. A putative pheromone receptor gene expressed in human olfactory mucosa. Nat Genet. 2000;26(1):18-19.
33. Grus WE, Shi P, Zhang YP, Zhang J. Dramatic variation of the vomeronasal pheromone receptor gene repertoire among five orders of placental and marsupial mammals. Proc Natl Acad Sci U S A. 2005;102(16):5767-5772.
34. Yoder AD, Larsen PA. The molecular evolutionary dynamics of the vomeronasal receptor (class 1) genes in primates: a gene family on the verge of a functional breakdown. Front Neuroanat. 2014;8:153.
35. Francia S, Pifferi S, Menini A, Tirindelli R. Vomeronasal Receptors and Signal Transduction in the Vomeronasal Organ of Mammals. C. Mucignat-Caretta ed. In: Neurobiology of Chemical Communication. Chapter Chapter 10, Boca Raton, FL. CRC Press/Taylor & Francis, 2014.
36. Monti-Bloch L. Patch recorded isolated adult human vomeronasal organ cells are electrically excitable and respond to skin steroidal substances androsta-4,16-dien-3-one and estra-1,3,5(10),16-tetraen-3-ol. Chemical Senses. 1995;20(6):745.
37. Monti-Bloch L, Jennings-White C, Berliner DL. The human vomeronasal system. A review. Ann N Y Acad Sci. 1998;855:373-389.
38. Liebowitz MR, Salmán E, Rosenthal N, Nicolini H, Monti L. Evaluation of a Unique Nanogram-Dose Intranasal Aerosol for the Acute Management of the Symptoms of Social Anxiety Disorder. in New Clinical Drug Evaluation Unit Conference. 2011. Boca Raton, FL.
39. Liebowitz MR, Hanover R, Draine A, Lemming R, Careri J, Monti L. Effect of as-needed use of intranasal PH94B on social and performance anxiety in individuals with social anxiety disorder. Depress Anxiety. 2016;33(12):1081-1089.
40. Liebowitz MR, Salman E, Nicolini H, Rosenthal N, Hanover R, Monti L. Effect of an acute intranasal aerosol dose of PH94B on social and performance anxiety in women with social anxiety disorder. Am J Psychiatry. 2014;171(6):675-682.
41. Winegar B, Monti L. Pherines increase cytosolic Ca in isolated living human vomeronasal chemosensory neurons. ACHEMS abstract. 2003.
42. Herman R, Monti-Bloch L. Human VNO cDNA libraries: Pertussis toxin blockade of human VNO receptors (R1). Pherin Pharmaceuticals, Inc.; Los Altos, CA: Pherin Report MB 007; 1997.
43. Monti L. Dose dependent effect of pherine PH94B in isolated female human vomeronasal organ cells. Pherin Study Report # CL009; Report date: May 18, 1999.
44. Monti L, Liebowitz M, Smith M. PH94B: A new intranasal neuroactive steroid with rapid onset of anxiolytic activity but a mechanism of action different from benzodiazepines. ADAA, 2021.

45. ICH Topic E 1: Note for Guidance on Population Exposure: The Extent of Population Exposure to Assess Clinical Safety (CPMP/ICH/375/95). June 1995.

18. ATTACHMENTS

18.1. Investigator's Agreement

PROTOCOL NUMBER:	PH94B-CL030
PROTOCOL TITLE:	A Phase 3 Open-label Safety Trial of PH94B Nasal Spray in the Acute Treatment of Anxiety in Adult Subjects with Social Anxiety Disorder (SAD)
FINAL PROTOCOL:	12-Aug-2021
AMENDMENT 1	14-Mar-2022

I have read this protocol and agree to conduct this clinical study as outlined herein. I will ensure that all subinvestigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with VistaGen Therapeutics, Inc. and [redacted] during the study. I will adhere to all FDA, ICH, and other applicable regulations and guidelines regarding clinical studies on an IP during and after study completion.

Principal Investigator:

Printed Name:

_____

Signature:

_____

Date:

_____

19. APPENDICES

A. Liebowitz Social Anxiety Scale

B. [redacted]

C. [redacted]

D. Hamilton Depression Rating Scale

E. Clinical Global Impression Scale of Improvement

F. Clinical Global Impression Scale of Severity

G. [redacted]

H. [redacted]

I. Regulations and Good Clinical Practice Guidelines

J. Summary of Amended Sections

A. Liebowitz Social Anxiety Scale

VistaGen® Therapeutics

PALISADE LTS CLINICAL TRIAL

Subject Initials	Subject #	Date	Visit #
		DD/MMM/YYYY	

Source Document: Protocol PH94B-CL030

Liebowitz Social Anxiety Scale (LSAS)

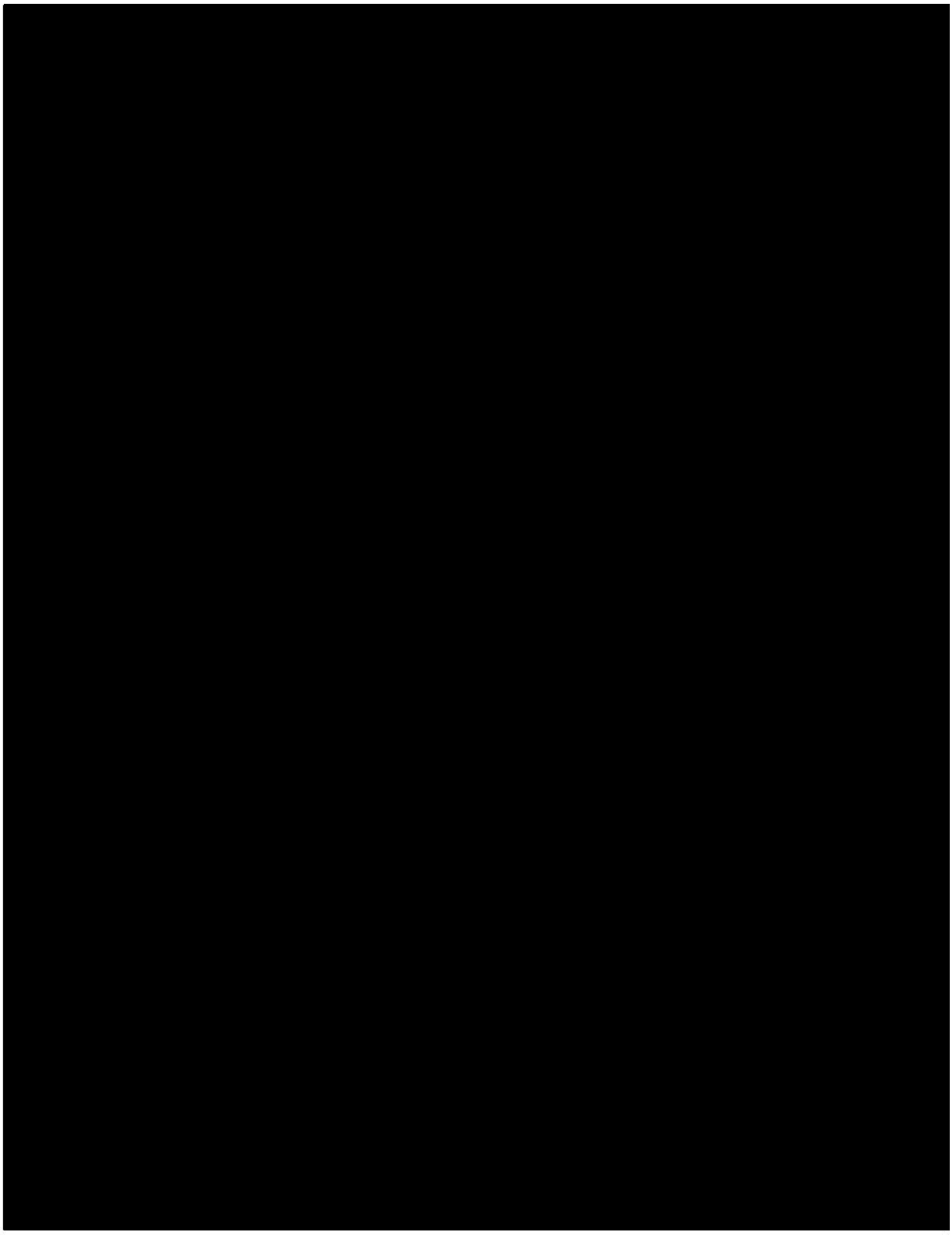
		Fear or Anxiety 0 = None 1 = Mild 2 = Moderate 3 = Severe		Avoidance 0 = Never (0%) 1 = Occasionally (1 33%) 2 = Often (34-66%) 3 = Usually (67-100%)	
	Item	Anxiety (S)	Anxiety (P)	Avoidance (S)	Avoidance (P)
1.	Telephoning in public. (P)				
2.	Participating in small groups. (P)				
3.	Eating in public places. (P)				
4.	Drinking with others in public places. (P)				
5.	Talking to people in authority. (S)				
6.	Acting, performing or giving a talk in front of an audience. (P)				
7.	Going to a party. (S)				
8.	Working while being observed. (P)				
9.	Writing while being observed. (P)				
10.	Calling someone you don't know very well. (S)				
11.	Talking with people you don't know very well. (S)				
12.	Meeting strangers. (S)				
13.	Urinating in a public bathroom. (P)				
14.	Entering a room when others are already seated. (P)				
15.	Being the center of attention. (S)				
16.	Speaking up at a meeting. (P)				
17.	Taking a test. (P)				
18.	Expressing a disagreement or disapproval to people you don't know very well. (S)				
19.	Looking at people you don't know very well in the eyes. (S)				
20.	Giving a report to a group. (P)				
21.	Trying to pick up someone. (P)				
22.	Returning good to a store. (S)				
23.	Giving a party. (S)				
24.	Resisting a high pressure sales person. (S)				
	Total Performance (P) Subscore				
	Total Social (S) Subscore				
	Total Anxiety & Avoidance Subscore				
	Total LSAS Score				

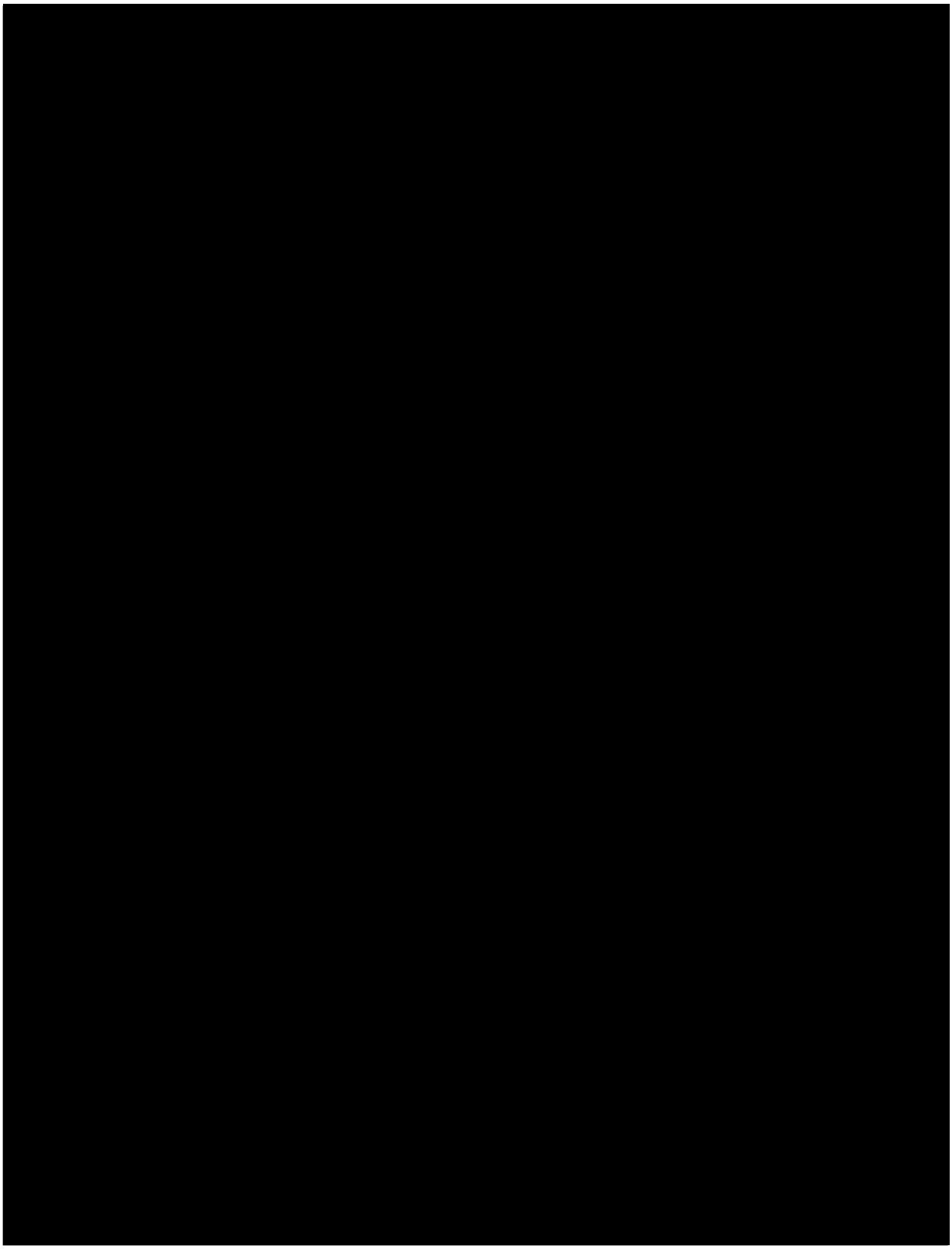
Rater Signature: _____ **Initials:** _____ **Date:** _____/_____/_____

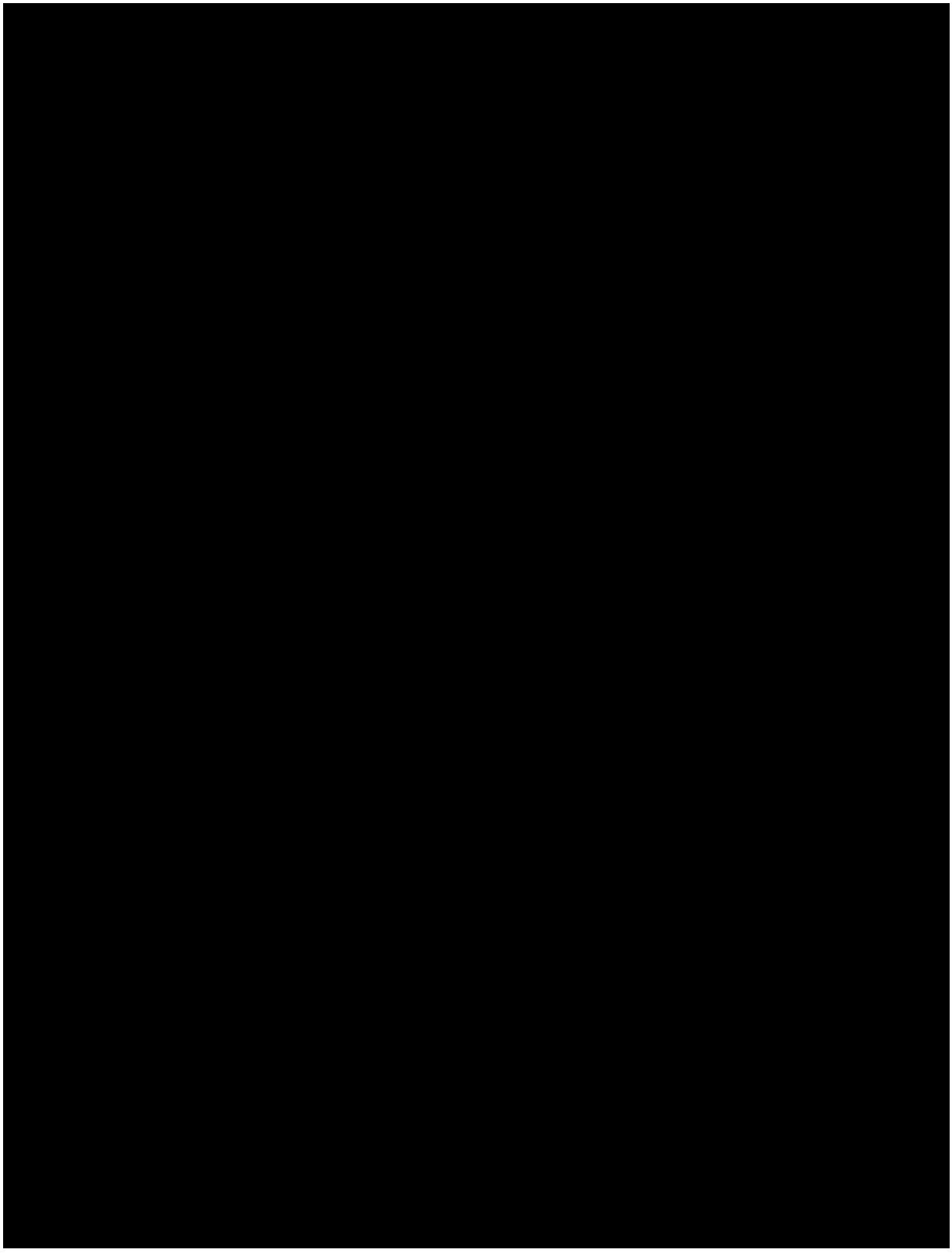
Version: 16 November 2021 Page 1 of 1

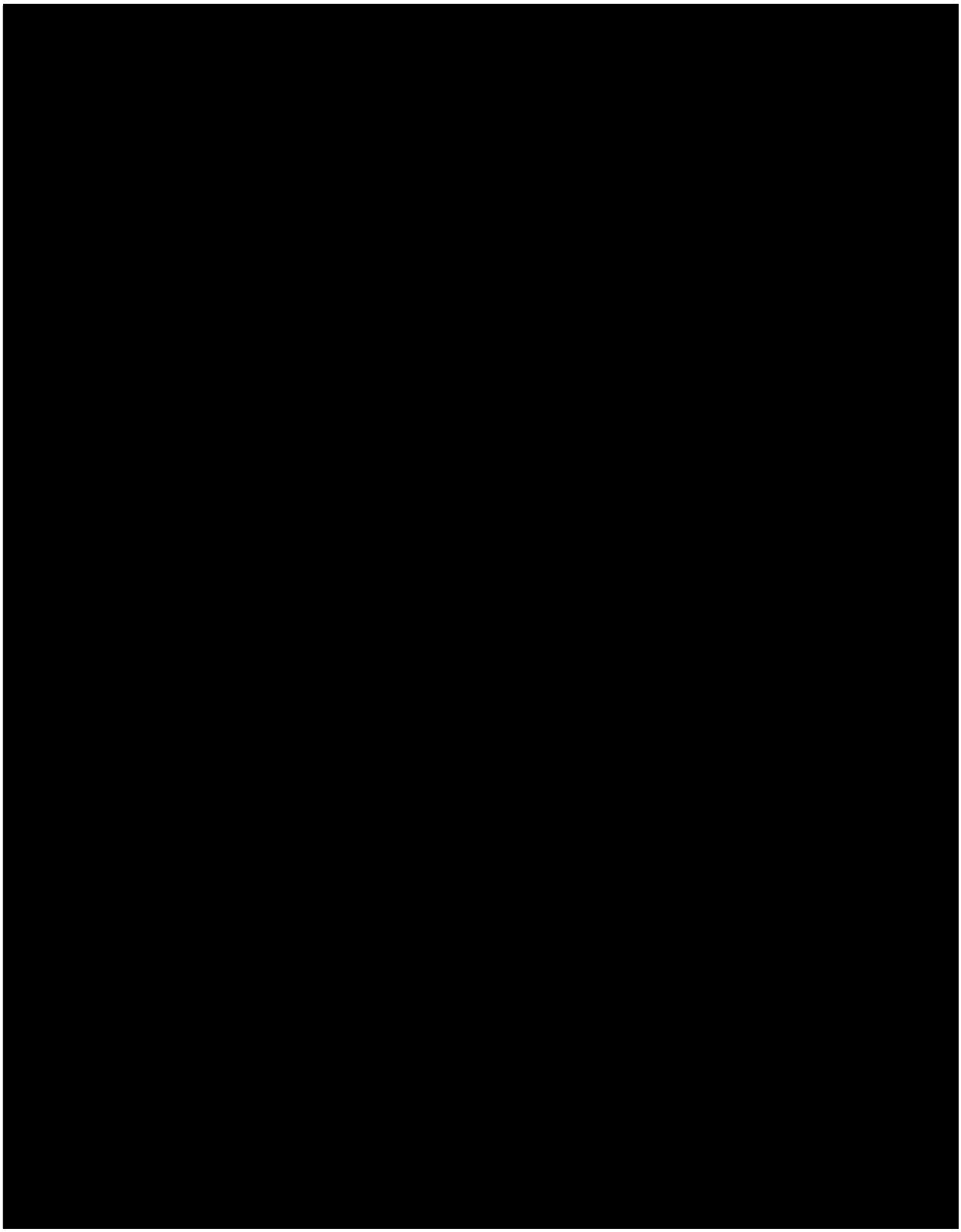
B. [redacted]

[redacted]









C. [redacted]

[redacted]

D. Hamilton Depression Rating Scale

[redacted]

VistaGen® Therapeutics

PALISADE LTS CLINICAL TRIAL

Subject Initials	Subject #	Date	Visit #
		DD/MMM/YYYY	

Source Document: Protocol PH94B-CL030

Hamilton Depression Rating Scale (HAM-D)

Check the appropriate response for each item according to how the subject has felt during the ***past week***.

1. **DEPRESSED MOOD** (sadness, hopeless, helpless, worthless)
   - ❑ 0 Absent.
   - ❑ 1 These feeling states indicated only on questioning.
   - ❑ 2 These feeling states spontaneously reported verbally.
   - ❑ 3 Communicates feeling states non-verbally, i.e. through facial expression, posture, voice, tendency to weep.
   - ❑ 4 Patient reports virtually only these feeling states in his/her spontaneous verbal and non-verbal communication.

2. **FEELINGS OF GUILT**
   - ❑ 0 Absent.
   - ❑ 1 Self-reproach, feels he/she has let people down.
   - ❑ 2 Ideas of guilt or rumination over past errors or sinful deeds.
   - ❑ 3 Present illness is a punishment. Delusions of guilt.
   - ❑ 4 Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations.

3. **SUICIDE**
   - ❑ 0 Absent.
   - ❑ 1 Feels life is not worth living.
   - ❑ 2 Wishes he/she were dead or any thoughts of possible death to self.
   - ❑ 3 Ideas or gestures of suicide.
   - ❑ 4 Attempts at suicide (any serious attempt rates 4).

4. **INSOMNIA – EARLY IN THE NIGHT**
   - ❑ 0 No difficulty falling asleep.
   - ❑ 1 Complains of occasional difficulty falling asleep, i.e. more than ½ hour.
   - ❑ 2 Complains of nightly difficulty falling asleep.

5. **INSOMNIA – MIDDLE OF THE NIGHT**
   - ❑ 0 No difficulty.
   - ❑ 1 Patient complains of being restless and disturbed during the night.
   - ❑ 2 Waking during the night - any getting out of bed rates 2 (except for purposes of voiding).

6. **INSOMNIA – EARLY HOURS OF THE MORNING**
   - ❑ 0 No difficulty.
   - ❑ 1 Waking in early hours of the morning but goes back to sleep.
   - ❑ 2 Unable to fall asleep again if gets out of bed.

Rater Signature: _____ **Initials:** _____ **Date:** ____/____/____

Version: 16 November 2021 Page 1 of 4

VistaGen® Therapeutics

PALISADE LTS

Subject Initials	Subject #	Date	Visit #
		DD/MMM/YYYY	

Source Document: Protocol PH94B-CL030

Hamilton Depression Rating Scale (HAM-D)

Check the appropriate response for each item according to how the subject has felt during the ***past week***.

7. **WORK AND ACTIVITIES**
   - ❑ 0 No difficulty.
   - ❑ 1 Thoughts and feelings of incapacity, fatigue or weakness related to activities, work, or hobbies.
   - ❑ 2 Loss of interest in activity, hobbies or work - either directly reported by patient, or indirect listlessness, indecision and vacillation (feels he/she has to push self to work or activities).
   - ❑ 3 Decrease in actual time spent in activities or decrease in productivity. Rate 3 if the patient does not spend at least three hours a day in activities (job or hobbies) excluding routine chores.
   - ❑ 4 Stopped working because of present illness. Rate 4 if patient engages in no activities except routine chores, or if patient fails to complete routine chores unassisted.

8. **RETARDATION** (slowness of thought and speech, impaired ability to concentrate, decreased motor activity)
   - ❑ 0 Normal speech and thought.
   - ❑ 1 Slight retardation during the interview.
   - ❑ 2 Obvious retardation during the interview.
   - ❑ 3 Interview difficult.
   - ❑ 4 Complete stupor.

9. **AGITATION**
   - ❑ 0 None.
   - ❑ 1 Fidgetiness.
   - ❑ 2 Playing with hands, hair, etc.
   - ❑ 3 Moving about, can't sit still.
   - ❑ 4 Hand wringing, nail-biting, hair pulling, biting of lips.

10. **ANXIETY PSYCHIC**
    - ❑ 0 No difficulty.
    - ❑ 1 Subjective tension and irritability.
    - ❑ 2 Worrying about minor matters.
    - ❑ 3 Apprehensive attitude apparent in face or speech.
    - ❑ 4 Fears expressed without questioning.

Rater Signature: _____ **Initials:** _____ **Date:** _____/_____/_____

Version: 16 November 2021 Page 2 of 4

VistaGen® Therapeutics

PALISADE LTS

Subject Initials	Subject #	Date	Visit #
		DD/MMM/YYYY	

Source Document: Protocol PH94B-CL030

Hamilton Depression Rating Scale (HAM-D)

Check the appropriate response for each item according to how the subject has felt during the ***past week***.

11. **ANXIETY SOMATIC (Physiological concomitants of anxiety), such as:**
    Gastrointestinal - dry mouth, wind, indigestion, diarrhea, stomach cramps, belching
    Cardiovascular - palpitations, headaches
    Respiratory - hyperventilation, sighing, sweating
    Urinary frequency
    Sweating
    ❑ 0 Absent.
    ❑ 1 Mild.
    ❑ 2 Moderate.
    ❑ 3 Severe.
    ❑ 4 Incapacitating.

12. **SOMATIC SYMPTOMS GASTROINTESTINAL**
    ❑ 0 None.
    ❑ 1 Loss of appetite but eating without encouragement. Heavy feelings in abdomen.
    ❑ 2 Difficulty eating without urging. Requires laxatives or medication for bowels or medication for gastrointestinal symptoms.

13. **GENERAL SOMATIC SYMPTOMS**
    ❑ 0 None.
    ❑ 1 Heaviness in limbs, back or head. Backaches, headaches, muscle aches. Loss of energy and fatigability.
    ❑ 2 Any clear-cut symptom rates 2.

14. **GENITAL SYMPTOMS** (symptoms such as loss of libido, menstrual disturbances)
    ❑ 0 Absent.
    ❑ 1 Mild.
    ❑ 2 Severe.

15. **HYPOCHONDRIASIS**
    ❑ 0 Not present.
    ❑ 1 Self-absorption (bodily).
    ❑ 2 Preoccupation with health.
    ❑ 3 Frequent complaints, requests for help, etc.
    ❑ 4 Hypochondriacal delusions.

16. **LOSS OF WEIGHT** (according to the patient)
    ❑ 0 No weight loss.
    ❑ 1 Probable weight loss associated with present illness.
    ❑ 2 Definite (according to patient) weight loss.
    ❑ 3 Not assessed.

Rater Signature: _____ **Initials:** _____ **Date:** ____/____/____

Version: 16 November 2021 Page 3 of 4

VistaGen® Therapeutics

PALISADE LTS CLINICAL TRIAL

Subject Initials	Subject #	Date	Visit #
		DD/MMM/YYYY	

Source Document: Protocol PH94B-CL030

Hamilton Depression Rating Scale (HAM-D)

Check the appropriate response for each item according to how the subject has felt during the ***past week***.
17. **INSIGHT** ❑ 0 Acknowledges being depressed and ill. ❑ 1 Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc. ❑ 2 Denies being ill at all.
Total (17 Items):

Rater Signature: _____ **Initials:** _____ **Date:** _____/_____/_____

Version: 16 November 2021 Page 4 of 4

E. Clinical Global Impression Scale of Improvement

[redacted]

VistaGen® Therapeutics

PALISADE LTS

Subject Initials	Subject #	Date	Visit #
		DD/MMM/YYYY	

Source Document: Protocol PH94B-CL030

Clinical Global Impression (CGI) Improvement Scale

[redacted]

Rater Signature: _____ Initials: _____ Date: ____/____/____

Version: 16 November 2021 Page 1 of 1

[redacted]

F. Clinical Global Impression of Severity

[redacted]

VistaGen® Therapeutics

PALISADE LTS CLINICAL TRIAL

Subject Initials	Subject #	Date	Visit #
		DD/MMM/YYYY	

Source Document: Protocol PH94B-CL030

Clinical Global Impression (CGI) Severity Scale

[redacted]

Considering your total clinical experience with this particular patient population, how mentally ill is the patient at this time? *(Based on the past week.)*

- ❑ **1 Normal, Not at All Ill**
  No social anxiety in excess of normal. No avoidance or impairment. May still become somewhat anxious before an important event (e.g. a job interview), but anxiety is not persistent.
- ❑ **2 Borderline Mentally Ill**
  Some social anxiety in excess of normal, but rare avoidance or significant anxiety. No clear impairment in functioning and no more than mild concern about having the fear.
- ❑ **3 Mildly Ill**
  Almost meets criteria for social phobia, but phobic situations are not regularly avoided or endured with intense anxiety; or there is only minimal impairment in functioning and no marked distress about having the fear.
- ❑ **4 Moderately Ill**
  Modest kinds of impairment, i.e. discomfort, but not significant disability in either social or work area. However, there are clear episodes of marked anxiety. With a 4 you have the symptoms but no significant disability. With a5 you have significant disability; with a 6 you have marked disability; an with a 7 you are dysfunctional.
- ❑ **5 Markedly Ill**
  Significant impairment in work and social activity, but no gross impairment. He/she can hold a reasonably decent job and have some social activities that are fairly comfortable although he or she has limitations in both areas.
- ❑ **6 Severely Ill**
  Not totally impaired in both work and social activities. He/she might be severely impaired in both or totally impaired in one but less in the other. So, these patients are not totally disabled, but a reasonable observer wouldbe able to see severe problems in functioning in these areas.
- ❑ **7 Among the Most Extremely Ill Patients**
  A patient is totally disabled in social and work functions.

[redacted]

Rater Signature: _____ Initials: _____ Date: ____/____/____

Version: 16 November 2021 Page 1 of 1

G. [redacted]

[redacted]

H. [redacted]

[redacted]

I. Regulations and Good Clinical Practice Guidelines

1. Regulations

Refer to the following United States CFR:

- FDA Regulations 21 CFR, Parts 50.20 – 50.27
  Subpart B – Informed Consent of Human Subjects
- FDA Regulations 21 CFR, Parts 56.107 – 56.115
  Part 56 – Institutional Review Boards
  Subpart B – Organization and Personnel
  Subpart C – IRB Functions and Operations
  Subpart D – Records and Reports
- FDA Regulations 21 CFR, Parts 312.50 – 312.70
  Subpart D – Responsibilities of Sponsors and Investigators

2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URLs:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf

J. Summary of Amended Sections

In addition to editorial changes throughout, the following changes have been made:

Section 1. Approval Signatures

New:

Medical Monitor: [redacted]

VistaGen Therapeutics, Inc

[redacted]

Text formerly read: [redacted]
Now reads: [redacted]

Section 2.1. Synopsis

Text formerly read: Objectives: The primary objective of the study is to evaluate the safety and tolerability of repeated dosing of PH94B over a period of up to 12 months as assessed by documenting adverse events (AEs) and standard clinical measurements (physical examination, vital signs, clinical chemistry, hematology, and 12-lead electrocardiogram [ECG]).

Now reads: Objectives: The primary objective of the study is to evaluate the safety and tolerability of repeated dosing of PH94B over a period of up to 12 months as assessed by documenting adverse events (AEs), standard clinical measurements (physical examination, vital signs, clinical chemistry, hematology, **suicidality, level of depression,** and 12-lead electrocardiogram [ECG])**, and withdrawal symptoms**.

Text formerly read: Rationale: The study is designed to evaluate the safety and tolerability of the long-term administration of 3.2 µg of PH94B as needed, up to 4 times a day, in adult subjects with SAD prior to anxiety-provoking situations in daily life.

Now reads: Rationale: The study is designed to evaluate the safety and tolerability of the long-term administration of 3.2 µg of PH94B as needed, up to 4 times a day, in adult subjects with SAD prior to **acute** anxiety-provoking **social** situations in daily life.

Text formerly read: Study Design: In addition to "New" subjects, subjects who have participated in a PH94B Phase 3 SAD study will be given the option to enroll in this study if they meet requirements of the inclusion and exclusion criteria.

Now reads: Study Design: **The study will enroll** subjects who have **previously** participated in **any PH94B SAD study (for example, PALISADE-1 [PH94B-CL026] or PALISADE-2 [PH94B CL032]) who** meet

requirements of the inclusion and exclusion criteria **for the present study**.

Text formerly read: Study Design (Procedures): Subject participation in the study will last up to approximately 12 to 13 months, depending on the duration of the screening period and intervals between visits. Upon signing the informed consent form, subjects will complete Visit 1 and enter a screening period lasting between 7 and 30 days. Subjects who meet all eligibility criteria will return to the clinic to complete Visit 2 (Baseline, Day 0) and undergo baseline measurements of clinical laboratory assessments (clinical chemistry, hematology, urinalysis, pregnancy test [if female and of childbearing potential], and urine drug screening), 12-lead ECG, vital signs, physical examination, Hamilton Rating Scale for Depression (HAM-D17), [redacted] LSAS, Columbia-Suicide Severity Rating Scale (C-SSRS), and Clinical Global Impression Scale of Severity (CGI-S). At Visit 2 (Baseline), subjects will be trained on how to use and store the PH94B nasal spray delivery device, and how to use an electronic diary (eDiary) application; subjects will be instructed to record each incidence of PH94B use in the eDiary. Adverse events (AEs) and concomitant medications will be reported and recorded. The subject will receive a 1-month supply of PH94B (6 vials) for use (up to 4 times per day) at the subject's discretion, as needed for social anxiety.

Subjects will be instructed to return to the clinic for Visit 3 after 30 days (±3 days). At Visit 3, subjects will undergo clinical laboratory assessments (clinical chemistry, hematology, urinalysis, pregnancy test, and urine drug screening), vital signs, 12-lead ECG, physical examination, HAM-D17, [redacted] LSAS, C-SSRS, CGI-S, Clinical Global Impression Scale of Improvement (CGI-I), and self-evaluation by Patient Global Impression of Change (PGI-C). At Visit 3, PH94B use recorded in the eDiary application will be reviewed, and AEs and concomitant medications will be reported and recorded. Subjects will receive a 1-month supply of PH94B (6 vials).

Subjects will return to the clinic at monthly intervals (±7 days, Visits 4 to 13), and will repeat the same assessments as those performed at Visit 3. PH94B use recorded in the eDiary application will be reviewed, AEs and concomitant medications will be reported and recorded, and at each visit subjects will receive a 1-month supply of PH94B (6 vials).

At Visit 14 (1 year ±2 weeks), treatment will conclude, and subjects will undergo clinical laboratory assessments (clinical chemistry, hematology, urinalysis, pregnancy test, and urine drug screening), vital signs, 12-lead ECG, physical examination, HAM-D17, [redacted] LSAS, C-SSRS, CGI-S, CGI-I, and PGI-C. Also, PH94B use recorded in the eDiary application will be reviewed and AEs and concomitant

medications will be recorded and reported. Subjects will also be informed of their follow-up visit (Visit 15).
Subjects will return to the clinic for a follow-up visit (Visit 15, 54 weeks ±3 days), approximately 2 weeks after the last PH94B administration, to undergo C-SSRS and vital signs assessments, and record AEs.

Now reads: Study Design (Procedures): Subject participation in the study will last up to approximately 12 to 13 months, depending on the duration of the screening period and intervals between visits. Upon signing the informed consent form, subjects will **begin participation in the present study at Visit 1 or Visit 2, depending on when they finished participation in their antecedent study:**

- **Subjects who finished participation in their antecedent PH94B SAD study more than 14 days before entering the present study will** complete Visit 1 and enter a screening period lasting between 7 and **35** days. Subjects who meet all eligibility criteria will return to the clinic to complete Visit 2 (Baseline)
- **Subjects who finished participation in their antecedent PH94B SAD study within the last 14 days will enter the present study at Visit 2 (Baseline)**

At Visit 2 (Baseline, Day 0), all subjects will undergo baseline measurements of clinical laboratory assessments (clinical chemistry, hematology, urinalysis, pregnancy test [if female and of childbearing potential], and urine drug screening), 12-lead ECG, vital signs, physical examination, Hamilton Rating Scale for Depression (HAM-D17), [redacted] LSAS, Columbia-Suicide Severity Rating Scale (C-SSRS), and Clinical Global Impression Scale of Severity (CGI-S). At Visit 2 (Baseline), subjects will be trained on how to use and store PH94B **Nasal Spray**, and how to use an electronic diary (eDiary) application **each day** to record **their dosing** of PH94B **(including a record of days when PH94B was not used) and any health problems they experienced that day**. Adverse events (AEs) and concomitant medications will be reported and recorded. The subject will receive a 1-month supply of PH94B for use (up to 4 times per day) at the subject's discretion, as needed for social anxiety.
Subjects will be instructed to return to the clinic for Visit 3 after 30 days (±3 days). At Visit 3, subjects will undergo clinical laboratory assessments (clinical chemistry, hematology, urinalysis, pregnancy test, and urine drug screening), vital signs, 12 lead ECG, physical examination **(limited to nasal passage and oropharynx examination unless any AEs are reported), HAM-D17,** [redacted] LSAS, C-SSRS, CGI-S, Clinical Global Impression Scale of Improvement (CGI-I), and self-evaluation by Patient Global Impression of Change (PGI-C). At Visit 3, PH94B use **and any daily reports of health problems that have been** recorded in the eDiary will be reviewed, and AEs and

concomitant medications will be reported and recorded. Subjects will receive a 1-month supply of PH94B.
Subjects will return to the clinic at monthly intervals (±7 days, Visits 4 to 13), and will repeat the same assessments as those performed at Visit 3. PH94B use **and any daily reports of health problems that have been** recorded in the eDiary application will be reviewed, AEs and concomitant medications will be reported and recorded. **Subjects** will receive a 1-month supply of PH94B **at each monthly visit**.
At Visit 14 (**12 months**±2 weeks), treatment will conclude, and subjects will undergo clinical laboratory assessments (clinical chemistry, hematology, urinalysis, pregnancy test, and urine drug screening), vital signs, 12-lead ECG, physical examination, HAM-D17, [redacted] LSAS, C-SSRS, CGI-S, CGI-I, PGI-C**, and the Penn Physician Withdrawal Checklist (PWC-20)**. Also, PH94B use **and any daily reports of health problems that have been** recorded in the eDiary application will be reviewed and AEs and concomitant medications will be recorded and reported. Subjects will also be informed of their follow-up visit (Visit 15).
Subjects will return to the clinic for a follow-up visit (Visit 15, 54 weeks ±3 days), approximately 2 weeks after the last PH94B administration, to undergo C-SSRS**, PWC-20**, and vital signs assessments, and record AEs.
Subjects who discontinue study treatment without completing 12 months of treatment will attend an Early Termination Visit (Visit 14) as soon as possible after discontinuing treatment, and return to the clinic for a follow-up visit (Visit 15) approximately 2 weeks later.

Text formerly read: Study Design (Safety Considerations): Safety and tolerability of PH94B (≤ 4 doses per day up to 12 months in up to 600 subjects) will be assessed and summarized through changes from Visit 2 (Baseline) to end of treatment (Visit 14) in AEs, laboratory values, 12-lead ECGs, physical examinations, and vital sign assessments following exposure to PH94B.

Now reads: Study Design (Safety Considerations): Safety and tolerability of PH94B (≤ 4 doses per day up to 12 months in up to 600 subjects) will be assessed and summarized through changes from Visit 2 (Baseline) to end of treatment (Visit 14) in AEs, laboratory values, 12-lead ECGs, physical examinations, **suicidality, level of depression,** vital sign assessments, **and withdrawal symptoms** following exposure to PH94B.

Text formerly read: Planned Number of Subjects: An estimated 800 subjects will be screened or rolled over from previous PH94B Phase 3 studies to obtain up to 600 subjects to receive up to 1 year of PH94B treatment.

Now reads: Planned Number of Subjects: **A sufficient number of subjects from previous PH94B SAD studies** will be screened or rolled over to

obtain up to 600 subjects to receive up to **12 months** of PH94B treatment.

Text formerly read: Study Entry Criteria: In addition to "New" subjects, subjects who have participated in a previous PH94B Phase 3 SAD study, either PALISADE-1 (PH94B-CL026) or PALISADE-2 (PH94B CL032), will be given the option to enroll in the present study.

- New Subjects: Subjects with no prior experience in a PH94B study, and those who participated in either PALISADE-1 or PALISADE-2 more than 14 days before entry in the present study
- P1/P2 Completers: Subjects who enter the present study within 14 days after completing Visit 2, 3, or 4 of either PALISADE-1 (P1) or PALISADE-2 (P2) without meeting any of the exclusion criteria of PALISADE-1/ PALISADE-2, with the exception of SUDS < 75 at Visit 2.

Now reads: Study Entry Criteria: **Subjects who have participated in a previous PH94B SAD study will be enrolled in the present study if they meet the following eligibility criteria.**

Text formerly read: Inclusion Criteria:

All Subjects

To be considered eligible to participate in the study, all subjects must meet the following inclusion criteria:

1. Written informed consent provided prior to conducting any study-specific assessment.
2. Male and female adults, 18 through 65 years of age, inclusive.
3. Women of childbearing potential must be able to commit to the consistent and correct use of an effective method of birth control throughout the study, and must also have a negative urine pregnancy test result at both Screening (Visit 1) (for subjects who attend Visit 1) and Baseline (Visit 2), prior to IP administration. Effective methods of contraception include: condoms with spermicide, diaphragm with spermicide, hormonal contraceptive agents (oral, transdermal, or injectable), or implantable contraceptive devices.
4. Current diagnosis of SAD as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, and confirmed by the Mini-International Neuropsychiatric Interview (MINI).
5. Clinician-rated HAM-D17 total score < 18 at study entry (Screening [Visit 1] or Visit 2 [Baseline] as applicable).
6. Negative COVID-19 test for subjects with COVID-19 symptoms or who had direct exposure to someone with a positive COVID-19 test, as determined by the investigator.

New Subjects

In order to qualify for participation in this study, new subjects must meet the following criteria, in addition to the "All Subjects" criteria.

7. Clinician-rated LSAS total score ≥ 50 at Screening (Visit 1).

P1/P2 Completers

In addition to the "All Subjects" criteria, P1/P2 Completers must meet all the following criteria.
7. Have participated in PALISADE-1 or PALISADE-2 and completed Visit 2, 3, or 4 within the last 14 days without meeting any of the exclusion criteria of PALISADE-1/ PALISADE-2 with the exception of SUDS < 75 at Visit 2.
8. Clinician-rated LSAS total score requirement does not apply.

Now reads: Inclusion Criteria:

To be considered eligible to participate in the study, all subjects must meet the following inclusion criteria:

1. Subject must have participated in a previous PH94B SAD study.

Note: Subjects who have not participated in a prior PH94B SAD study may be permitted to enroll following approval by the sponsor on a case-by-case basis.

2. Written informed consent provided prior to conducting any study-specific assessment.
3. Male and female adults, 18 through 65 years of age, inclusive.
4. Women of childbearing potential must be able to commit to the consistent and correct use of an effective method of birth control throughout the study and must also have a negative urine pregnancy test result at both Screening (Visit 1) (for subjects who attend Visit 1) and Baseline (Visit 2), prior to IP administration. Effective methods of contraception include: condoms with spermicide, diaphragm with spermicide, hormonal contraceptive agents (oral, transdermal, or injectable), or implantable contraceptive devices.
5. Current diagnosis of SAD as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, and confirmed by the Mini-International Neuropsychiatric Interview (MINI).
6. Clinician-rated HAM-D17 total score < 18 at study entry (Screening [Visit 1] or Visit 2 [Baseline] as applicable).
7. Negative COVID-19 test for subjects with COVID-19 symptoms or **those** who had direct exposure to someone with a positive COVID-19 test, **and/or completion of quarantine period consistent with requirements at the study site** as determined by the investigator.

Text formerly read: Exclusion Criteria:

All Subjects

To be considered eligible for entry into the study, a subject must not meet any of the following exclusion criteria at study entry.

1. Women who have a positive urine pregnancy test prior to IP administration.
2. Subjects with a positive urine drug screen at study entry [redacted]
3. Any current clinically significant and/or uncontrolled medical condition, based on medical history or as evidenced in screening

assessments, such as COVID-19, HIV, cancer, stroke, congestive heart failure, uncontrolled diabetes mellitus, or any other medical condition or disease that, in the clinical judgment of the Investigator, could place the subject at undue risk, interfere with study participation, or confound the results of the study.

4. History of cancer or malignant tumor not in remission for at least 2 years. Basal cell skin cancers are not exclusionary.

New Subjects

New subjects will be excluded from the present study if they meet any of the exclusion criteria in this section.

1. Any history of bipolar disorder (I or II), schizophrenia, schizoaffective disorder, psychosis, anorexia or bulimia, autism-spectrum disorder, or obsessive-compulsive disorder.

Any other current Axis I disorder, other than SAD, which is the primary focus of treatment. Note that subjects with concurrent Generalized Anxiety Disorder are eligible for the study provided that Generalized Anxiety Disorder is not the primary diagnosis.

2. Subjects who meet criteria for moderate or severe alcohol or substance use disorder within the 1 year prior to study entry.
3. In the opinion of the Investigator, the subject has a significant risk for suicidal behavior during the course of their participation in the study, or

a. At Screening (Visit 1): the subject scores “yes” on items 4 or 5 in the Suicidal Ideation section of the C-SSRS with reference to a 6-month period prior to screening; or

b. At Screening (Visit 1): the subject has had 1 or more suicidal attempts with reference to a 2-year period prior to screening; or

c. At Baseline (Visit 2): the subject scores “yes” on items 4 or 5 in the Suicidal Ideation section of the C-SSRS with reference to screening; or

d. The subject is considered to be an imminent danger to themself or others.

4. Clinically significant nasal pathology or history of significant nasal trauma, nasal surgery, total anosmia, or nasal septum perforation that may have damaged the nasal chemosensory epithelium.
5. An acute or chronic condition, including an infectious illness, uncontrolled seasonal allergies at the time of the study, or significant nasal congestion that potentially could affect drug delivery to the nasal chemosensory epithelium.
6. Subjects using the following psychotropic medications: anticonvulsants, mood stabilizers, antipsychotic medications, gabapentin, pregabalin, opioids, naltrexone, esketamine, and ketamine at enrollment.

Subjects using lower doses of atypical antipsychotics at Screening may be eligible after discussion with the Medical Monitor (e.g., quetiapine < 100 mg).

In general, subjects using antidepressants or buspirone can continue to receive these provided that they have been taking them for a minimum of 2 months, and have been on a stable dose for a minimum of 1 month.

7. Use of anxiolytics, such as benzodiazepines or unapproved treatments such as beta blockers, within 30 days before study entry; concomitant use is prohibited during the study. Subjects who have been taking benzodiazepines daily for 1 month or longer at the time of Visit 1 are not eligible to participate.
8. Use of any over-the-counter product, prescription product, or herbal preparation for treatment of the symptoms of anxiety or social anxiety within 30 days before study entry; concomitant use is prohibited during the study.
9. Subjects with clinically significant abnormalities in hematology, blood chemistry, urinalysis, 12-lead ECG, or physical examination identified at the Screening visit or Baseline visit that in the clinical judgment of the Investigator, could place the subject at undue risk, interfere with study participation, or confound the results of the study.

P1/P2 Completers

P1/P2 completers will be excluded from the present study if they meet any of the exclusion criteria in this section.

1. Any history of bipolar disorder (I or II), schizophrenia, schizoaffective disorder, psychosis, anorexia or bulimia, autism-spectrum disorder, or obsessive-compulsive disorder as determined at the time of entry into the legacy study.

Any other current Axis I disorder, other than SAD, which is the primary focus of treatment. Note that subjects with concurrent Generalized Anxiety Disorder are eligible for the study provided that Generalized Anxiety Disorder is not the primary diagnosis.

2. Subjects who meet criteria for moderate or severe alcohol or substance use disorder within the 1 year prior to entry into the legacy study.
3. In the opinion of the Investigator, the subject has a significant risk for suicidal behavior during the course of their participation in the study, or

a. At Baseline (Visit 2): the subject scores “yes” on items 4 or 5 in the Suicidal Ideation section of the C-SSRS with reference to last visit; or

b. The subject is considered to be an imminent danger to themself or others.

4. Clinically significant nasal pathology or history of significant nasal trauma, nasal surgery, total anosmia, or nasal septum perforation that may have damaged the nasal chemosensory epithelium.
5. An acute or chronic condition, including an infectious illness, uncontrolled seasonal allergies at the time of the study, or significant

nasal congestion that potentially could affect drug delivery to the nasal chemosensory epithelium.
6. Subjects using the following psychotropic medications: anticonvulsants, mood stabilizers, antipsychotic medications, gabapentin, pregabalin, opioids, naltrexone, esketamine, and ketamine at enrollment.
Subjects using lower doses of atypical antipsychotics at Screening may be eligible after discussion with the Medical Monitor (e.g., quetiapine < 100 mg).
In general, subjects using antidepressants or buspirone can continue to receive these provided that they have been taking them for a minimum of 2 months, and have been on a stable dose for a minimum of 1 month.
7. Use of anxiolytics, such as benzodiazepines or unapproved treatments such as beta blockers, within 30 days before study entry; concomitant use is prohibited during the study. Subjects who have been taking benzodiazepines daily for 1 month or longer at the time of study entry are not eligible to participate.
8. Use of any over-the-counter product, prescription product, or herbal preparation for treatment of the symptoms of anxiety or social anxiety within 30 days before study entry; concomitant use is prohibited during the study.
9. Subjects with clinically significant abnormalities in hematology, blood chemistry, urinalysis, 12-lead ECG, or physical examination identified at study entry or during the legacy study which, in the clinical judgment of the Investigator, could place the subject at undue risk, interfere with study participation, or confound the results of the study.

Now reads: Exclusion Criteria:
To be considered eligible for entry into the study, a subject must not meet any of the following exclusion criteria at study entry.
1. Any history of bipolar disorder (I or II), schizophrenia, schizoaffective disorder, psychosis, anorexia or bulimia, **premenstrual dysphoric disorder,** autism-spectrum disorder, obsessive-compulsive disorder**, or treatment-refractory major depressive disorder**.
Any other current Axis I disorder, other than SAD, which is the primary focus of treatment. Note that subjects with concurrent Generalized Anxiety Disorder are eligible for the study provided that Generalized Anxiety Disorder is not the primary diagnosis.
2. In the opinion of the Investigator, the subject has a significant risk for suicidal behavior during the course of their participation in the study, or
a. At Screening (**for subjects who attend** Visit 1): the subject scores "yes" on items 4 or 5 in the Suicidal Ideation section of the Columbia-

Suicide Severity Rating Scale (C-SSRS) with reference to a 6-month period prior to screening; or
b. At Screening (**for subjects who attend** Visit 1): the subject has had 1 or more suicidal attempts with reference to a 2-year period prior to screening; or
c. At Baseline (Visit 2): the subject scores "yes" on items 4 or 5 in the Suicidal Ideation section of the C-SSRS with reference to last visit; or
d. The subject is considered to be an imminent danger to themself or others.
3. Subjects using the following psychotropic medications **at enrollment or within 30 days before study entry: antidepressants (including monoamine oxidase inhibitors), anxiolytics, stimulants,** anticonvulsants, mood stabilizers, antipsychotic medications, gabapentin, pregabalin, opioids, naltrexone, esketamine, and ketamine. **Eszopiclone, ramelteon, melatonin, zaleplon, zolpidem, or anti-histamines prescribed for insomnia are allowed.**
4. Use of benzodiazepines or unapproved treatments such as beta blockers, within 30 days before study entry and during the study. **Use of beta blockers for treatment of hypertension or cardiac conditions is allowed.** Subjects who have been taking benzodiazepines daily for 1 month or longer at the time of Visit 1 are not eligible to participate.
5. Use of any over-the-counter product or herbal preparation for treatment of the symptoms of anxiety or social anxiety within 30 days before study entry; concomitant use is prohibited during the study.
6. Clinically significant nasal pathology or history of significant nasal trauma, nasal surgery, total anosmia, or nasal septum perforation that may have damaged the nasal chemosensory epithelium.
7. Subjects who meet criteria for moderate or severe alcohol or substance use disorder within the 1 year prior to entry into the study.
8. Subjects with a positive urine drug screen at study entry [redacted].
9. An acute or chronic condition, including an infectious illness, uncontrolled seasonal allergies at the time of the study, or significant nasal congestion that potentially could affect drug delivery to the nasal chemosensory epithelium.
10. Any current clinically significant and/or uncontrolled medical condition, based on medical history or as evidenced in screening assessments, such as COVID-19, HIV, cancer, stroke, congestive heart failure, uncontrolled diabetes mellitus, or any other medical condition or disease that, in the clinical judgment of the Investigator, could place the subject at undue risk, interfere with study participation, or confound the results of the study.

	11. Women who have a positive urine pregnancy test prior to IP administration. **Women who are currently breastfeeding are not eligible.** 12. History of cancer or malignant tumor not in remission for at least 2 years. Basal cell skin cancers are not exclusionary. 13. Subjects with clinically significant abnormalities in hematology, blood chemistry, urinalysis, 12-lead ECG, or physical examination identified at study entry or during the legacy study which, in the clinical judgment of the Investigator, could place the subject at undue risk, interfere with study participation, or confound the results of the study.
Text formerly read:	Treatment Regimens: Treatment with PH94B should be self-administered approximately 15 minutes prior to an anxiety-provoking situation or event. Consecutive nasal administrations of IP should be at least 1 hour apart, with no more than 4 administrations per day.
Now reads:	Treatment Regimens: Treatment with PH94B should be self-administered **as needed** approximately 15 minutes prior to **or during** an anxiety-provoking **social** situation or event. Consecutive nasal administrations of IP should be at least 1 hour apart, with no more than 4 administrations per day. **Treatment does not need to be administered every day.**
Text formerly read:	Planned Study Sites: The study is designed as a multicenter study conducted in the USA with 20-30 clinical study sites, with each site enrolling approximately 25 to 34 subjects.
Now reads:	Planned Study Sites: The study is designed as a multicenter study conducted in the USA with **approximately 40** clinical study sites.
Text formerly read:	Criteria for Evaluation: The primary outcome variable for the study is the change from Baseline (Visit 2) in AEs after the administration of PH94B prior to anxiety-provoking situations in daily life for subjects with SAD. In addition to the primary outcome variable, the change from Baseline (Visit 2) in standard clinical measurements and behavioral assessment scores (LSAS, CGI-S, CGI-I, and PGI-C) in response to anxiety-provoking situations in daily life after the administration of PH94B will be evaluated in subjects with SAD.
Now reads:	Criteria for Evaluation: The primary outcome variable for the study is the change from Baseline (Visit 2) in AEs after the administration of PH94B prior to anxiety-provoking **social** situations in daily life for subjects with SAD. In addition to the primary outcome variable, the change from Baseline (Visit 2) in standard clinical measurements and behavioral assessment scores (LSAS, CGI-S, CGI-I, and PGI-C) in response to anxiety-provoking **social** situations in daily life after the administration of PH94B will be evaluated in subjects with SAD.
New:	Criteria for Evaluation (Safety endpoints): • **PWC-20 scores after termination of PH94B**

Text formerly read: Criteria for Evaluation (Exploratory endpoints):
- Change in total LSAS scores over time with daily use of PH94B
- Change in proportion of subjects with CGI-S scores >4 over time with daily use of PH94B
- Change in proportion of subjects with CGI-I scores of 1 (Very much improved) or 2 (Much improved) over time with daily use of PH94B
- Change in proportion of subjects with PGI-C scores of 1 (Very much improved) or 2 (Much improved) over time with daily use of PH94B
- Changes in patterns of PH94B use (daily frequency and dosing interval) over time
- Change in patterns of PH94B use (daily frequency and dosing interval) in designated subgroups over time
- [redacted]

Now reads: Criteria for Evaluation (Exploratory endpoints):
- Change in total LSAS scores over time with use of PH94B
- Change in proportion of subjects with CGI-S scores >4 over time with use of PH94B
- Change in proportion of subjects with CGI-I scores of 1 (Very much improved) or 2 (Much improved) over time with use of PH94B
- Change in proportion of subjects with PGI-C scores of 1 (Very much improved) or 2 (Much improved) over time with use of PH94B
- Changes in patterns of PH94B use (frequency and dosing interval) over time
- Change in patterns of PH94B use (frequency and dosing interval) in designated subgroups over time
- [redacted]

Text formerly read: Statistical Methods (Analysis Populations):

Safety Population: All subjects who are dispensed IP will be included in the safety population.

Now reads: Statistical Methods (Analysis Populations):

Safety Population: All subjects who **receive** IP.

Text formerly read: Study Treatment and Duration:
1. Screening and washout: From 7 to 30 days

Now reads: Study Treatment and Duration:
1. Screening and washout **(if applicable)**: From 7 to **35** days

Text formerly read: Study Treatment and Duration:
The maximum study duration for each subject is approximately 54 weeks.

Now reads: Study Treatment and Duration:
The maximum study duration for each subject is approximately **59** weeks.

Section 2.2	Schedule of Events The order of assessments in the Schedule of Events was adjusted to match the order defined in Section 10.2
Text formerly read:	Screening visit window: Day -30 to Day -7
Now reads:	Screening visit window: Day -**35** to Day -7
New:	**PWC-20** added to list of assessments at Visits 14 and 15
Text formerly read:	Assessment/Evaluation: Training on use of Spray Device
Now reads:	Assessment/Evaluation: Training on use of **PH94B**
Text formerly read:	Assessment/Evaluation: Training on eDiary App to Record PH94B Use
Now reads:	Assessment/Evaluation: Training on eDiary App to Record PH94B Use **and Health Problems**
New:	Abbreviations: **PWC-20 = Penn Physician Withdrawal Checklist**
Text formerly read:	Footnotes: a Subjects entering the study having participated in a previous PH94B Phase 3 SAD study will sign an informed consent form for the present study at either Visit 1 or Visit 2, depending on when they enter the study (see Table 2-2). b For subjects entering the study having participated in a previous PH94B Phase 3 SAD study, a review of inclusion and exclusion criteria will be conducted at either Visit 1 or Visit 2, depending on when they enter the study (see Table 2-2). c Pregnancy tests will only be given to female subjects of childbearing potential and not post-menopausal females. d 12-Lead electrocardiograms will be administered to subjects at the Screening and Baseline visits and then every month during the study. e Physical examination will include measurement of weight and an examination of the nasal passages. Height will be measured at Screening and at Visit 14. f If total anosmia is suspected during review of the nasal passages at Visit 1, the Quick Olfactory Test (QOT) is to be administered. Note: Long-term C-SSRS will be administered at screening. All other C-SSRS will be “Since Last Visit”. Note: If central laboratory urine drug screen testing is positive for a subject, then the participation of the subject in the study may have to be discontinued. The Medical Monitor should be consulted on these cases. An unscheduled repeat urine drug screen may be obtained to investigate whether drug use is continuing.
Now reads:	Footnotes: a Subjects will sign an informed consent form for the present study at either Visit 1 or Visit 2, depending on when they enter the study. b Pregnancy tests will only be given to female subjects of childbearing potential and not post-menopausal females. c Physical examination will include measurement of weight and an examination of the nasal passages. Height will be measured at Screening and at Visit 14. **The physical examinations done at**

Visit 1, Visit 2 and Visit 14 will be comprehensive. The physical examinations done at Visit 3 to Visit 13 will be focused but must include examination of the nasal passages and oropharynx. Other organ systems should be examined at Visit 3 to Visit 13 if the subject reports AEs or if the investigator has specific concerns.
d If total anosmia is suspected during review of the nasal passages at Visit 1, the Quick Olfactory Test (QOT) is to be administered.
e 12-Lead electrocardiograms will be administered **in a supine position after the subject has rested for 5 minutes.**
f **For all subjects, a review of inclusion and exclusion criteria will be conducted at Visit 2 to confirm eligibility**.
Note: Long-term C-SSRS will be administered at screening. All other C-SSRS **evaluations** will be "Since Last Visit."
Note: If central laboratory urine drug screen testing is positive for a subject [redacted]**,** then the participation of the subject in the study may have to be discontinued. The Medical Monitor should be consulted on these cases. An unscheduled repeat urine drug screen may be obtained to investigate whether drug use is continuing.

Deleted: Table 2-2: Enrollment of Subjects From Previous PH94B Phase 3 SAD Studies – Management of Visit 1 and Visit 2

(*references to this table were removed throughout the protocol*)

Section 4. List of Abbreviations and Definitions of Terms

New: **MAO: monoamine oxidase**
PWC-20: Penn Physician Withdrawal Checklist
UDS: urine drug screen

Section 6.1. Primary objective

Text formerly Read: The primary objective of the study is to evaluate the safety and tolerability of repeated dosing of PH94B over a period of up to 12 months as assessed by documenting AEs and standard clinical measurements (physical examination, vital signs, clinical chemistry, hematology, and 12-lead electrocardiogram [ECG]).

Now reads: The primary objective of the study is to evaluate the safety and tolerability of repeated dosing of PH94B over a period of up to 12 months as assessed by documenting AEs, standard clinical measurements (physical examination, vital signs, clinical chemistry, hematology, **suicidality, level of depression**, 12-lead electrocardiogram [ECG])**, and withdrawal symptoms**.

Section 6.3. Endpoint mapping

Text formerly read: Objectives (Primary): The primary objective of the study is to evaluate the safety and tolerability of repeated dosing of PH94B over a period of up to 12 months as assessed by documenting AEs and standard

clinical measurements (physical examination, vital signs, clinical chemistry, hematology, and 12-lead ECG)

Now reads: Objectives (Primary): The primary objective of the study is to evaluate the safety and tolerability of repeated dosing of PH94B over a period of up to 12 months as assessed by documenting AEs, standard clinical measurements (physical examination, vital signs, clinical chemistry, hematology, **suicidality, level of depression,** 12-lead ECG**), and withdrawal symptoms**.

New: Endpoints (Primary): **PWC-20 scores after termination PH94B**

Text formerly read: Endpoints (Exploratory):
Change in total LSAS scores over time with daily use of PH94B
Change in proportion of subjects with CGI-S scores >4 over time with daily use of PH94B
Change in proportion of subjects with CGI-I scores of 1 (Very much improved) or 2 (Much improved) over time with daily use of PH94B
Change in proportion of subjects with PGI-C scores of 1 (Very much improved) or 2 (Much improved) over time with daily use of PH94B
Change in patterns of PH94B use (daily frequency and dosing interval) over time
Change in patterns of PH94B use (daily frequency and dosing interval) in designated subgroups over time
[redacted]

Now reads: Endpoints (Exploratory):
Change in total LSAS scores over time with use of PH94B
Change in proportion of subjects with CGI-S scores >4 over time with use of PH94B
Change in proportion of subjects with CGI-I scores of 1 (Very much improved) or 2 (Much improved) over time with use of PH94B
Change in proportion of subjects with PGI-C scores of 1 (Very much improved) or 2 (Much improved) over time with use of PH94B
Change in patterns of PH94B use (frequency and dosing interval) over time
Change in patterns of PH94B use (frequency and dosing interval) in designated subgroups over time
[redacted]

New: Abbreviations: **PWC-20 = Penn Physician Withdrawal Checklist**

Section 7. Study Design

Text formerly read: An estimated 800 subjects will be screened or rolled over from previous PH94B Phase 3 studies to obtain up to 600 subjects to receive up to 1 year of PH94B treatment.

Now reads: **A sufficient number of subjects from previous PH94B SAD studies** will be screened or rolled over to obtain up to 600 subjects to receive up to **12 months** of PH94B treatment.

Section 7.1. Overall Study Design and Plan

Text formerly read: Subject participation in the study will last up to approximately 12 to 13 months, depending on the duration of the screening period and intervals between visits. Upon signing the informed consent form (ICF), subjects will complete Visit 1 and enter a screening period lasting between 7 and 30 days. Subjects who meet all eligibility criteria will return to the clinic to complete Visit 2 (Baseline, Day 0) and undergo baseline measurements of clinical laboratory assessments (clinical chemistry, hematology, urinalysis, pregnancy test [if female and of childbearing potential], and urine drug screening), 12-lead ECG, vital signs, physical examination, Hamilton Rating Scale for Depression (HAM-D17), [redacted] Liebowitz Social Anxiety Scale (LSAS), Columbia Suicide Severity Rating Scale (C-SSRS), and Clinical Global Impression Scale of Severity (CGI-S). At Visit 2 (Baseline), subjects will be trained on how to use and store the PH94B nasal spray delivery device, and how to use an electronic diary (eDiary) application; subjects will be instructed to record each incidence of PH94B use in the eDiary application. Adverse events (AEs) and concomitant medications will be reported and recorded. The subject will receive a 1-month supply of PH94B (6 vials) for use (up to 4 times per day) at the subject's discretion, as needed for social anxiety.

Subjects will be instructed to return to the clinic for Visit 3 after 30 days (±3 days). At Visit 3, subjects will undergo clinical laboratory assessments (clinical chemistry, hematology, urinalysis, pregnancy test, and urine drug screening), vital signs, 12-lead ECG, physical examination, HAM-D17, [redacted] LSAS, C-SSRS, CGI-S, CGI-I, and self-evaluation by the patient-reported outcome measure, Patient Global Impression of Change (PGI-C). At Visit 3, PH94B use recorded in the eDiary application will be reviewed and AEs and concomitant medications will be reported and recorded. Subjects will receive a 1-month supply of PH94B (6 vials).

Subjects will return to the clinic at monthly intervals (±7 days, Visits 4 to 13), and will repeat the same assessments as those performed at Visit 3. PH94B use recorded in the eDiary application will be reviewed, AEs and concomitant medications will be reported and recorded, and at each visit subjects will receive a 1-month supply of PH94B (6 vials).

At Visit 14 (1 year ±2 weeks), treatment will conclude, and subjects will undergo clinical laboratory assessments (clinical chemistry, hematology, urinalysis, pregnancy test, and urine drug screening), vital signs, 12-lead ECG, physical examination, HAM-D17, HAM-A, LSAS, C-SSRS CGI-S, CGI-I, and PGI-C. Also, PH94B use recorded in the eDiary application will be reviewed, and AEs and concomitant medications will be recorded and reported. Subjects will also be informed of their follow-up visit (Visit 15).

Subjects will return to the clinic for a follow-up visit (Visit 15, 54 weeks ±3 days), approximately 2 weeks after the last PH94B administration, to undergo C-SSRS and vital signs assessments, and record AEs.

Safety Considerations:

Safety and tolerability of PH94B (≤ 4 doses per day up to 12 months in up to 600 subjects) will be assessed and summarized through changes from baseline (Visit 2) to end of treatment (Visit 14) in AEs, laboratory values, 12-lead ECGs, physical examinations, and vital sign assessments following exposure to PH94B.

Now reads:

Subject participation in the study will last up to approximately 12 to 13 months, depending on the duration of the screening period and intervals between visits. Upon signing the informed consent form (ICF), subjects will **begin participation in the present study at Visit 1 or Visit 2, depending on when they finished participation in their antecedent study:**

- **Subjects who finished participation in their antecedent PH94B SAD study more than 14 days before entering the present study will** complete Visit 1 and enter a screening period lasting between 7 and **35** days. Subjects who meet all eligibility criteria will return to the clinic to complete Visit **2 (Baseline)**
- **Subjects who finished participation in their antecedent PH94B SAD study within the last 14 days will enter the present study at Visit 2 (Baseline)**

At Visit 2 (Baseline, Day 0)**, all subjects will** undergo baseline measurements of clinical laboratory assessments (clinical chemistry, hematology, urinalysis, pregnancy test [if female and of childbearing potential], and urine drug screening), 12-lead ECG, vital signs, physical examination, Hamilton Rating Scale for Depression (HAM-D17), [redacted] Liebowitz Social Anxiety Scale (LSAS), Columbia Suicide Severity Rating Scale (C-SSRS), and Clinical Global Impression Scale of Severity (CGI-S). At Visit 2 (Baseline), subjects will be trained on how to use and store PH94B **Nasal Spray**, and how to use an electronic diary (eDiary) application **each day** to record **their dosing of PH94B (including a record of days when PH94B was not used) and any health problems they experienced that day**. Adverse events (AEs) and concomitant medications will be reported and recorded. The subject will receive a 1-month supply of PH94B for use (up to 4 times per day) at the subject's discretion, as needed for social anxiety. Subjects will be instructed to return to the clinic for Visit 3 after 30 days (±3 days). At Visit 3, subjects will undergo clinical laboratory assessments (clinical chemistry, hematology, urinalysis, pregnancy test, and urine drug screening), vital signs, 12 lead ECG, physical examination **(limited to nasal passage and oropharynx examination unless any AEs are reported)**, HAM-D17, [redacted], LSAS, C-SSRS,

CGI-S, CGI-I, and self-evaluation by the patient-reported outcome measure, Patient Global Impression of Change (PGI-C). At Visit 3, PH94B use **and any daily reports of health problems that have been** recorded in the eDiary application will be reviewed and AEs and concomitant medications will be reported and recorded. Subjects will receive a 1-month supply of PH94B.

Subjects will return to the clinic at monthly intervals (±7 days, Visits 4 to 13), and will repeat the same assessments as those performed at Visit 3. PH94B use **and any daily reports of health problems that have been** recorded in the eDiary application will be reviewed, AEs and concomitant medications will be reported and recorded at each visit. **Subjects** will receive a 1-month supply of PH94B **at each monthly visit**.

At Visit 14 (**12 months**±2 weeks), treatment will conclude, and subjects will undergo clinical laboratory assessments (clinical chemistry, hematology, urinalysis, pregnancy test, and urine drug screening), vital signs, 12-lead ECG, physical examination, HAM-D17, HAM-A, LSAS, C-SSRS CGI-S, CGI-I, PGI-C**, and the Penn Physician Withdrawal Checklist (PWC-20)**. Also, PH94B use **and any daily reports of health problems that have been** recorded in the eDiary application will be reviewed, and AEs and concomitant medications will be recorded and reported. Subjects will also be informed of their follow-up visit (Visit 15).

Subjects will return to the clinic for a follow-up visit (Visit 15, 54 weeks ±3 days), approximately 2 weeks after the last PH94B administration, to undergo C-SSRS, **PWC-20,** and vital signs assessments, and record AEs.

Subjects who discontinue study treatment without completing 12 months of treatment will attend an Early Termination Visit (Visit 14) as soon as possible after discontinuing treatment, and return to the clinic for a follow-up visit (Visit 15) approximately 2 weeks later.

Safety Considerations:

Safety and tolerability of PH94B (≤ 4 doses per day up to 12 months in up to 600 subjects) will be assessed and summarized through changes from baseline (Visit 2) to end of treatment (Visit 14) in AEs, laboratory values, 12-lead ECGs, physical examinations, **suicidality, level of depression,** vital sign assessments, **and withdrawal symptoms** following exposure to PH94B.

Section 7.1.1. Enrollment From PALISADE-1 (PH94B-CL026) and PALISADE-2 (PH94B-CL032) Studies

Section deleted: Subjects who have participated in a previous PH94B Phase 3 SAD study, either PALISADE-1 (PH94B-CL026) or PALISADE-2 (PH94B-CL032), will be given the option to enroll in this study. Subjects who enter the present study within 14 days after completing

Visit 2, 3, or 4 of either PALISADE-1 (P1) or PALISADE-2 (P2) without meeting any of the exclusion criteria of PALISADE-1/ PALISADE-2, with the exception of SUDS < 75 at Visit 2, will be considered as "P1/P2 Completers", and will enter the present study at Visit 2 (see Table 2-2).
Subjects who participated in PALISADE-1 or PALISADE-2 more than 14 days before entry into the present study will be considered as "New" subjects and will enter the present study at Visit 1 (see Table 2-2).
Irrespective of whether they enroll in the present study at Visit 1 or Visit 2, all subjects entering from PALISADE-1 or PALISADE-2 must sign an ICF for the present study before receiving study treatment or undergoing any study-specific assessment.

Section 7.2. Rationale and Discussion of Study Design

Text formerly read: The present study has been designed to evaluate the safety and tolerability of PH94B with repeated dosing over a period of up to 12 months. Participating subjects will use PH94B up to 4 times a day when they encounter anxiety-provoking situations in daily life. Formal evaluation of the efficacy of PH94B is being conducted in 2 Phase 3 studies that have been designed and powered to assess its efficacy in reducing anxiety in a public speaking challenge. In the present study, evaluation of the efficacy of PH94B over the 12-month treatment period is an exploratory objective.
Given that evaluation of long-term safety is the primary objective of this study, an open-label study with no comparator is considered to be an appropriate design.
Safety assessments in this study are standard for the evaluation of an investigational medicinal product, and include collection of AEs and SAEs, and evaluation of vital signs, safety laboratory tests, 12-lead ECGs, and physical examinations; given the use of the i.n. route of administration, the physical examination will include an examination of the nasal passages. Given that subjects are patients with a confirmed diagnosis of SAD, the C-SSRS will be used at each study visit as a precautionary measure.

Now reads: The present study has been designed to evaluate the safety and tolerability of PH94B with repeated dosing over a period of up to 12 months**, in subjects who have participated in previous PH94B SAD studies**. Participating subjects will use PH94B up to 4 times a day when they encounter anxiety-provoking **social** situations in daily life. Formal evaluation of the efficacy of PH94B is being conducted in 2 Phase 3 studies, **which** have been designed and powered to assess its efficacy in reducing anxiety in a public speaking challenge. In the present study, evaluation of the efficacy of PH94B over the 12-month treatment period is an exploratory objective.

Given that evaluation of long-term safety is the primary objective of this study, an open-label study with no comparator is considered to be an appropriate design.
Safety assessments in this study are standard for the evaluation of an investigational medicinal product, and include collection of AEs and SAEs, and evaluation of vital signs, safety laboratory tests, 12-lead ECGs, and physical examinations; given the use of the i.n. route of administration, the physical examination will include an examination of the nasal passages. Given that subjects are patients with a confirmed diagnosis of SAD, the C-SSRS will be used at each study visit as a precautionary measure. **Withdrawal symptoms will also be assessed.**

Section 7.4. Study Sites

Text formerly read: The study is designed as a multicenter study conducted in the USA with 20-30 clinical study sites, with each site enrolling approximately 25 to 34 subjects.

Now reads: The study is designed as a multicenter study conducted in the USA with a**pproximately 40 clinical study sites.**

Section 8.1. Selection of Study Population

Deleted: "New" subjects may be recruited from the Investigator or sub-Investigator's clinical practices, the center's existing database, referring physicians, direct advertisement, or other lead generation sources.
In addition to "New" subjects, subjects who have participated in a PH94B Phase 3 SAD study will be given the option to enroll in this study.

- New Subjects: Subjects with no prior experience in a PH94B study, and those who participated in either PALISADE-1 or PALISADE-2 more than 14 days before entry in the present study
- P1/P2 Completers: Subjects who enter the present study within 14 days after completing Visit 2, 3, or 4 of either PALISADE-1 (P1) or PALISADE-2 (P2) without meeting any of the exclusion criteria of PALISADE-1/PALISADE-2, with the exception of SUDS < 75 at Visit 2.

Section 8.2.1. Inclusion Criteria.

Text formerly read: 8.2.1.1 All Subjects
To be considered eligible to participate in the study, all subjects must meet the following inclusion criteria:
1. Written informed consent provided prior to conducting any study-specific assessment.
2. Male and female adults, 18 through 65 years of age, inclusive.
3. Women of childbearing potential must be able to commit to the consistent and correct use of an effective method of birth control throughout the study, and must also have a negative urine pregnancy

test result at both Screening (Visit 1) (for subjects who attend Visit 1) and Baseline (Visit 2), prior to IP administration. Effective methods of contraception include: condoms with spermicide, diaphragm with spermicide, hormonal contraceptive agents (oral, transdermal, or injectable), or implantable contraceptive devices.
4. Current diagnosis of SAD as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, and confirmed by the Mini-International Neuropsychiatric Interview (MINI).
5. Clinician-rated HAM-D17 total score < 18 at study entry (Screening [Visit 1] or Visit 2 [Baseline] as applicable).
6. Negative COVID-19 test for subjects with COVID-19 symptoms or who had direct exposure to someone with a positive COVID-19 test, as determined by the investigator.

8.2.1.2 New Subjects

In order to qualify for participation in this study, new subjects must meet the following criteria, in addition to the "All Subjects" criteria.
7. Clinician-rated LSAS total score ≥ 50 at Screening (Visit 1).

8.2.1.3 P1/P2 Completers

In addition to the "All Subjects" criteria, P1/P2 Completers must meet all the following criteria.
7. Have participated in PALISADE-1 or PALISADE-2 and completed Visit 2, 3, or 4 within the last 14 days without meeting any of the exclusion criteria of PALISADE-1/ PALISADE-2 with the exception of SUDS < 75 at Visit 2.
8. Clinician-rated LSAS total score requirement does not apply.

Now reads: Inclusion Criteria:

To be considered eligible to participate in the study, all subjects must meet the following inclusion criteria:

1. Subject must have participated in a previous PH94B SAD study.

Note: Subjects who have not participated in a prior PH94B SAD study may be permitted to enroll following approval by the sponsor on a case-by-case basis.

2. Written informed consent provided prior to conducting any study-specific assessment.
3. Male and female adults, 18 through 65 years of age, inclusive.
4. Women of childbearing potential must be able to commit to the consistent and correct use of an effective method of birth control throughout the study and must also have a negative urine pregnancy test result at both Screening (Visit 1) (for subjects who attend Visit 1) and Baseline (Visit 2), prior to IP administration. Effective methods of contraception include: condoms with spermicide, diaphragm with spermicide, hormonal contraceptive agents (oral, transdermal, or injectable), or implantable contraceptive devices.

5. Current diagnosis of SAD as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, and confirmed by the Mini-International Neuropsychiatric Interview (MINI).
6. Clinician-rated HAM-D17 total score < 18 at study entry (Screening [Visit 1] or Visit 2 [Baseline] as applicable).
7. Negative COVID-19 test for subjects with COVID-19 symptoms or **those** who had direct exposure to someone with a positive COVID-19 test, **and/or completion of quarantine period consistent with requirements at the study site** as determined by the investigator.

Section 8.2.2. Exclusion Criteria.

Text formerly read:

8.2.2.1 All Subjects

To be considered eligible for entry into the study, a subject must not meet any of the following exclusion criteria at study entry.

1. Women who have a positive urine pregnancy test prior to IP administration.
2. Subjects with a positive urine drug screen at study entry [redacted]
3. Any current clinically significant and/or uncontrolled medical condition, based on medical history or as evidenced in screening assessments, such as COVID-19, HIV, cancer, stroke, congestive heart failure, uncontrolled diabetes mellitus, or any other medical condition or disease that, in the clinical judgment of the Investigator, could place the subject at undue risk, interfere with study participation, or confound the results of the study.
4. History of cancer or malignant tumor not in remission for at least 2 years. Basal cell skin cancers are not exclusionary.

8.2.2.2 New Subjects

New subjects will be excluded from the present study if they meet any of the exclusion criteria in this section.

1. Any history of bipolar disorder (I or II), schizophrenia, schizoaffective disorder, psychosis, anorexia or bulimia, autism-spectrum disorder, or obsessive-compulsive disorder.
Any other current Axis I disorder, other than SAD, which is the primary focus of treatment. Note that subjects with concurrent Generalized Anxiety Disorder are eligible for the study provided that Generalized Anxiety Disorder is not the primary diagnosis.
2. Subjects who meet criteria for moderate or severe alcohol or substance use disorder within the 1 year prior to study entry.
3. In the opinion of the Investigator, the subject has a significant risk for suicidal behavior during the course of their participation in the study, or
a. At Screening (Visit 1): the subject scores “yes” on items 4 or 5 in the Suicidal Ideation section of the C-SSRS with reference to a 6-month period prior to screening; or

b. At Screening (Visit 1): the subject has had 1 or more suicidal attempts with reference to a 2-year period prior to screening; or
c. At Baseline (Visit 2): the subject scores "yes" on items 4 or 5 in the Suicidal Ideation section of the C-SSRS with reference to screening; or
d. The subject is considered to be an imminent danger to themself or others.

4. Clinically significant nasal pathology or history of significant nasal trauma, nasal surgery, total anosmia, or nasal septum perforation that may have damaged the nasal chemosensory epithelium.
5. An acute or chronic condition, including an infectious illness, uncontrolled seasonal allergies at the time of the study, or significant nasal congestion that potentially could affect drug delivery to the nasal chemosensory epithelium.
6. Subjects using the following psychotropic medications: anticonvulsants, mood stabilizers, antipsychotic medications, gabapentin, pregabalin, opioids, naltrexone, esketamine, and ketamine at enrollment.

Subjects using lower doses of atypical antipsychotics at Screening may be eligible after discussion with the Medical Monitor (e.g., quetiapine < 100 mg).

In general, subjects using antidepressants or buspirone can continue to receive these provided that they have been taking them for a minimum of 2 months, and have been on a stable dose for a minimum of 1 month.

7. Use of anxiolytics, such as benzodiazepines or unapproved treatments such as beta blockers, within 30 days before study entry; concomitant use is prohibited during the study. Subjects who have been taking benzodiazepines daily for 1 month or longer at the time of Visit 1 are not eligible to participate.
8. Use of any over-the-counter product, prescription product, or herbal preparation for treatment of the symptoms of anxiety or social anxiety within 30 days before study entry; concomitant use is prohibited during the study.
9. Subjects with clinically significant abnormalities in hematology, blood chemistry, urinalysis, 12-lead ECG, or physical examination identified at the Screening visit or Baseline visit that in the clinical judgment of the Investigator, could place the subject at undue risk, interfere with study participation, or confound the results of the study.

8.2.2.3 P1/P2 Completers

P1/P2 completers will be excluded from the present study if they meet any of the exclusion criteria in this section.

1. Any history of bipolar disorder (I or II), schizophrenia, schizoaffective disorder, psychosis, anorexia or bulimia, autism-spectrum disorder, or obsessive-compulsive disorder as determined at the time of entry into the legacy study.

Any other current Axis I disorder, other than SAD, which is the primary focus of treatment. Note that subjects with concurrent Generalized Anxiety Disorder are eligible for the study provided that Generalized Anxiety Disorder is not the primary diagnosis.

2. Subjects who meet criteria for moderate or severe alcohol or substance use disorder within the 1 year prior to entry into the legacy study.

3. In the opinion of the Investigator, the subject has a significant risk for suicidal behavior during the course of their participation in the study, or

a. At Baseline (Visit 2): the subject scores "yes" on items 4 or 5 in the Suicidal Ideation section of the C-SSRS with reference to last visit; or

b. The subject is considered to be an imminent danger to themself or others.

4. Clinically significant nasal pathology or history of significant nasal trauma, nasal surgery, total anosmia, or nasal septum perforation that may have damaged the nasal chemosensory epithelium.

5. An acute or chronic condition, including an infectious illness, uncontrolled seasonal allergies at the time of the study, or significant nasal congestion that potentially could affect drug delivery to the nasal chemosensory epithelium.

6. Subjects using the following psychotropic medications: anticonvulsants, mood stabilizers, antipsychotic medications, gabapentin, pregabalin, opioids, naltrexone, esketamine, and ketamine at enrollment.

Subjects using lower doses of atypical antipsychotics at Screening may be eligible after discussion with the Medical Monitor (e.g., quetiapine < 100 mg).

In general, subjects using antidepressants or buspirone can continue to receive these provided that they have been taking them for a minimum of 2 months, and have been on a stable dose for a minimum of 1 month.

7. Use of anxiolytics, such as benzodiazepines or unapproved treatments such as beta blockers, within 30 days before study entry; concomitant use is prohibited during the study. Subjects who have been taking benzodiazepines daily for 1 month or longer at the time of study entry are not eligible to participate.

8. Use of any over-the-counter product, prescription product, or herbal preparation for treatment of the symptoms of anxiety or social anxiety within 30 days before study entry; concomitant use is prohibited during the study.

9. Subjects with clinically significant abnormalities in hematology, blood chemistry, urinalysis, 12-lead ECG, or physical examination identified at study entry or during the legacy study which, in the clinical judgment of the Investigator, could place the subject at undue

risk, interfere with study participation, or confound the results of the study.

Now reads: Exclusion Criteria:

To be considered eligible for entry into the study, a subject must not meet any of the following exclusion criteria at study entry.

1. Any history of bipolar disorder (I or II), schizophrenia, schizoaffective disorder, psychosis, anorexia or bulimia, **premenstrual dysphoric disorder,** autism-spectrum disorder, obsessive-compulsive disorder**, or treatment-refractory major depressive disorder**.

Any other current Axis I disorder, other than SAD, which is the primary focus of treatment. Note that subjects with concurrent Generalized Anxiety Disorder are eligible for the study provided that Generalized Anxiety Disorder is not the primary diagnosis.

2. In the opinion of the Investigator, the subject has a significant risk for suicidal behavior during the course of their participation in the study, or

a. At Screening (**for subjects who attend** Visit 1): the subject scores "yes" on items 4 or 5 in the Suicidal Ideation section of the Columbia-Suicide Severity Rating Scale (C-SSRS) with reference to a 6-month period prior to screening; or

b. At Screening (**for subjects who attend** Visit 1): the subject has had 1 or more suicidal attempts with reference to a 2-year period prior to screening; or

c. At Baseline (Visit 2): the subject scores "yes" on items 4 or 5 in the Suicidal Ideation section of the C-SSRS with reference to last visit; or

d. The subject is considered to be an imminent danger to themself or others.

3. Subjects using the following psychotropic medications **at enrollment or within 30 days before study entry: antidepressants (including monoamine oxidase inhibitors), anxiolytics, stimulants,** anticonvulsants, mood stabilizers, antipsychotic medications, gabapentin, pregabalin, opioids, naltrexone, esketamine, and ketamine. **Eszopiclone, ramelteon, melatonin, zaleplon, zolpidem, or anti-histamines prescribed for insomnia are allowed.**

4. Use of benzodiazepines or unapproved treatments such as beta blockers, within 30 days before study entry and during the study. **Use of beta blockers for treatment of hypertension or cardiac conditions is allowed.** Subjects who have been taking benzodiazepines daily for 1 month or longer at the time of Visit 1 are not eligible to participate.

5. Use of any over-the-counter product or herbal preparation for treatment of the symptoms of anxiety or social anxiety within 30 days before study entry; concomitant use is prohibited during the study.

6. Clinically significant nasal pathology or history of significant nasal trauma, nasal surgery, total anosmia, or nasal septum perforation that may have damaged the nasal chemosensory epithelium.
7. Subjects who meet criteria for moderate or severe alcohol or substance use disorder within the 1 year prior to entry into the study.
8. Subjects with a positive urine drug screen at study entry [redacted]
9. An acute or chronic condition, including an infectious illness, uncontrolled seasonal allergies at the time of the study, or significant nasal congestion that potentially could affect drug delivery to the nasal chemosensory epithelium.
10. Any current clinically significant and/or uncontrolled medical condition, based on medical history or as evidenced in screening assessments, such as COVID-19, HIV, cancer, stroke, congestive heart failure, uncontrolled diabetes mellitus, or any other medical condition or disease that, in the clinical judgment of the Investigator, could place the subject at undue risk, interfere with study participation, or confound the results of the study.
11. Women who have a positive urine pregnancy test prior to IP administration. **Women who are currently breastfeeding are not eligible.**
12. History of cancer or malignant tumor not in remission for at least 2 years. Basal cell skin cancers are not exclusionary.
13. Subjects with clinically significant abnormalities in hematology, blood chemistry, urinalysis, 12-lead ECG, or physical examination identified at **study entry or during the legacy study which,** in the clinical judgment of the Investigator, could place the subject at undue risk, interfere with study participation, or confound the results of the study.

Section 8.4 Subject Replacement Criteria

Text formerly read: Withdrawn subjects will not be replaced. If a substantial number of subjects are withdrawn from the study, the sponsor will evaluate the need for developing replacement criteria.

Now reads: Withdrawn subjects will not be replaced. If a substantial number of subjects are withdrawn from the study, the sponsor will evaluate the need for developing replacement criteria. **Rescreening will be permitted on a case-by-case basis after discussion with the medical monitor.**

Section 9.1. Identification of Investigational Product

Text formerly read: The IP is defined as the spray delivery device containing PH94B (PH94B Nasal Spray).
[redacted]

PH94B will be supplied [redacted]. Each spray from the metered dose spray nozzle delivers 1.6 µg per 100 µL spray. There is sufficient volume in each vial to deliver at least 60 sprays of PH94B. The spray delivery device consists of an [redacted] which contains 8 mL of PH94B.
Use of the i.n. route is essential given the site of action of PH94B on nasal sensory chemoreceptors (see Section 5.1).
PH94B and placebo will be supplied by [redacted]
When needed, a new device should be primed and allowed to come to room temperature for 30 minutes before use. The IP spray delivery device should be primed 5 times per vial before use.

Now reads: The IP (PH94B Nasal Spray) **is** [redacted]
PH94B will be supplied in **monthly kits consisting of a** [redacted] Each metered dose spray delivers 1.6 µg per 100 µL spray. There is [redacted]
Use of the i.n. route is essential given the site of action of PH94B on nasal sensory chemoreceptors (see Section 5.1).
PH94B will be supplied by [redacted]
New vials should be allowed to come to room temperature for 30 minutes **and primed** before use **according to the instructions provided**.

Section 9.2. Selection of Timing of Dose for Each Subject

Text formerly read: Treatment with PH94B should be self-administered approximately 15 minutes prior to an anxiety-provoking situation or event.
Consecutive nasal administrations of IP should be at least 1 hour apart, with no more than 4 administrations per day.
Site personnel will instruct the subject to self-administer the IP by 1 spray into each nostril (right and left nasal passages), for 2 total sprays per dosing event.
Subjects must record all PH94B administrations in the provided eDiary (see Section 9.4.1).

Now reads: Treatment with PH94B should be self-administered approximately 15 minutes prior to **or during** an anxiety-provoking **social** situation or event. Consecutive nasal administrations of IP should be at least 1 hour apart, with no more than 4 administrations per day.

Site personnel will instruct the subject to self-administer the IP by 1 spray into each nostril (right and left nasal passages), for 2 total sprays per dosing event.
Subjects **are instructed to** record all PH94B administrations in the provided eDiary**, even if they have not used PH94B that day** (see Section 9.4.1).

Section 9.4. Treatment Compliance

Text formerly read: Subjects will self-administer the IP up to 4 times per day between visits. The study personnel will be responsible for recording the self-administration of the IP in the eCRF based on the subject's documented use of the IP in the eDiary application. If a discrepancy is observed between the measured weight of IP used and the expected weight based on reported use by a subject, the study staff should question the subject during their in-clinic visit on whether there was a malfunction of the pump, improper administration of IP, or inaccurate eDiary entries. Depending on the reason for the discrepancy, subjects may be retrained on the proper use and administration of the IP to maintain compliance.

Now reads: Subjects will self-administer the IP up to 4 times per day between visits. The study personnel will be responsible for **reviewing** the self-administration of the IP in the eDiary.

Section 9.4.1. eDiary for Dosing Record (now reads "eDiary")

Text formerly read: Subjects participating in the study will be required to record their use of PH94B in an eDiary application. The eDiary will be made available to subjects as an "application" to be downloaded and used on their smartphone or a similar device.
Subjects will be instructed to complete the eDiary at the end of each day, providing information on the number of doses they self-administered that day and the approximate time of each dose. The eDiary will also be used to prompt the subject to start a new vial of PH94B.

Now reads: Subjects participating in the study will be **instructed** to record their use of PH94B in an eDiary application. The eDiary will be made available to subjects as an "application" to be downloaded and used on their smartphone or a similar device.
Subjects will be instructed to complete the eDiary at the end of each day **even if zero doses are taken that day. They will be instructed to provide** information on the number of doses they self-administered that day and the approximate time of each dose.
After the subject has completed the dosing section, the eDiary will prompt the subject to **answer if they have experienced any health problems that day. If they answer yes, the subject is asked to write a brief summary text in the eDiary. The Investigator or a delegate will review these summary texts at each visit and determine**

whether they are to be recorded in the EDC system as AEs, with their severity, duration, and relationship to the study drug.

Section 9.5. Method of Assigning Subjects to Treatment Groups

Text formerly read: Subject numbers will be allocated by the study site. Subject numbers will be sequentially assigned 4-digit numbers, will include the site number and will not be sex-specific. Instructions on subject number assignments will be included in the Study Procedures Manual.

Now reads: Subject numbers will be allocated by the **IRT**. **Subjects** will be sequentially assigned **6**-digit numbers **as shown below**. **The subject number** will include the site number. Instructions on subject number assignments will be included in the **IRT manual**.

Source[a]	**Site Number**	**Subject ID**	**Example**
New Subjects[b]	**001**	**Starting with 001**	**001-001** **001-002**
PALISADE-1 Study (Completers)	**001**	**Starting with 101**	**001-101** **001-102**
PALISADE-2 Study (Completers)	**001**	**Starting with 501**	**001-501** **001-502**

a Participants from other antecedent studies will follow a similar systematic numbering convention.

b Subjects who have not participated in a prior PH94B SAD study may be permitted to enroll following approval by the sponsor on a case-by-case basis.

Section 9.7.1. Permitted Therapies

Deleted: Subjects who are receiving stimulant medications may enroll in the study provided that there is documentation of their prolonged daily use and that the dose has been stable. The Investigator should discuss these cases with the Medical Monitor before enrolling the subject in the study.

Text formerly read: In general, subjects using antidepressants (e.g., serotonin selective re-uptake inhibitors, serotonin/nor-epinephrine reuptake inhibitors, bupropion, mirtazapine) or buspirone can continue to receive these, provided that they have been taking them for a minimum of 2 months, and have been on a stable dose for a minimum of 1 month at the time of enrollment. The antidepressant must have been approved for treatment of SAD or major depressive disorder by the FDA. Use of low doses of atypical antipsychotics (e.g., quetiapine < 100 mg) should be discussed with the Medical Monitor. In general, starting an antidepressant during the study is allowed but the investigator should inform the Medical Monitor of this decision.

Now reads: In general, **starting treatment with antidepressants and buspirone during the study is allowed but the investigator should inform the Medical Monitor of this decision; for antidepressants, initiating treatment is permitted provided that the antidepressant has been approved for the treatment of SAD or major depressive disorder by the FDA. However, while subjects may begin treatment with**

antidepressants, use of MAO inhibitors or ketamine is not permitted.

Section 9.7.2. Prohibited Therapies

Text formerly read: For subjects who use a prohibited medication (see below) during the study, or who require a change in the dose of their antidepressant treatment, Investigators should discuss the subject with the Medical Monitor. Such treatment might not be a cause for discontinuing the subject from the study immediately; this will be discussed on a case-by-case basis.

Now reads: For subjects who use a prohibited medication (see below) during the study, Investigators should discuss the subject with the Medical Monitor. Such treatment might not be a cause for discontinuing the subject from the study. **In particular, one-time use or very short term use (≤ 3 days) of prohibited medications, e.g., in cases of legitimate medical requirement such as minor surgeries or procedures, will not necessarily lead to exclusion from the study. These subjects should be discussed on a case-by-case basis with the Medical Monitor.**

Text formerly read:

- Prior use of PH94B is not permitted, except for subjects who have participated in a PH94B Phase 3 SAD study

Use of the following psychotropic medications is prohibited: anticonvulsants, mood stabilizers, antipsychotic medications, gabapentin, pregabalin, opioids, naltrexone, esketamine, and ketamine

- Use of anxiolytics such as benzodiazepines and unapproved anxiety treatments such as beta blockers

o Subjects requiring daily treatment with benzodiazepines are excluded from the study. If a subject develops the need to use benzodiazepines for management of anxiety, their participation in the study will be discontinued and the subject will be excluded from the study.

o One-time use or very short-term use (≤ 3 days) will not necessarily lead to exclusion from the study. These subjects should be discussed on a case-by-case basis with the Medical Monitor

Now reads:

- Prior use of PH94B is not permitted, except for subjects who have participated in a PH94B SAD study.
- Use of the following psychotropic medications is prohibited: **anxiolytics,** anticonvulsants, mood stabilizers, antipsychotic medications, **stimulants,** gabapentin, pregabalin, opioids, naltrexone, esketamine, and ketamine.

o Use of **antidepressants is prohibited at enrollment or within 30 days before the study. However, treatment with antidepressants or buspirone can be initiated during the study (see Section 9.7.1). Note: Treatment with MAO inhibitors or ketamine is prohibited at all times.**

• **Use of** benzodiazepines and unapproved anxiety treatments such as beta blockers **is not permitted within 30 days before study entry (Visit 2), or during the study.**
o Subjects requiring daily treatment with benzodiazepines are excluded from the study. If a subject develops the need to use benzodiazepines for management of anxiety, their participation in the study will be discontinued and the subject will be excluded from the study.
o Use of beta blockers for treatment of hypertension or cardiac conditions is allowed.
• **Use of any over-the-counter product or herbal preparation for treatment of the symptoms of anxiety or social anxiety is not permitted within 30 days before study entry, or during the study.**

Section 9.9.1. Dispensing

Text formerly read: At each visit from Visit 2 (Baseline) through the final monthly visit (Visit 13), subjects will be dispensed the appropriate number of vials of IP from the respective clinical site: a [redacted] The vial numbers of the dispensed vials will be recorded in the eCRF for each subject. Each study site will be provided with an appropriate supply of IP, and each vial will be individually numbered with a unique identification code.
Prior to the subject receiving the IP at each in-clinic visit, the Investigator or study staff will use an identified vial to instruct the subject how to prime the spray vial (push actuator 5 times), how to adequately position the spray nozzle in each nasal passage, and to ensure the IP is used at room temperature. At least 1 vial of the IP will be primed at each clinic visit following Visit 2 (Baseline) as needed. The IP will be weighed prior to priming, and again when returned to study staff. [redacted]
Subjects should use a fresh vial at the start of each week. Subjects will be instructed to [redacted] The clinic will provide vials with unique serialized vial identification codes. Each vial will be dispensed to the subject in order from the lowest to highest serial number.

Now reads: At each visit from Visit 2 (Baseline) through the final monthly visit (Visit 13), subjects will be dispensed **a monthly kit containing a sufficient number of PH94B Nasal Spray** vials from the respective clinical site. Each study site will be provided with an appropriate supply of IP, and each vial will be individually numbered with a unique identification code.
Prior to the subject receiving the IP at each in-clinic visit, the Investigator or study staff will use **a vial from their assigned kit** to instruct the subject **on** how to ensure the IP is [redacted] At least 1 vial of the IP will be primed at each clinic visit following Visit 2 (Baseline) as needed. The IP will be

weighed prior to priming, and again when returned to study staff. [redacted] The clinic will **dispense a kit of** vials with unique serialized vial identification codes **at each visit**.

Section 9.9.2. Storage

Text formerly read: All IP supplied to each site by the sponsor will be maintained in a safe and secure (locked) area, [redacted]. Access should be restricted to the designated responsible member(s) of the Investigator's staff and to the clinical monitor. The Investigator agrees that neither he/she nor any of the study staff will supply IP to any person other than subjects enrolled in the study.
Secure access to the storage area is the responsibility of the Investigator and designated staff.
New (unused) IP spray delivery devices should be stored in the refrigerator. The IP spray delivery device should be primed 5 times per vial before use. This device, "in use", has a shelf life of 1 month at room temperature. New devices stored in the refrigerator have a shelf life of 6 months from the date of manufacture.

Now reads: All IP supplied to each site by the sponsor will be maintained in a safe and secure (locked) area, stored upright in a refrigerator between **2°C (36°F)** and 8°C (46°F), until dispensed, and away from direct sunlight and ultraviolet light. Access should be restricted to the designated responsible member(s) of the Investigator's staff and to the clinical monitor. The Investigator agrees that neither he/she nor any of the study staff will supply IP to any person other than subjects enrolled in the study.
Secure access to the storage area is the responsibility of the Investigator and designated staff.
New (unused) IP should be stored in the refrigerator. The spray **actuator of the IP** should be primed before use **according to the instructions provided**.

Section 9.10. Drug Accountability

Text formerly read: Upon receipt of each IP shipment, an inventory must be performed, and a drug receipt log filled out and signed by the person accepting the shipment. The IP will be provided with each vial assembled individually to its pump device. It is important that the designated study staff count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable IP in each shipment (active drug) will be documented in the study files.

Now reads: Upon receipt of each IP shipment, an inventory must be performed, and a drug receipt log filled out and signed by the person accepting the shipment. [redacted] It is important that the designated study staff count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable IP in each shipment (active drug) will be documented in the study files.

Section 9.11.1. Labeling

Text formerly read: The vials will have a label affixed that meets the applicable regulatory requirements and may include the following: IP name, dosage strength, lot number, protocol number, specified volume of contents, caution statement ("New Drug – Limited by United States Law to Investigational Use" and "Keep out of reach of children"), storage information, date of expiration, vial identification code, user instructions and the sponsor's name.

Now reads: The vials will have a label affixed that meets the applicable regulatory requirements and may include the following: IP name, dosage strength, lot number, protocol number, specified volume of contents, caution statement ("New Drug – Limited by United States Law to Investigational Use" and "Keep out of reach of children"), storage information, vial identification code, and the sponsor's name.

Section 9.11.2. Packaging

Text formerly read: PH94B will be supplied in [redacted]

PH94B Nasal Spray dosage units are not childproof and should be stored out of reach of children.

Section 10. Study Procedures

Text formerly read: Subjects must provide written informed consent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

Now reads: Subjects must provide written informed consent **for the present study** before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

Section 10. Study Procedures

Text formerly read: Subjects who have participated in a previous PH94B Phase 3 SAD study will be given the option to enroll in this study, as follows:

- Subjects who enter the present study within 14 days after completing Visit 1, 2, 3, or 4 of either PALISADE-1 (PH94B-CL026) or PALISADE-2 (PH94B CL032) without meeting any of the

exclusion criteria of PALISADE-1/PALISADE-2, with the exception of SUDS < 75 at Visit 2, will be considered as "P1/P2 Completers", and will enter the present study at Visit 2 (see Table 2-2). For these subjects, Investigators can use the data from Visit 1 of the legacy study for demographics, the MINI and SAD Diagnostic Criteria checklist, and medical and psychiatric history, but if there have been changes these details should be updated.

Now reads: Subjects who have participated in a previous PH94B SAD study will be **enrolled** in this study **and attend Visit 1 or Visit 2 depending on the interval since they finished participation in their antecedent study,** as follows:

***>14 Days Since Antecedent Study*: Subjects who finished participation in their antecedent PH94B SAD study more than 14 days before entering the present study will attend Visit 1 of the long-term safety study and complete all necessary screening assessments as shown in the schedule of events (Table 2-1).**

For the purposes of enrollment, these subjects are referred to as "New Subjects".

***≤14 Days Since Antecedent Study*: Subjects who enter the present study within 14 days after finishing participation in their antecedent PH94B SAD study without meeting any of the exclusion criteria of this long-term safety study will enter the present study at Visit 2 (see Table 2-1).**

For the purposes of enrollment, these subjects are referred to as "Completers".

- **While these subjects enter the long-term safety study at Visit 2, Investigators must transcribe the following screening data (Visit 1) from the antecedent study to the present long-term safety study: demographics, the MINI, medical and psychiatric history, and the SAD Diagnostic Criteria checklist. If there have been any changes, these details should be updated. This data from the antecedent study must be re-entered into the Visit 1 eCRF for the present study. All other assessments scheduled for Visit 2 must be performed as indicated in the schedule of events (see Table 2-1).**
- **If the subject enters the present study on the same day as the last visit of their antecedent study, results from the assessments on that day may be used to enter data into the eCRFs for the antecedent study and for Visit 2 of the present study without repeating them.**
  - **For example, [redacted] completed for the last visit of the antecedent study may be transcribed for this long-term safety study provided that the last visit occurred on the same day as Visit 2 for the present study. Details on preparing a certified**

copy of the results will be provided in the eCRF completion guidelines.

- **For clinical laboratory assessments, 2 sets of blood and urine samples should be obtained and sent to the lab for analysis: one for the antecedent study and one for the long-term study. Note that these can be collected at the same time to avoid unnecessary needlesticks.**

Subjects who have not participated in a prior PH94B SAD study may be permitted to enroll following approval by the sponsor on a case-by-case basis. For the purposes of enrollment, these subjects are referred to as "New Subjects".

Section 10.1 Study Duration

Text formerly read: The study comprises a 7- to 30-day screening period and a treatment period of up to 12 months, and a follow-up visit at 54 weeks.

Now reads: The study comprises a 7- to **35**-day screening period and a treatment period of up to 12 months, and a follow-up visit at **2 weeks after the last visit**.

Section 10.2 Study Periods and Visits

Text formerly read: A comprehensive schedule of study assessments is presented in Table 2-1 and described in the following sections. Every effort should be made to complete all required procedures and evaluations at the designated visits. A physician must see the subject at every visit. A window of ±3 days is permitted for Visit 3 and the follow-up visit (Visit 15), with a window of ±7 days permitted for Visits 4 through 13, and ±2 weeks for Visit 14.

Now reads: A comprehensive schedule of study assessments is presented in Table 2-1 and described in the following sections. Every effort should be made to complete all required procedures and evaluations at the designated visits. A window of ±3 days is permitted for Visit 3 and the follow-up visit (Visit 15), with a window of ±7 days permitted for Visits 4 through 13, and ±2 weeks for Visit 14.

Section 10.2.1.1 Screening (Visit 1)

Text formerly read:
- o Subjects who enter this study as "New" subjects (i.e., subjects who have not participated in a previous PH94B Phase 3 study) will be required to undergo all the screening procedures to ensure they meet eligibility
- o Similarly, subjects who have participated in a PH94B Phase 3 SAD study more than 14 days before entry into the present study must undergo all the screening procedures at Visit 1 to ensure they meet eligibility (see Table 2-2)

Now reads: o Subjects who enter this study more than 14 days **after finishing participation in their antecedent** study must undergo all the screening procedures at Visit 1 to ensure they meet eligibility

Text formerly read: To meet these objectives, the duration of screening must be tailored to the individual subject and may last from a minimum of 7 to a maximum of 30 days. Subjects continuing to meet all eligibility requirements at Visit 2 (Baseline) will undergo treatment with IP (PH94B) up to Visit 14.

Now reads: To meet these objectives, the duration of screening must be tailored to the individual subject and may last from a minimum of 7 to a maximum of **35** days. Subjects continuing to meet all eligibility requirements at Visit 2 (Baseline) will undergo treatment with IP

Text formerly read: Generally, healthy subjects who are thought to meet inclusion and exclusion criteria and express an interest in participating will be informed about the study, the IP, required visits and scheduling, and asked whether they wish to participate.

Now reads: Generally, **subjects who have participated in an antecedent PH94B SAD study** will be informed about the study, the IP, required visits and scheduling, and asked whether they wish to participate.

Text formerly read: The following procedures will be performed in the order below at Screening, which is to occur at least 7 days, but no more than 30 days prior to Visit 2:

- Obtain informed consent
- Review all inclusion and exclusion criteria
- Collect demographic information
- Assign subject number determined by study site
- Obtain medical history (including nicotine, alcohol use, and menstrual information on women of childbearing potential) and psychiatric history
- Record prior and concomitant treatment and medication use (medication name, dose, and frequency)
- Complete SAD diagnostic criteria checklist
- Obtain blood and urine samples for evaluation by the central clinical laboratory, including hematology, chemistry, thyroid functioning, and urinalysis (refer to Section 10.3.1.1.1 for complete list)
- Obtain urine sample for urine drug screen: Instant Exam to be performed on site, with results thoroughly documented in the source; urine sample to be sent to central laboratory for confirmation if on-site urine drug screen is positive. If the central laboratory urine drug screen result is positive, the subject in the study may have to be excluded from the study; the Medical Monitor should be consulted on these cases
- For females of childbearing potential, obtain urine sample and complete on-site urine pregnancy test
- Obtain 12-lead ECG

• Perform physical examination, including height (inches) and body weight (pounds). The physical examination includes a review of the nasal passages. If total anosmia is suspected, Quick Olfactory Test (QOT) is to be administered.
• Measure vital signs after the subject has rested for 5 minutes: seated systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (°F)
• Administer MINI 7.0.2
• Administer LSAS
• Administer HAM-D17
• [redacted]
• Administer C-SSRS (Long Term)
• Complete CGI-S

Now reads: The following **numbered** procedures **should** be performed in **a block fashion as per the order indicated. Assessments within a block, except for the first block, may be conducted in any order as per clinical judgement** at Screening, which is to occur at least 7 days, but no more than **35** days prior to Visit 2:

1. ICF will be reviewed and completed before any other assessments. Collect demographic information; and assign subject number.

2. Urine sample for drug screen and pregnancy test (if appropriate) will be collected early in the screening visit to determine eligibility and to guide diagnostic interviews, especially with regards to substance use assessment. The urine sampling is to include:

a. Obtain urine sample for urine drug screen **(UDS):** Instant Exam to be performed on site, with results thoroughly documented in the source; urine sample to be sent to central laboratory for confirmation if on-site **UDS** is positive[redacted]**.**

b. For females of **child-bearing** potential, obtain urine sample and complete on-site urine pregnancy test.

3. Medical and psychiatric history and diagnosis (usually starting with MINI) to include:

a. Administer MINI (7.0.2).

b. Obtain medical history (including nicotine, alcohol use, and menstrual information on women of childbearing potential) and psychiatric history.

c. Record prior and concomitant treatment and medication use (medication name, dose, and frequency).

d. Complete SAD diagnostic criteria checklist.

4. Standardized assessments (usually starting with LSAS but per investigator judgement based on the MINI) to include:

a. Administer LSAS.

b. Administer HAM-D17.

c. [redacted]
d. Administer C-SSRS (Baseline).
e. Complete CGI-S with a recall period of 1 week (by the trained clinician).
5. Physical assessments (recommend blood draw last to avoid any potential impact on vitals and ECG assessment) to include:
a. Perform physical examination, including height (inches) and body weight (pounds). The physical examination includes a review of the nasal passages. If total anosmia is suspected, Quick Olfactory Test (QOT) is to be administered.
b. Measure vital signs after the subject has rested for 5 minutes: seated systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (°F).
c. Obtain 12-lead ECG in supine position after the subject has rested for 5 minutes.
d. Obtain blood and urine samples for evaluation by the central clinical laboratory, including hematology, chemistry, thyroid functioning, and urinalysis (refer to Section 10.3.1.1.1 for complete list).
6. After these assessments are complete, review all inclusion and exclusion criteria.

Section 10.2.2.1. Visit 2 (Baseline)

Text formerly read: Subjects entering the study as "P1/P2 Completers" (as defined in Section 10) will enter this study at Visit 2 (see Table 2-2). These subjects will sign an ICF for the present study at this visit and complete all Visit 2 assessments as noted in the schedule of events (Table 2-1) and detailed in this section.

Now reads: Subjects entering the study **within 14 days of their antecedent PH94B SAD study** will enter this study at Visit 2. These subjects will sign an ICF for the present study at this visit and complete all Visit 2 assessments as noted in the schedule of events (Table 2-1) and detailed in this section.

NOTE: In the text describing the assessments to be conducted at this visit, the order of assessments was modified to match the Schedule of Events – this rearrangement is not captured in this section to allow specific changes in text to be identified.

Text formerly read:
- Obtain urine sample for urine drug screen: Instant Exam to be performed on site, with results thoroughly documented in the source; urine samples will be sent to the central laboratory for confirmation as needed if on-site urine drug screen is positive. If the central laboratory urine drug screen result is positive, the subject may have to be excluded from the study; the Medical Monitor should be consulted on these cases
- For females of childbearing potential, obtain urine sample and complete on-site urine pregnancy test

- Obtain 12-lead ECG
- Perform physical examination, including body weight (pounds). The physical examination includes a review of the nasal passages
- Measure vital signs after the subject has rested for 5 minutes: seated systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (°F)

For subjects meeting all study inclusion criteria and no study exclusion criteria, the following Visit 2 procedures will be performed:

- Administer the LSAS

Note: Although "P1/P2 Completers" will undergo LSAS assessment at this visit, a score of ≥ 50 is not required for these subjects.

- Administer the HAM-D17 (by the trained clinician)
- [redacted]
- Administer the C-SSRS (Since Last Visit)
- Complete the CGI-S with a recall period of 1 week (by the trained clinician)
- Train subjects on the use, dosing, and storage of IP. The subject will be given instructions on:
  - how to position the nozzle in the nasal passages and self-administer IP
  - [redacted]
  - how to store the nasal spray

Now reads:

- Obtain urine sample for urine drug screen: Instant Exam to be performed on site, with results thoroughly documented in the source; urine samples will be sent to the central laboratory for confirmation as needed if on-site urine drug screen is positive. If the central laboratory urine drug screen result is positive [redacted], the subject may have to be excluded from the study; the Medical Monitor should be consulted on these cases
- For females of childbearing potential, obtain urine sample and complete on-site urine pregnancy test
- **Record concomitant medication use**
- Perform physical examination, including body weight (pounds). The physical examination includes a review of the nasal passages
- Measure vital signs after the subject has rested for 5 minutes: seated systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (°F)
- Obtain 12-lead ECG **in supine position after the subject has rested for 5 minutes**
- Obtain blood and urine samples for evaluation by the central clinical laboratory, including hematology, chemistry, thyroid functioning, and urinalysis
- Review all inclusion and exclusion criteria

For subjects meeting all study inclusion criteria and no study exclusion criteria, the following Visit 2 procedures will be performed:

- Administer the LSAS
- Administer the HAM-D17
- [redacted]
- Administer the C-SSRS (Since Last Visit)
- Complete the CGI-S with a recall period of 1 week (by the trained clinician)
- Train subjects on the use, dosing, and storage of IP. The subject will be given instructions on:

o how to position the **actuator** nozzle in the nasal passages and self-administer IP
o the number of sprays per nostril per dose (1 per nostril)
o how to store the nasal spray
o Treatment with PH94B should be self-administered approximately 15 minutes prior to or during an anxiety-provoking social situation or event. Consecutive nasal administrations of IP should be at least 1 hour apart, with no more than 4 administrations per day. Treatment does not need to be administered every day.

- Train subjects on how to record study drug use on the eDiary application (see Study Procedures Manual for training on the eDiary application)
- Record any AEs

All prior, ongoing, or resolved AEs reported by subjects **at the time of study entry** will be considered as medical history during this study. Adverse events that become aggravated, accelerated, or exacerbated will be reported and considered as new AEs. Adverse events that recur will be considered as new AEs during this study.

- Dispense IP to subjects (1-month supply)

Section 10.2.2.2. Visit 3 (First Month in Clinic, ±3 Days)

NOTE: In the text describing the assessments to be conducted at these visits, the order of assessments was modified to match the Schedule of Events – this rearrangement is not captured in this section to allow specific changes in text to be identified.

Text formerly read:

- Record concomitant medication use
- Obtain blood and urine samples for evaluation by the central clinical laboratory, including hematology, chemistry, thyroid functioning, and urinalysis (refer to Section 10.3.1.1.1 for complete list)
- Conduct urine drug screen (Instant Exam, to be performed on site, with results documented in the source. If urine drug screen result is positive, then urine sample will be sent to central laboratory for confirmation as needed). If the urine drug screen is confirmed as positive, a repeat unscheduled urine drug screen may be obtained to investigate whether drug use is continuing. The Medical Monitor should be consulted regarding these cases.

- For females of childbearing potential, obtain urine sample and complete on-site urine pregnancy test
- Obtain 12-lead ECG
- Perform physical examination, including body weight (pounds). The physical examination includes a review of the nasal passages
- Measure vital signs after the subject has rested for 5 minutes: seated systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (°F)
- Administer the LSAS (by the trained clinician)
- Administer the HAM-D17 (by the trained clinician)
- [redacted]
- Administer the C-SSRS (Since Last Visit)
- Complete the CGI-S with a recall period of 1 week (by the trained clinician)
- Complete the CGI-I with a recall period of 1 week (by the trained clinician)
- Complete the PGI-C with a recall period of 1 week (by the subject)
- Review and record AEs
- Dispense study medication and provide the subject with the storage instructions of the IP (1-month supply of IP [6 vials])
- Review and record use of IP in eDiary (by study staff)

Now reads:

- Conduct urine drug screen (Instant Exam, to be performed on site, with results documented in the source. If urine drug screen result is positive [redacted] then urine sample will be sent to central laboratory for confirmation as needed). If the urine drug screen is confirmed as positive, a repeat unscheduled urine drug screen may be obtained to investigate whether drug use is continuing. The Medical Monitor should be consulted regarding these cases.
- For females of childbearing potential, obtain urine sample and complete on-site urine pregnancy test
- Record concomitant medication use
- Administer the LSAS
- Administer the HAM-D17
- [redacted]
- Administer the C-SSRS (Since Last Visit)
- Perform **focused** physical examination, including body weight (pounds). The physical examination includes a review of the nasal passages **and oropharynx but other organ systems should be examined only if the subject has symptoms or the investigator is concerned**
- Measure vital signs after the subject has rested for 5 minutes: seated systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (°F)
- Obtain 12-lead ECG **in supine position after the subject has rested for 5 minutes**

- Obtain blood and urine samples for evaluation by the central clinical laboratory, including hematology, chemistry, thyroid functioning, and urinalysis (refer to Section 10.3.1.1.1 for complete list)
- Complete the CGI-S with a recall period of 1 week (by the trained clinician)
- Complete the CGI-I **as compared to baseline visit (Visit 2)**, with a recall period of 1 week (by the trained clinician)
- Complete the PGI-C **as compared to baseline visit (Visit 2)**, with a recall period of 1 week (by the subject)
- Dispense study medication and provide the subject with the storage instructions of the IP (1-month supply of IP)
- Review and record AEs
- Review **the** use of IP **and any health problems they experienced as reported in the** eDiary (by study staff)

Section 10.2.3. Visit 14 End of Treatment (or Early Termination) Visit

Text formerly read: At Visit 14, or upon early termination of study participation, subjects should return to the study site and the following assessments will be completed:

- Record concomitant medication use
- Obtain blood and urine samples for evaluation by the central clinical laboratory, including hematology, chemistry, thyroid functioning, and urinalysis (refer to Section 10.3.1.1.1 for complete list)
- Conduct urine drug screen (Instant Exam, to be performed on site, with results documented in the source. If urine drug screen result is positive, then then urine sample will be sent to central laboratory for confirmation as needed)
- For females of childbearing potential, obtain urine sample and complete on-site urine pregnancy test
- Obtain 12-lead ECG
- Perform physical examination, including height (inches) and body weight (pounds). Also includes an examination of the nasal passages
- Measure vital signs after the subject has rested for 5 minutes: seated systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (°F)
- Administer the LSAS (Last Visit)
- Administer the HAM-D17
- [redacted]
- Administer the C-SSRS (Since Last Visit)
- Complete the CGI-S with a recall period of 1 week (by the trained clinician)
- Complete the CGI-I with a recall period of 1 week (by the trained clinician)
- Complete the PGI-C with a recall period of 1 week (by the subject)

• Review and record use of IP in eDiary (by the trained clinician)

Now reads: At Visit 14, subjects should return to the study site **for an End of Treatment visit, and undergo** the assessments shown in the schedule of events.

In addition, subjects who discontinue from the study early (for any reason other than loss to follow up) should return to the study site for an Early Termination Visit. Similarly, if the subject is attending a scheduled visit when the decision to discontinue is made, the investigator should perform the assessments indicated for Visit 14/Early Termination Visit in the schedule of events (Table 2-1).

The following assessments will be completed at Visit 14/Early Termination:

• Record concomitant medication use
• Obtain blood and urine samples for evaluation by the central clinical laboratory, including hematology, chemistry, thyroid functioning, and urinalysis (refer to Section 10.3.1.1.1 for complete list)
• Conduct urine drug screen (Instant Exam, to be performed on site, with results documented in the source. If urine drug screen result is positive [redacted] then then urine sample will be sent to central laboratory for confirmation as needed)
• For females of childbearing potential, obtain urine sample and complete on-site urine pregnancy test
• Obtain 12-lead ECG **in supine position after the subject has rested for 5 minutes**
• Perform physical examination, including height (inches) and body weight (pounds). Also includes an examination of the nasal passages
• Measure vital signs after the subject has rested for 5 minutes: seated systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (°F)
• Administer the LSAS
• Administer the HAM-D17
• [redacted]
• Administer the C-SSRS (Since Last Visit)
• Complete the CGI-S with a recall period of 1 week (by the trained clinician)
• Complete the CGI-I **as compared to baseline visit (Visit 2),** with a recall period of 1 week (by the trained clinician)
• Complete the PGI-C **as compared to baseline visit (Visit 2),** with a recall period of 1 week (by the subject)
• **Complete PWC-20**
• Review **the** use of IP **and any health problems they experienced as reported in the** eDiary (by the trained clinician)

Section 10.2.4. Visit 15 (Follow-up, 54 weeks ±3 Days)
New: • **Complete PWC-20**

Section 10.3.1. Safety Variables
Text formerly read: Safety assessments will include the evaluation of AEs, clinical laboratory assessments, vital signs, 12-lead ECGs, physical examinations, and C-SSRS evaluations.
Now reads: Safety assessments will include the evaluation of AEs, clinical laboratory assessments, vital signs, 12-lead ECGs, physical examinations, **HAM-D17,** C-SSRS evaluations**, and the PWC-20**.

Section 10.3.1.1.1. Clinical Laboratory Tests to be Performed
Text formerly read: Urine Drug Screen: If on-site urine drug screen is positive, urine sample must be submitted to central laboratory for confirmatory urine drug screen to be performed:
opiates, cocaine, amphetamines, barbiturates, cannabinoids, methadone, phencyclidine, propoxyphene, methamphetamine, buprenorphine, ecstasy, and oxycodone
Now reads: Urine Drug Screen: If on-site urine drug screen is positive, urine sample **will** be submitted to central laboratory for confirmatory urine drug screen to be performed:
opiates, cocaine, amphetamines, barbiturates**, benzodiazepines,** cannabinoids, methadone, phencyclidine, propoxyphene, methamphetamine, buprenorphine, ecstasy, and oxycodone
[redacted]

Section 10.3.1.2.2 Twelve-lead Electrocardiogram
Text formerly read: A standard 12-lead ECG will be performed after the subject has been seated for at least 5 minutes.
Now reads: A standard 12-lead ECG will be performed **in a supine position** after the subject has **rested** for 5 minutes**.**

Section 10.3.1.2.3 Physical Examination
New: **A focused physical examination will be performed at certain visits as per the schedule of events, but must include examination of the nasal passages and oropharynx; other organ systems should be examined if the subject has symptoms or if the investigator has specific concerns.**

Section 10.3.1.2.5. Penn Physician Withdrawal Checklist
New: **10.3.1.2.5 Penn Physician Withdrawal Checklist**
The PWC-20 is a 20-item simple instrument for assessing anxiolytic discontinuation symptoms. It should be administered by a suitably qualified physician or advanced practice provider.

The PWC-20 consists of 20 questions related to withdrawal from benzodiazepines or other anti-anxiety compounds (see APPENDIX H). The symptoms measured are based on those that are potentially related to anxiolytic withdrawal: gastrointestinal, mood, sleep, motor, somatic, perception, and cognition. The questions will cover any symptoms that might occur during the week following discontinuation of PH94B.

Section 10.3.2.1. Liebowitz Social Anxiety Scale

Text formerly read: The LSAS is a clinician-rated scale that has been shown to be sensitive to treatment-related change in social phobia symptoms.

Now reads: The LSAS is a clinician-rated scale that has been shown to be sensitive to treatment-related change in social **anxiety** symptoms.

Section 10.3.2.2. [redacted]

Section 10.3.2.3. Hamilton Rating Scale for Depression (17 Items)

Text formerly read: The HAM-D17 scale is a 17-item clinician-rated scale to measure the severity of depression, addressing symptoms experienced in the past week, The 17 items are scored on a scale from 0 (not present) to 4 (severe), with the total score ranging from 0 to 68. A score of 0 to 7 is considered to be within the normal range, while a score of 20 or more indicates at least moderate depression.

Now reads: The HAM-D17 scale is a 17-item clinician-rated scale to measure the severity of depression, addressing symptoms experienced in the past week, with the total score ranging from 0 to 68 **(see APPENDIX D)**. A score of 0 to 7 is considered to be within the normal range, while a score of 20 or more indicates at least moderate depression. **The time frame for rating symptomatology is the past week.**

Section 10.3.2.4. Clinical Global Impression Scales

Text formerly read: The Clinical Global Impression Scale (CGI) is a clinician-rated scale assessment of the clinician's view of the subject's global health prior to and after participation in a clinical study. The scale assesses the clinician's knowledge of the subject's history, psychosocial circumstances, symptoms, behavior and the effect of these parameters on the subject's capability to function since the last visit with the subject. The CGI consists of 2 components, severity (CGI-S) and improvement (CGI-I). The severity component consists of 1 question that assesses the disease severity of the patient population and is on a scale of 1 to 7 ranging from normal (1) to extremely ill (7). The improvement component evaluates the change of the subject's condition from the Baseline and is on a scale of 1 to 7 ranging from very much improved (1) to very much worse (7). The time frame for rating is the past week.

Now reads: The Clinical Global Impression Scale (CGI) is a clinician-rated scale assessment of the clinician's view of the subject's global health prior to and after participation in a clinical study. The scale assesses the clinician's knowledge of the subject's history, psychosocial circumstances, symptoms, behavior and the effect of these parameters on the subject's capability to function since the last visit with the subject. The CGI consists of 2 components, severity (CGI-S) and improvement (CGI-I). **A recall period of 1 week is used.**
The severity component **(CGI-S)** consists of 1 question that assesses the disease severity of the patient population and is on a scale of 1 to 7 ranging from normal (1) to extremely ill (7).
The improvement component **(CGI-I)** evaluates the change of the subject's condition from the Baseline and is on a scale of 1 to 7 ranging from very much improved (1) to very much worse (7).
In this study the disease severity refers to the severity of SAD. The scale scoring is anchored with reference to the severity of symptoms and functional impairment caused by SAD.

Section 10.3.2.5. Patient Global Impression of Change

Text formerly read: The Patient Global Impression of Change (PGI-C) is a self-administered instrument that measures change in subjects' overall improvement with treatment on a scale where 1 = "very much improved" and 7 = "very much worse."

Now reads: The Patient Global Impression of Change (PGI-C) is a self-administered instrument that measures change in subjects' overall improvement with treatment on a scale where 1 = "very much improved" and 7 = "very much worse" **(see APPENDIX G). The time frame for rating is compared to the baseline visit (Visit 2).**

Section 11.1.1.	Adverse Events
Text formerly read:	For P1/P2 completers, AEs ongoing at a time of enrollment into the present study will be recorded in the medical history section of the present study.
Now reads:	For **subjects who enter the present study within 14 days of their antecedent PH94B SAD study,** AEs ongoing at the time of enrollment into the present study will be recorded in the medical history section of the present study.
Section 11.2.1.	Assessment
New:	**In addition, the Investigator will review the eDiary summary text for health problems and determine whether they are to be recorded in the EDC system as AEs.**
Section 11.2.2.3.	Actions Taken
Deleted:	Dose increased: An indication that a medication schedule was modified by addition; either by changing the frequency, strength, or amount. Dose reduced: An indication that a medication schedule was modified by subtraction, either by changing the frequency, strength, or amount. Dose interrupted: An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication.
Section 11.3.1.	Pregnancy
Text formerly read:	If the partner of a male subject becomes pregnant during his IP treatment or within 14 days of his discontinuing the IP, the Investigator must report the pregnancy within 48 hours of learning of the pregnancy, to [redacted] Pharmacovigilance, as described above.
Now reads:	**Male subjects with partners of childbearing potential should be advised to use contraception throughout their participation in the study.** If the partner of a male subject becomes pregnant during his IP treatment or within 14 days of his discontinuing the IP, the Investigator must report the pregnancy within 48 hours of learning of the pregnancy, to [redacted] Pharmacovigilance, as described above.
Section 13.1.1.	Analysis Populations
Text formerly read:	Safety: All subjects who are dispensed IP will be included in the safety population.
Now reads:	Safety **population**: All subjects who **receive IP**.

Section 13.1.2.1. Disposition and Withdrawals

Text formerly read: The numbers of subjects randomized, completing, and withdrawing, along with reasons for withdrawal, will be tabulated. Details on the number of subjects participating in previous PH94B Phase 3 SAD studies will also be provided.

Now reads: The numbers of subjects randomized, completing, and withdrawing, along with reasons for withdrawal, will be tabulated. Details on the number of subjects participating in **the individual antecedent PH94B SAD studies** will also be provided.

Section 13.1.2.2. Protocol Deviations

Text formerly read: Documentation of the deviations and corrective actions will be included in the data quality assessment during blinded review.

Now reads: Documentation of the deviations and corrective actions will be included in the data quality assessment during review.

Section 13.1.2.3. Demographics and Other Baseline Characteristics

Text formerly read: For all participating subjects, baseline is defined as Visit 2. For subjects coming from previous PH94B studies (PALISADE-1 [PH94B-CL026] or PALISADE-2 [PH94B CL032]), Visit 2 assessments should be conducted as described in the schedule of events (Table 2-1). Demographics, medical and psychiatric history, MINI findings, SAD Diagnostic Criteria Checklists, and baseline characteristics such as gender, age, race, weight, height and baseline physical examination reports, and vital signs will be carried over.

Now reads: For all participating subjects, baseline is defined as Visit 2. For subjects **who enter the present study within 14 days of their antecedent PH94B SAD study**, Visit 2 assessments should be conducted as described in the schedule of events (Table 2-1). Demographics, medical and psychiatric history, MINI findings, SAD Diagnostic Criteria Checklists, and baseline characteristics such as gender, age, race, weight, height and baseline physical examination reports, and vital signs will be carried over.

Section 13.1.4. Safety and Tolerability Analyses

Text formerly read: Safety analyses will be conducted using data from the safety population (as defined in Section 13.1.1). Safety variables include treatment emergent AEs, clinical laboratory values, vital signs, ECG readings, and physical examination results. No formal inferential analyses will be conducted for safety variables, unless otherwise noted.

Now reads: Safety analyses will be conducted using data from the safety population (as defined in Section 13.1.1). Safety variables include treatment emergent AEs, clinical laboratory values, vital signs, **changes in suicidality (C-SSRS), level of depression (HAM-D17), PWC-20 results,** ECG readings, and physical examination results. No

formal inferential analyses will be conducted for safety variables, unless otherwise noted.

Text formerly read: Descriptive statistics will be used to portray safety and tolerability of PH94B as measured by reports of AEs and SAEs, changes in laboratory values, 12-lead ECGs, and physical examination.

Now reads: Descriptive statistics will be used to portray safety and tolerability of PH94B as measured by reports of AEs and SAEs, changes in laboratory values, 12-lead ECGs, physical examination, **vital signs, and withdrawal symptoms.**

New text:
- **PWC-20 scores after termination of PH94B**

Section 13.1.4.5. Penn Physician Withdrawal Checklist

New: **13.1.4.5 Penn Physician Withdrawal Checklist**
Descriptive summaries (mean, SD, median, minimum, and maximum) will be presented for scores from the PWC-20 checklist, completed at Visits 14 and 15.

Section 13.1.5.1. Exploratory Endpoints

Text formerly read: The change in LSAS, CGI-I, and PGI-C scores from the Baseline Visit 2 to Visit 14 may also be explored using generalized linear model for repeated measures.

Now reads: The change in LSAS, CGI-I, and PGI-C scores from Baseline to Visit 14 may also be explored using generalized linear model for repeated measures.

Text formerly read:
- Change in total LSAS scores over time with daily use of PH94B
- Change in proportion of subjects with CGI-S scores >4 over time with daily use of PH94B
- Change in proportion of subjects with CGI-I scores of 1 (Very much improved) or 2 (Much improved) over time with daily use of PH94B
- Change in proportion of subjects with PGI-C scores of 1 (Very much improved) or 2 (Much improved) over time with daily use of PH94B
- Changes in patterns of PH94B use (daily frequency and dosing interval) over time
- Change in patterns of PH94B use (daily frequency and dosing interval) in designated subgroups over time
- [redacted]

Now reads:
- Change in total LSAS scores over time with use of PH94B
- Change in proportion of subjects with CGI-S scores >4 over time with use of PH94B
- Change in proportion of subjects with CGI-I scores of 1 (Very much improved) or 2 (Much improved) over time with use of PH94B
- Change in proportion of subjects with PGI-C scores of 1 (Very much improved) or 2 (Much improved) over time with use of PH94B

- Changes in patterns of PH94B use (frequency and dosing interval) over time
- Change in patterns of PH94B use (frequency and dosing interval) in designated subgroups over time
- [redacted]

Section 14.3. Screen Failures

Text formerly read: Subjects who fail inclusion and/or exclusion criteria may be rescreened for the study. Subjects may only be rescreened once 30 days or more after the original Screening visit. If a subject is eligible to enter the study after having previously failed screening, the subject will be assigned a new subject identification number.

Now reads: Subjects who fail inclusion and/or exclusion criteria may be rescreened for the study **on a case-by-case basis after discussion with the medical monitor**. Subjects may only be rescreened once 30 days or more after the original Screening visit. If a subject is eligible to enter the study after having previously failed screening, the subject will be assigned a new subject identification number.

Section 14.7.2. Sample Retention

Text formerly read: Samples may be used for purposes related to this research. The samples will be stored until the sponsor has determined that specimens are no longer needed, and the decision has been made that none of the samples needs to be reanalyzed. In addition, identifiable samples can be destroyed at any time at the request of the subject.

Now reads: Samples may be used for purposes related to this research. The samples will be **destroyed after testing is complete**. In addition, identifiable samples can be destroyed at any time at the request of the subject.

New appendices were added (not shown here):

SAD Diagnostic Checklist

[redacted]

Hamilton Depression Rating Scale

Clinical Global Impression Scale of Improvement

Clinical Global Impression Scale of Severity

Patient Global Impression of Change

Penn Physician Withdrawal Checklist