CONFIDENTIAL

CLINICAL TRIAL PROTOCOL

TITLE OF CLINICAL TRIAL:

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

Clinical Trial Protocol PH94B-CL026

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

Signatures of Approval of Clinical Trial Protocol (Version 2.0)

This Clinical Trial Protocol was subject to critical review and has been approved by the following persons:

Affiliation		
[redacted]	[redacted]	
Principal Investigator: The Medical Research Network, LLC 134 East 93rd Street New York, NY, 10128		

Acknowledgment of Responsibilities (Clinical Trial Protocol Version 2.0)

This Phase 3 Clinical Trial Protocol (the Protocol) is the property of VistaGen Therapeutics, Inc., a Nevada corporation (VistaGen). I understand that the information within it is confidential and is provided to me for review by myself, my staff, and applicable institutional review board or independent ethics committee. I understand that the Protocol must be kept in a confidential manner and must be returned to VistaGen, or destroyed per VistaGen's instructions, upon request. No part of this Protocol may be reproduced in any form without prior written permission from VistaGen. By accepting this Protocol, I agree that I will not disclose the information contained herein to any third-party without prior written authorization from VistaGen.

I have read and understood the Protocol and agree that it contains all of the necessary information to carry out the Phase 3 clinical trial described therein.

I agree to conduct this Phase 3 clinical trial in accordance with all stipulations of the current Protocol and in accordance with the following: Good Clinical Practice, the ethical principles that have their origin in the Declaration of Helsinki; Title 21 of the Code of Federal Regulations, Parts 50 (Protection of Human Subjects), and 56 (Institutional Review Boards), and 312 (Investigational New Drug Application); and International Council for Harmonisation E6 (Guideline for Good Clinical Practice).

I agree that I will not modify or deviate from the Protocol without obtaining the prior written approval of VistaGen and of the institutional review board or independent ethics committee, except when necessary to protect the safety, rights, or welfare of subjects.

Affiliation	Name	Signature	Date:
Investigator:			

Investigator:	NAME, DEGREE(S) TITLE Phone: ###-###-#### Fax: ###-###-#### E-mail:
Research facilities:	NAME ADDRESS
Institutional review boards/ independent ethics committees	NAME ADDRESS Phone: ###-###-#### Fax: ###-###-#### E-mail:

STUDY SYNOPSIS

Name of sponsor company: VistaGen Therapeutics, Inc., a Nevada corporation (VistaGen)	
Name of finished product: PH94B Nasal Spray (PH94B)	
Name(s) of active ingredient(s): PH94B	
Title of study: A Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled Clinical Trial of PH94B Nasal Spray for the Acute Treatment of Anxiety Induced by a Public Speaking Challenge in Adult Subjects with Social Anxiety Disorder (PALISADE-1, the Study)	
Investigator(s): To be determined	
Number of sites: The Study is designed as a multi-center trial and it is projected that up to approximately 18 centers will be involved, with each center providing up to approximately 14 randomized subjects on average.	
Study period: [redacted] phase on 1 day, followed by a [redacted] exposure on 1 day approximately 1 week later.	**Phase of development:** Phase 3
Rationale: The Study is designed to evaluate the efficacy, safety, and tolerability of the acute administration of 3.2 µg of PH94B to relieve symptoms of acute anxiety in adult subjects with social anxiety disorder (SAD) during a public speaking challenge.	
Objectives: The primary efficacy objective of the Study is to evaluate whether the efficacy of PH94B to relieve acute anxiety induced during a public speaking challenge in adult subjects with SAD is greater than that for placebo as measured by the Subjective Units of Distress Scale (SUDS). The secondary efficacy objective of the Study is the comparison of PH94B-treated subjects with placebo-treated subjects with regard to clinician-observed change in subject's response to the anxiety-provoking situation between Visit 2 and Visit 3 as measured by Clinical Global Impression Scale of Improvement (CGI-I). The safety objective of the Study is the determination of safety and tolerability of PH94B compared to placebo in adult subjects with SAD from reported adverse events and changes in laboratory parameters and physical examinations.	
Methodology: Randomized, double-blind, placebo-controlled, 1-day parallel design group study.	
Number of subjects (planned): Estimated the need to screen up to 470 subjects to obtain 208 subjects to be randomized 1:1 to PH94B or placebo	
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. Current diagnosis of Social Anxiety Disorder as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, as confirmed by the Mini International Neuropsychiatric Interview (MINI). 4. Clinician-rated Liebowitz Social Anxiety Scale (LSAS) total score ≥70 at Screening (Visit 1). 5. Clinician-rated Hamilton Depression Score 17-items total score <18 at Screening (Visit 1).	

STUDY SYNOPSIS (continued)

6. Women of child bearing-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) and Baseline (Visit 2), prior to investigational product (IP) administration. Effective methods of contraception include: condoms with spermicide, diaphragm with spermicide, hormonal contraceptive agents (oral, transdermal, or injectable), or implantable contraceptive devices.
7. Negative COVID-19 test either in the presence of COVID-19 symptoms or after direct exposure to someone with a positive COVID-19 test.

Exclusion criteria:

1. Any history of bipolar disorder (I or II), schizophrenia, schizoaffective disorder, psychosis, anorexia or bulimia, premenstrual dysphoric disorder, 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 Columbia-Suicide Rating Scale (C-SSRS) with reference to a 6-month period prior to screening; or
   b. At Screening (Visit 1): the subject has had one 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. Considered to be an imminent danger to themselves or others.
4. Clinically significant nasal pathology or history of significant nasal trauma, nasal surgery, 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. Two or more documented failed treatment trials with a registered medication approved for SAD, taken at any time during the lifetime of the patient, whereby an adequate treatment trial is defined as that documented in the package insert for a particular drug during which the subject received an adequate medication dosage (defined as the treatment dose indicated in the package insert to obtain efficacy for that particular drug).
7. Use of any psychotropic medication within 30 days before Study entry (other than allowed medication for insomnia, such as eszopiclone, ramelteon, melatonin, zaleplon, zolpidem, or antihistamines).
8. Concomitant use of any anxiolytics, such as benzodiazepines or unapproved treatments such as beta blockers, during the Study and within 30 days before Study entry. Subjects who have been taking benzodiazepines daily for 1 month or longer at the time of Visit 1 are not eligible to participate.
9. Concomitant use of any over-the-counter, prescription product, or herbal preparation for treatment of the symptoms of anxiety or social anxiety during the Study and within 30 days before Study entry.
10. Prior participation in a clinical trial involving PH94B.

STUDY SYNOPSIS (continued)

11. Women who have a positive serum or urine pregnancy test prior to IP administration. Women who are currently breastfeeding are not eligible unless they are willing to stop breastfeeding for the duration of time between Visit 2 and Visit 4.
12. Subjects with clinically significant abnormalities in hematology, blood chemistry, urinalysis, electrocardiogram, 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.
13. Subjects with a positive urine drug screen at either the Screening visit or Baseline visit (not including tetrahydrocannabinol).
14. Any current clinically significant and/or uncontrolled medical condition, based on medical history or as evidenced in screening assessments, such as SARS-Cov-2, 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.
15. History of cancer or malignant tumor not in remission for at least 2 years. Basal cell skin cancers are not exclusionary.

Test product, dose, and mode of administration:
PH94B, 3.2 µg administered as an intranasal (i.n.) solution (a 1.6 µg spray to each nostril per dose).

Reference therapy, dose and mode of administration:
PH94B will be compared to placebo i.n. solution dosed at one spray to each nostril per dose.

Duration of treatment:
A single dose of [redacted] at Visit 2 (Baseline) and a single dose of [redacted] at Visit 3 (Treatment).

Criteria for evaluation:
The primary outcome variable for the Study is the change from baseline average SUDS score during a public speaking challenge from Visit 2 (Baseline), where all subjects receive [redacted] to Visit 3 (Treatment) where subjects are randomized to treatment with [redacted]

Study design:
This is a multicenter, randomized, double-blind, placebo-controlled, parallel design, single-dose, Phase 3 clinical study in adult subjects diagnosed with SAD. Subjects with diagnosed SAD by MINI and with LSAS of 70 or greater are to be enrolled.

Experimental procedures:
Subject participation in the Study will last a total of 3 to 7 weeks, depending on the duration of the screening period and intervals between visits. Upon signing an informed consent, all subjects will complete Visit 1 (Screening) and enter a screening period lasting between 3 and 35 days. If subjects meet all eligibility criteria at the end of the screening period, subjects will complete Visit 2 (Baseline) and will participate in a 5-minute public speaking challenge after receiving a single-blind dose of [redacted] in each nostril. [redacted] t Visit 3 (Treatment), the subject will be randomized to receive [redacted]. The subject will self-administer randomized IP and will then undergo a 5-minute public speaking challenge [redacted] At the end of the Visit 3 public

STUDY SYNOPSIS (continued)

speaking challenge, [redacted], and the trained observer will complete the CGI-I assessment. One week (±2 days) after the completion of Visit 3 public speaking challenge, the subject will come back for Visit 4 (Follow-up) that will involve a repeat of the safety and psychiatric assessments conducted at Screening [redacted]

Safety considerations:
Safety and tolerability of PH94B will be assessed and summarized through changes from screening in laboratory values, electrocardiograms, physical examinations, and vital sign assessments following exposure to PH94B, as well as by comparison of adverse events reported during treatment with PH94B and placebo. To date, limited exposure to PH94B (<2 weeks, <4 doses per day) in over 200 subjects has resulted in no serious adverse events and no adverse events occurring with statistically greater frequency for the PH94B group than the placebo group.

Statistical methods:
The sample size calculation was based on the similarly designed Phase 2 randomized, double-blind, placebo-controlled clinical study of PH94B with the primary outcome variable of average subjective anxiety based on SUDS scores. [redacted] Based on these considerations, 208 subjects (104 in each arm) will be included in the Study.

The primary endpoint for the Study is the difference in average SUDS score during the double-blind Visit 3 public speaking challenge versus the average SUDS score in the single blind Visit 2 public speaking challenge for PH94B compared to placebo. [redacted] Change from Visit 2 to Visit 3 in average SUDS scores between PH94B- and placebo-treated subjects will be used. An analysis of covariance model with baseline SUDS as covariate will be used to test the null hypothesis that there is no difference in change from baseline average SUDS scores between PH94B- and placebo-treated subjects.

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AE	adverse event
C-SSRS	Columbia Suicidality Severity Rating Scale
CGI-I	Clinical Global Impression Scale of Improvement
ECG	electrocardiogram
eCRF	electronic case report form
[redacted]	[redacted]
HAM-D	Hamilton Depression Scale
ICF	informed consent form
i.n.	intranasal
IP	investigational product
IRB	institutional review board
LSAS	Liebowitz Social Anxiety Scale
MINI	Mini International Neuropsychiatric Interview
[redacted]	[redacted]
PH94B	PH94B Nasal Spray
SAD	social anxiety disorder
SAE	serious adverse event
SUDS	Subjective Units of Distress Scale
UDS	urine drug screen
VistaGen	VistaGen Therapeutics, Inc., a Nevada corporation

1.0 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 (Food and Drug Administration Title 21 part 312 and International Council for Harmonisation guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 BACKGROUND

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, judgement, 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.

1.1.1 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]

1.2 STUDY RATIONALE

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 trials 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]

1.2.1 Phase 1 Studies

[redacted].

[redacted]

[redacted]

1.2.2 Phase 2 Studies

Two previously completed Phase 2 clinical studies have had similar population and efficacy endpoints of Protocol PH94B-CL026. These double-blind, randomized, placebo-controlled Phase 2 clinical studies (PH94B-CL016 and -CL022), included a total of 91 female subjects who met criteria for SAD (generalized subtype) as defined by the DSM-4. PH94B (1.6 µg) was administered i.n. in spray form [redacted] prior to both a performance (public speaking) challenge and a social interaction challenge simulation which took place at the clinical sites. [redacted] The primary outcome measures were the Clinical Global Impression Scale of Improvement (CGI-I) and the Subjective Units of Distress Scale (SUDS). SUDS scores range from zero to 100, with higher scores indicating greater levels of anxiety. Subjects receiving PH94B were more likely than those who received placebo to show improvement on the CGI-I following treatment. In the PH94B group, 34 of 45 subjects (75.6%) were rated very much less anxious or much less anxious compared to only 17 of 46 subjects (37%) in the placebo group. A test for the difference between proportions indicated a Z value of 4.03, p = 0.0001 (Fisher's exact test).

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. No SAEs were reported, and no subjects were terminated prematurely from the study due to AEs.

1.3 DOSE RATIONALE

PH94B is a Phase 2 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. [redacted] The i.n. route of administration is required in order 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 Investigator's Brochure. Nonclinical and clinical data have shown that PH94B is safe for use in human subjects at increasing doses up to [redacted]. PH94B could not be quantified in blood samples of human subjects administered [redacted] µg i.n. in a Phase 1 trial. No SAEs associated with the administration of PH94B have been observed in any clinical study to date. To date, the safety margin-based no-observed-adverse-effect level from toxicity studies have indicated that the proposed doses are safe. The profile of physiological and behavioral responses to PH94B was similar for males and females, [redacted]. This Study proposes the self-administration of a single dose of PH94B, 3.2 µg (one 1.6 µg spray per nostril), for males and females, based on Phase 1 and Phase 2 study outcomes in general, [redacted]. The investigational product (PH94B or placebo) will be self-administered i.n. once in a [redacted] parallel group fashion during a clinic-based public speaking challenge. Subjects will be randomly assigned to treatment with either PH94B or placebo.

2.0 OBJECTIVES

2.1 PRIMARY EFFICACY OBJECTIVE

The primary efficacy objective of the Study is to evaluate whether the efficacy of PH94B to relieve acute anxiety induced during a public speaking challenge in adult subjects with SAD is greater than that for placebo as measured by the SUDS.

2.2 SECONDARY EFFICACY OBJECTIVE

The secondary efficacy objective of the Study is the comparison of PH94B-treated subjects with placebo-treated subjects with regard to clinician observed change in subject's response to the anxiety-provoking situation between Visit 2 and Visit 3 as measured by CGI-I.

2.3 [redacted]

[redacted]

2.4 SAFETY OBJECTIVE

The safety objective of the Study is the determination of safety and tolerability of PH94B compared to placebo in adult subjects with SAD from reported AEs and changes in laboratory parameters, suicidality, level of depression, and physical examinations.

3.0 STUDY DESIGN

3.1 BASIC DESIGN CHARACTERISTICS

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

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

3.2 STUDY POPULATION

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

3.2.1 Inclusion Criteria

To be considered eligible to participate in the Study, a subject must meet the inclusion criteria listed below:

1. Written informed consent provided prior to conducting any study-specific assessment.

2. Male or female adult, 18 through 65 years of age, inclusive.

3. Current diagnosis of SAD as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, as confirmed by the Mini International Neuropsychiatric Interview (MINI).

4. Clinician-rated LSAS total score ≥70 at Screening (Visit 1).

5. Clinician-rated Hamilton Depression Scale (HAM-D) 17-item total score <18 at Screening (Visit 1).

6. Women of child bearing-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) 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.

7. Negative COVID-19 test either in the presence of COVID-19 symptoms or after direct exposure to someone with a positive COVID-19 test.

3.2.2 Exclusion Criteria

To be considered eligible for entry into the Study, the subject must not meet any of the exclusion criteria listed below:

1. Any history of bipolar disorder (I or II), schizophrenia, schizoaffective disorder, psychosis, anorexia or bulimia, premenstrual dysphoric disorder, 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 (including cannabinoids) 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 Columbia Suicidality Severity Rating Scale (C-SSRS) with reference to a 6-month period prior to screening; or

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

    c. At the 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. Considered to be an imminent danger to themselves or others.

4. Clinically significant nasal pathology or history of significant nasal trauma, nasal surgery, 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 mucosa.

6. Two or more documented failed treatment trials with a registered medication approved for SAD during the lifetime of the patient, whereby an adequate treatment trial is defined as that documented in package insert for a particular drug during which the subject received an adequate medication dosage (defined as the treatment dose indicated in the package insert to obtain efficacy for that particular drug).

7. Use of any psychotropic medication within 30 days prior to Study entry (other than allowed medication for insomnia as described in Section 4.5).

8. Concomitant use of any anxiolytics, such as benzodiazepines, or unapproved treatments such as beta blockers, during the Study and within 30 days prior to Study entry. Subjects who have been taking benzodiazepines daily for 1 month or longer at the time of Visit 1 are not eligible to participate.

9. Concomitant use of any over-the-counter, prescription product, or herbal preparation for treatment of the symptoms of anxiety or SAD during the study and within 30 days prior to Study entry.

10. Prior participation in a clinical trial involving PH94B.

11. Women who have a positive serum or urine pregnancy test prior to IP administration. Women who are currently breastfeeding are not eligible unless they are willing to stop breastfeeding for the duration of time between Visit 2 and Visit 4.

12. Subjects with clinically significant abnormalities in hematology, blood chemistry, urinalysis, ECG, or physical examination identified at the Screening 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.

13. Subjects with a positive urine drug screen at either the Screening visit or Baseline visit (not including tetrahydrocannabinol).

14. Any current clinically significant and/or uncontrolled medical condition, based on medical history or as evidenced in screening assessments, such as SARS-Cov-2, 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.

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

3.3 ENDPOINTS

3.3.1 Efficacy

3.3.1.1 Primary Efficacy Endpoints

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

3.3.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoint of the Study is the comparison between the PH94B and placebo groups on CGI-I scores at Visit 3.

3.3.2 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.3.3 Safety

Safety and tolerability of PH94B will be assessed and summarized through changes from Screening in laboratory values, ECGs, physical examinations, and vital sign assessments following exposure to PH94B, as well as by comparison of AEs, suicidal ideation (C-SSRS), and level of depression (HAM-D) reported during treatment with PH94B and placebo.

3.4 RANDOMIZATION AND BLINDING

Overall, the randomization will be stratified by study site with a ratio of 1:1.

Each study site will be provided with a supply of blinded IP, each vial individually numbered with a unique alpha-numeric identification code. For Visit 2 and Visit 3, the interactive system will provide a unique vial identification code indicating the medication vial to be dispensed to the subject. The vial identification codes will be recorded in the drug dispensing record and the electronic case report form (eCRF).

The vial number can be used to break the blind if necessary. Contact information will be provided to the study site.

3.5 WITHDRAWAL OF SUBJECTS

3.5.1 When and How to Withdraw Subjects

A subject may voluntarily discontinue from participating in the Study at any time. The Investigator, at his or her discretion, may also withdraw a subject from participating in the Study at any time. Criteria for premature withdrawal from the Study include:

- Withdrawal of informed consent (subject's decision to withdraw for any reason).

- Any AE, laboratory abnormality, 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.
- Disease progression that, in the Investigator's opinion, precludes the subject's continued participation in the Study.
- Significant non-compliance with the requirements of the protocol or treatment.
- The subject requires a medication prohibited by the protocol.
- Termination of the Study by VistaGen.
- At the discretion of the Investigator or VistaGen.

A subject will be considered to have completed the primary efficacy endpoint in the Study when he or she starts the Visit 3 public speaking challenge and has at least one SUDS value recorded following a single dose of [redacted] treatment with the PH94B or placebo.

3.5.2 Data Collection and Follow-up for Withdrawn Subjects

All attempts will be made to have subjects return to the study center to complete Visit 4 in the event of early withdrawal from Visit 3 after IP administration. All attempts, including phone or email, to contact the subject must be recorded in the source documents. If the subject fails to respond to those methods, a certified, return receipt letter must be sent to the subject's address indicating that they should contact the study center, with a copy retained in the source documents. Only if all of these attempts fail will it be deemed that the subject is in fact Lost to Follow-Up and no final safety data can be collected.

4.0 DRUGS AND DOSAGES

4.1 IDENTIFICATION AND DESCRIPTION OF INVESTIGATIONAL PRODUCT

4.1.1 Investigational Product

PH94B nasal spray solution is [redacted] The placebo is odorless and contains the identical excipients without PH94B. PH94B nasal spray solution and placebo nasal spray solution are similar in appearance. [redacted]

4.1.2 Appearance and Labeling

[redacted] In addition, the PH94B nasal spray solution and placebo nasal spray solution are indistinguishable in appearance and both are odorless.

Vials will be labelled with a unique vial identifier. All vials dispensed at Visit 2 will contain [redacted] Labels [redacted] will be identical and indistinguishable except for the unique vial identifier on each individual vial.

4.2 DOSING INSTRUCTIONS AND SCHEDULE

4.2.1 Administration of Investigational Product

[redacted]

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

4.2.2 Treatment Regimen

IP will be administered once in each nostril before each public speaking challenge. Men and women will be treated with the same dose of PH94B: 3.2 µg. [redacted] Therefore, the spray volume administered to each nostril (100 µL) will be below the nasal retention volume and will be retained in the nasal passages.

[redacted]

[redacted]

4.3 HANDLING OF INVESTIGATIONAL PRODUCT

4.3.1 Receipt of Drug Supplies

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. It is important that the designated Study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable IP in a given shipment (active drug or comparator) will be documented in the Study files.

4.3.2 Storage

[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.

4.3.3 Drug Dispensing and Return Procedures

At Visit 2 and Visit 3, subjects will be dispensed the appropriate vial of IP as supplied by the interactive system. The vial number of the dispensed vial will be recorded in the eCRF for each subject.

[redacted]

Current and accurate inventory and dispensing records will be kept for all IP, and upon Study completion a final inventory of all clinical supplies will be compiled. All IP containers, whether empty or containing unused IP, will be returned per the Sponsor's instructions from the clinical monitor. A copy of the Drug Receipt Form and the Drug Accountability Form will be retained in the Investigator's files.

4.4 COMPLIANCE WITH INVESTIGATIONAL PRODUCT

Subjects will self-administer the IP in the presence of Study personnel at each visit. The Study personnel will be responsible for documenting the administration in the eCRF.

4.5 PRIOR AND CONCOMITANT MEDICATIONS

All medications taken by or administered to the subject during the month prior to Screening (Visit 1) should be recorded in the eCRF. With the exception of those noted in the protocol (refer to Section 3.2.2, Exclusion Criteria) all medications (prescription or over-the-counter) that were started prior to Screening may be continued during the course of the trial. 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 the protocol.

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.

Where washout of prohibited medications is required before Baseline (Visit 2), 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 PK of the medication being discontinued. The subject must be consented before any tapering is started.

With the exception of eszopiclone, ramelteon, melatonin, zaleplon, zolpidem, or anti-histamines as allowable concomitant medications for the treatment of insomnia, no other psychotropic medication besides IP is permitted to be used by any subject between Screening (Visit 1) and Follow-up (Visit 4). At Visit 1, the investigator should consider checking the local Prescription Drug Monitoring Database to verify the lack of use of scheduled central nervous system active drugs, such as benzodiazepines.

[redacted]

5.0 EXPERIMENTAL PROCEDURES

5.1 OVERVIEW: SCHEDULE OF TIME AND EVENTS

The required efficacy and safety endpoints for subject evaluation are outlined in Section 3.3, with a comprehensive schedule of Study assessments included in the following sections. Every effort should be made to complete all required procedures and evaluations at the designated visits. For each Study visit, a window of ± 2 days is permissible.

Following participation in the PALISADE-1 study, subjects will have the option to participate in the PALISADE LTS study (PH94B-30), pending their provision of consent and confirmation of eligibility. The PALISADE LTS is an open-label study in which subject participate for up to 12 months. Participating subjects will self-administer PH94B nasal spray before or during anxiety-provoking social situations or events, as needed.

[redacted]

5.2 VISIT PROCEDURES

5.2.1 Visit 1 (Screening)

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

- Ensure that appropriate subjects are entered into the trial;
- Determine that the subject meets all eligibility criteria;
- Collect demographic and medical data permitting characterization of the subject;
- Ensure that prohibited medications are discontinued; and
- Determine that subjects are willing to undertake up to two anxiety-provoking situations at the site.

To meet these objectives, the duration of screening must be tailored to the individual subject and may last from a minimum of 3 to a maximum of 35 days. Subjects continuing to meet all eligibility requirements at Baseline (Visit 2) will undergo a Visit 2 public speaking challenge.

Generally, healthy subjects who are thought to meet inclusion and exclusion criteria and express an interest in participating will be informed about the Study, investigational product (PH94B and placebo), 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 informed consent form (ICF) before any study-related procedures are performed (including tapering of prohibited medications). 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 ICF process is complete, a subject number will be allocated by the site, by assigning the next sequential subject number available. Subject numbers will be four-digit numbers beginning with the site number. Subject numbers will not be sex-specific and will be assigned sequentially in the order in which the ICF is signed, and the Screening (Visit 1) occurs.

[redacted] which is to occur at least 3 days, but no more than 35 days prior to Visit 2:

1. The 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 (with the exception of UDS positive for cannabinoids only).

    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).

    [redacted]

4. Standardized assessments ([redacted] but per investigator judgement based on the MINI) to include:

    a. Administer LSAS.

    b. Administer HAM-D.

[redacted]

d. Administer C-SSRS (Long Term/Recent).

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

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

   c. Obtain blood and urine samples for evaluation by the central clinical laboratory, including hematology, chemistry, thyroid functioning, and urinalysis (refer to Section 5.1 for complete list).

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

7. Train subjects on the use of IP and dosing. The subject will be given instructions on:

   a. how to position the nozzle in the nasal passages and self-administer IP, using a demonstration vial,

   b. number of sprays per nostril per dose (one per nostril).

5.2.2 Visit 2 (Baseline)

For subjects continuing to meet all eligibility criteria, the following Visit 2 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.
- 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 UDS is positive [redacted].

- For females of child-bearing potential, obtain urine sample and complete on-site urine pregnancy test.
- Record concomitant medication use including the completion of any washout.
- 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:

- Introduce the self-rated anxiety scale, the Subjective Units of Distress Scale (SUDS), to the subject and review the descriptions of the various SUDS scores (Appendix A).
- [redacted]
- Dispense and instruct subject to self-administer IP [redacted]
- The subject will be returned to a waiting area after IP dosing.
- [redacted] the subject will be informed that they must give a 5-minute speech to a live audience of [redacted]
- [redacted]
- The subject will be given 3 minutes to organize their thoughts on their upcoming speech.
- The subject will be escorted into a room to give a 5-minute speech in front of three neutral observers after the last SUDS anticipatory anxiety score is collected [redacted]

[redacted]

- [redacted], the subject will be given information on attending the next visit (Visit 3), else the subject will complete the remaining assessments for Visit 2, will not be randomized, and will be discharged from the study [redacted]

- If the subject cannot complete the speech due to anxiety levels, the SUDS level will be requested from them before they leave the room and all remaining time points will be marked as not done.

- Record any AEs reported.

- [redacted]

For the subject attending the next visit (Visit 3), it will be scheduled 1 week (± 2 days) after the date of Visit 2.

[redacted]

5.2.3 Visit 3 (Treatment)

At Visit 3, 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.
- Urine Drug Screen (Instant Exam, to be performed on site, with results documented in the source).
- Record Concomitant Medication use.
- Review and record AEs.
- Randomize the subject.
- [redacted] follow the instructions for the Visit 3 public speaking challenge (as described in Section 5.2.2 and Figure 5-1) with the same trained observer as in Visit 2.

After the completion of the Visit 3 public speaking challenge:

- [redacted]
- Complete the CGI-I (by the trained observer of the public speaking challenge).
- Review and record AEs.
- Administer C-SSRS (Since Last Visit) [redacted]

The Follow-Up visit (Visit 4) will be scheduled for 1 week ±2 days after the date of Visit 3.

5.2.4 Visit 4 (Follow-Up)

At Visit 4, the following assessments will be completed:

- Obtain 12-lead ECG in supine position after 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 5.4 for complete list).
- Perform physical examination, including height (inches), body weight (pounds), body temperature (°F), and vital signs after the subject has rested for 5 minutes: seated systolic and diastolic blood pressure, heart rate, and respiratory rate. Also includes an examination of the nasal passages.
- 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 UDS is positive (with the exception of on-site UDS positive for cannabinoids only).
- For females of child-bearing potential, obtain urine sample and complete on-site urine pregnancy test.
- Administer LSAS.
- Administer HAM-D.
- [redacted]
- [redacted]
- Record Concomitant Medication use.
- Review and record AEs.
- [redacted]
- Complete the Subject Summary Record.

5.3 EFFICACY ASSESSMENTS

5.3.1 Public Speaking Challenge

The public speaking challenge has been used in previous studies as an anxiety-provoking situation and has been designed to be consistently applied across all clinical sites. [redacted]

5.3.2 Subjective Units of Distress Scale

The Subjective Units of Distress Scale (SUDS), used at Visit 2 and Visit 3 as part of each public speaking challenge, is scored in the range of 0 to 100 (operationalized for the participants in this study as 0 = totally relaxed or no anxiety and 100 = most distress of anxiety imaginable). It is a standard instrument for rating social and performance anxiety in patients with SAD during role playing situations. [redacted]

[redacted]

5.3.3 Liebowitz Social Anxiety Scale

The Liebowitz Social Anxiety Scale (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 two ratings: fear or anxiety on scale of 0 to 3 and avoidance on a scale of 0 to 3 with the total maximum overall score of 144. The items in the scale can be divided into performance and social interaction items, and corresponding subscores can be derived.

5.3.4 [redacted]

[redacted]

5.4 LABORATORY ASSESSMENTS

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

- 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

- Hematology/ Hemogram Panel: hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular concentration, mean corpuscular volume, platelets, red blood cell count, white blood cell count, red blood cell morphology

- Hematology Differential Panel: basophils, eosinophils, lymphocytes, monocytes, neutrophils

- Thyroid stimulating hormone

- Free thyroxine (T4) (if thyroid stimulating hormone is above the upper or below the lower normal limits, then Free thyroxine will automatically be performed)

- Urinalysis macroscopic panel: bilirubin, blood, clarity, color, glucose, ketones, leucocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen

- Urine Drug Screen (if on-site UDS is positive, urine sample will be submitted to central laboratory for confirmatory UDS, [redacted]: antidepressants, opiates, cocaine, benzodiazepines, amphetamines, barbiturates, cannabinoids, methadone, phencyclidine, propoxyphene, methamphetamine, buprenorphine, ecstasy, oxycodone

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

- Urine pregnancy test (for all female subjects of child-bearing potential)
- Urine Drug Screen

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 and will be provided to Sponsor or designated data manager with agreed 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. 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.

6.0 PROCEDURES FOR HANDLING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

6.1 MEDICAL MONITORING

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.

6.2 DEFINITIONS OF ADVERSE EVENT AND SERIOUS ADVERSE EVENT

6.2.1 Adverse Event

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in intensity during the course of the study. Any newly developed illnesses or injuries should be regarded as adverse events.

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

- results in study withdrawal and is associated with a serious adverse event
- 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 one 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.

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an AE if the frequency, intensity, or the character of the condition worsens during the study period (between after IP administration at Visit 2 and Visit 4/Follow-Up).

At Screening through IP administration at Visit 2, any clinically significant abnormality should be recorded as a preexisting condition in the medical history, not as an AE. At the end of the Study, any new clinically significant findings/abnormalities that meet the definition of an AE must also be recorded and documented as an AE.

Pregnancy is not considered an AE, but it is an important medical event, which must be followed up as described in Section 6.5.3.

6.2.2 Serious Adverse Event

Adverse events are classified as serious or non-serious. A serious adverse event (SAE) is any AE that is:

- fatal,
- life-threatening,
- requires or prolongs hospital stay,
- results in persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event.

Important medical events are those that may not be immediately life-threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

AEs that do not meet any of the criteria for SAEs should be regarded as non-serious AEs.

6.2.3 Hospitalization, Prolonged Hospitalization or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an AE if the condition meets the criteria for an AE.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an AE in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an AE if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the Study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the Study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical Investigator.

6.3 RECORDING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

6.3.1 Recording of Adverse Events

At each contact with the subject, the Investigator must seek information on AEs by questioning and, as appropriate, by examination. Information on all AEs should be recorded immediately in the source document, and also in the appropriate AE module of the eCRF. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All AEs occurring during the Study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the Study period must be followed up to

determine the final outcome. Any SAE that occurs after the Study period and is considered to be possibly related to either or both IP administered and/or study participation should be recorded and reported immediately.

6.4 ASSESSMENT OF INTENSITY

A clinical determination will be made of the intensity of an AE. The intensity assessment for a clinical AE must be completed using the following definitions as guidelines.

Table 6-1. Classification of AEs by Intensity

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

AE = adverse event.

6.5 ASSESSMENT OF CAUSALITY

6.5.1 Relationship to Investigational Product or Study Procedure

The Investigator is to determine whether or not there is a reasonable causal relationship between the IP and the AE. 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.

The relationship assessment for an AE is to be completed by indicating if an AE is related or not related to IP administered.

6.5.2 Reporting of Serious Adverse Events and Unanticipated Problems

For any SAE occurring during the Study period starting at Visit 1 after signing the informed consent, whether or not related to the treatment, expected or not, the Investigator is to take the following steps:

- Take prompt and appropriate medical action, if necessary. The safety of Study subjects is the first priority.
- Immediately inform VistaGen of the event and if necessary, contact the Medical Monitor by telephone to discuss any immediate and/or further steps to be taken.
- Complete as fully as possible the AE page in the eCRF.
- Complete the SAE form provided in the Study Procedures Manual at the Study start. Fax or scan and email the completed SAE form along with copies of the eCRF pages documenting demography, medical history, Concomitant Medications, and AEs, and any other relevant information (e.g., test results) within 24 hours to VistaGen.
- Report the SAE to the IRB, following the IRB's reporting guidelines and requirements.
- Monitor and record the progress of the event until it resolves or reaches a clinically stable outcome, with or without sequelae. For all additional follow-up evaluations, fax or scan and email all additional follow-up information to VistaGen within 24 hours.
- SAEs will be followed until the Investigator at the Study site and Sponsor agree that the event is satisfactorily resolved.
- Obtain and maintain in the source documents all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject. If necessary, contact the subject's personal physician or hospital staff to obtain further details.
- Inform the Sponsor of the final outcome of the event. Send a revised or updated SAE Form and AE form, if appropriate.

- Comply with the applicable regulatory requirement/s related to the reporting of SAEs to the IRB.

Table 6-2. Timeline for Reporting SAEs

Initial SAE Report		Follow-up SAE Report	
Time Frame	**Documents**	**Time Frame**	**Documents**
24 hours	SAE report	7 days	Updated SAE report

SAE = serious adverse event.

6.5.3 Pregnancy

Any pregnancy occurring during the Study where the fetus may have been exposed to the IP must be reported to VistaGen. Follow-up information will be obtained regarding the course and outcome of the pregnancy, including any post-natal sequelae in the infant. All information will be documented on appropriate forms. (see the Study Procedures Manual).

7.0 STUDY OR SITE TERMINATION AND SUBJECT DISCONTINUATION

7.1 EARLY WITHDRAWAL OF SUBJECTS

A subject may voluntarily discontinue from participating in the Study at any time. The Investigator, at his or her discretion, may also withdraw a subject from participating in the Study at any time. Criteria for premature withdrawal from the Study include:

- Withdrawal of informed consent (subject's decision to withdraw for any reason).
- Any AE, laboratory abnormality, 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.
- Disease progression that, in the Investigator's opinion, precludes the subject's continued participation in the Study.
- Significant non-compliance with the requirements of the protocol or treatment.
- The subject requires a medication prohibited by the protocol.
- Termination of the Study by VistaGen.
- At the discretion of the Investigator or VistaGen.

A subject will be considered to have completed the Study when he or she completes Visit 4.

7.2 PREMATURE STUDY OR SITE TERMINATION

If the Sponsor, Investigator, Medical Monitor, study monitor, or appropriate regulatory officials discover conditions arising during the Study that indicate that the Study should be halted or that the site should be terminated, this action may be taken after appropriate consultation among the Sponsor, Investigator, Medical Monitor, and study monitor. Conditions that may warrant termination of the Study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the Study

- A decision on the part of the sponsor to suspend or discontinue testing, evaluation, or development of the product

A study conducted at a single site in a study may also warrant termination under the following conditions:

- Failure of the Investigator to enroll subjects into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent regulations of appropriate regulatory authorities
- Submission of knowingly false information from the site to the sponsor, study monitor, or appropriate regulatory authority
- Insufficient adherence to protocol requirements

Study termination and follow-up will comply with the conditions set forth in International Council for Harmonisation E6, Guideline for Good Clinical Practice, Sections 4.12, 4.13, 5.20, and 5.21.

8.0 DATA COLLECTION AND PROCESSING AND STATISTICAL ANALYSIS

8.1 DATA COLLECTION AND PROCESSING

Electronic case report forms (eCRFs) will be used to capture Study assessments and data. The Investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. All eCRFs will be reviewed and source verified by the study monitor during periodic site visits, and the study monitor will ensure that all data in the eCRF are correct and complete. Before or between visits, the Medical Monitor or study monitor may conduct a preliminary medical review of the eCRFs. Once the eCRFs are completed and source-verified, the investigator must electronically sign all required eCRF pages, verifying the accuracy of all data contained in the eCRFs.

Training will be provided for the electronic data capture (EDC) system. All Study staff using the EDC system must have the necessary education, training, and experience or any combination of these. The Investigator will be responsible for documenting employee education, training, and previous experience that pertain to the EDC system for all Study site staff using the EDC system.

The Investigator must maintain adequate security of the EDC system, including documentation that all users have been trained on the appropriate standard operating procedure and a list of authorized users. To ensure all data entries can be tracked, all personnel responsible for data entry must obtain a unique user identification (user ID) and password before any data can be entered in the eCRFs. Authorized Study staff will be assigned a unique user ID only after receiving standard operating procedure training.

If electronic data systems other than those provided and maintained by the Sponsor are used for documentation and data capture, the Investigator must ensure that the systems are validated, and that data are backed up.

8.2 STATISTICAL ANALYSIS

The data will be summarized in tables, as appropriate, showing the number of subjects with non-missing data (n), mean, standard deviation, median, minimum, and maximum for continuous data and showing counts and percentage for categorical data. Data will also be listed as deemed appropriate. All statistical analyses will be performed, and data appendices will be created by using SAS.

The statistical analysis plan will be finalized and approved before final database lock and unblinding of the randomization code.

8.2.1 Populations for Analyses

8.2.1.1 Intent to Treat Population

The Intent-to-Treat Population in the Study includes all subjects who are randomized.

8.2.1.2 Safety Populations

The safety population will include all subjects who receive IP.

8.2.2 Efficacy Analysis

8.2.2.1 Primary Endpoint

The primary endpoint for the Study is the difference in average SUDS scores during the [redacted] Visit 3 public speaking challenge versus the average SUDS scores during [redacted] Visit 2 public speaking challenge [redacted]

[redacted]
Change from Visit 2 to Visit 3 in average SUDS scores [redacted] will be used.

An ANCOVA model with baseline SUDS as covariate will be used to test the null hypothesis that there is no difference in change from baseline average SUDS scores between PH94B- and placebo-treated subjects.

8.2.2.2 Secondary Endpoints

The secondary efficacy endpoint in the Study is the difference between proportions of PH94B- and placebo-treated groups in Clinical Global Impression Scale of Improvement (CGI-I) scores of 1 [redacted]) or 2 [redacted] recorded at the end of Visit 3.

This secondary endpoint will be analyzed using a normal approximation test for the difference between two binomial proportions. The null hypothesis to be tested is that the population proportions are equal.

8.2.2.3 [redacted]

[redacted]

8.2.3 Estimand Framework and Sensitivity Analyses

8.2.3.1 Primary Estimand

The treatment of interest is PH94B, 3.2 µg administered as an i.n. solution [redacted] The population of interest is adult patients with SAD as defined by the protocol inclusion and exclusion criteria (Section 3.2). [redacted] Intercurrent events are expected to be rare. Any intercurrent event that does occur will be handled using the treatment policy strategy, i.e., included in the treatment regimen under evaluation. The difference of means from Visit 2 to Visit 3 in SUDS will be estimated for each treatment group. PH94B will be compared to placebo using differences in group means.

8.2.3.2 Secondary Estimand

The treatment of interest is PH94B, 3.2 µg administered as an i.n. solution [redacted]. The population of interest is adult patients with SAD as defined by the protocol inclusion and exclusion criteria (Section 3.2). The endpoint to be measured is the CGI-I score at Visit 3. Intercurrent events are expected to be rare. Any intercurrent event that does occur will be handled using the treatment policy strategy, i.e., included in the treatment regimen under evaluation. The proportion of subjects with CGI-I scores of 1 [redacted] or 2 [redacted] for PH94B will be compared to placebo using a comparison of binomial proportions.

8.2.3.3 Sensitivity Analyses

Sensitivity analysis focusing on the assumptions about missing data can be performed by varying assumptions about the change in the SUDs scores. Details around sensitivity analyses will be finalized in the Statistical Analysis Plan.

8.2.4 Safety Analysis

8.2.4.1 Safety and Tolerability

Descriptive statistics will be used to portray safety and tolerability of PH94B (3.2 µg) as measured by reports of AEs and SAEs, changes in laboratory values, ECGs, and physical examination.

8.2.4.2 Safety Procedures

Safety in this Study will be determined from evaluation of AEs, clinical laboratory assessments, vital signs assessments, changes in suicidality (C-SSRS) and level of depression (HAM-D), physical examinations including examination of the nasal passages, and ECGs. Specific visits for obtaining clinical laboratory assessment samples are listed in the Schedule of Time and Events (Table 5-1). The schedule of clinical laboratory tests is listed in Section 5.4.

8.2.5 Subgroups

The primary and secondary endpoints may also be summarized by subgroups of interest including age, sex, and by site.

8.2.6 [redacted]

[redacted]

8.2.7 Missing Data

8.2.7.1 Prevention of Missing Data

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

Case report forms will be designed to capture all relevant background information as well as objective reasons for early discontinuation when it cannot be prevented.

8.2.7.2 Unavoidable Loss of Data

It is expected that all Study subjects who are randomized at Visit 3 will complete the Visit 3 public speaking challenge immediately after randomization and be included in the primary efficacy analysis. If Visit 3 SUDS scores are missing for unanticipated

reasons (intercurrent events) that arise during Visit 3, appropriate imputation will be performed.

Details around missing data treatments will be finalized in the Statistical Analysis Plan.

9.0 STUDY ADMINISTRATION

9.1 INFORMED CONSENT AND AUTHORIZATION FOR USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION

Written informed consent and authorization of use and disclosure of protected health information must be obtained from each subject (or the subject's legally acceptable representative) before performing any Study-specific screening or baseline period evaluations. One copy of the signed informed consent form (ICF) and authorization for use and disclosure of protected health information form will be given to the subject, and the Investigator will retain the original. The ICF and authorization for use and disclosure of protected health information, which is prepared by the Investigator or the Study site, must have been reviewed and approved by the Sponsor, the Study monitor, and the Investigator's IRB or IEC and privacy board (if separate from the IRB) before the initiation of the Study. The ICF must contain the 20 elements of informed consent described in International Council for Harmonisation E6, Section 4.8. The authorization for use and disclosure of protected health information must contain the elements required by Title 45 of the Code of Federal Regulations, Section 164.508(b), and any local regulations for valid authorizations.

9.2 STUDY DOCUMENTATION

9.2.1 Investigator Information

Investigator information is included in the Study Procedures Manual, which is updated as needed.

9.2.2 Investigator Study Files

Documentation about the Investigator and Study staff, the IRB, and the institution is required before site initiation. Copies of these documents will be kept on-site in site-specific binders or electronic folders, along with the following supplemental information: a list of Investigator's obligations, the Investigator's Brochure, the Protocol and amendments, safety information, information about the IP, biological samples, and the laboratory, the Study Procedures Manual and study logs, electronic case report forms (eCRFs), records of monitoring activities, and correspondence between Sponsor or Study monitor and the Investigator.

Audit trails are generated automatically for eCRFs.

9.2.3 Case Report Forms and Source Documentation

The Investigator must make Study data accessible to the site monitor, other authorized representatives of the Sponsor, and the appropriate regulatory authority inspectors. The eCRF for each subject will be checked by the site monitor, and a final copy of the eCRF will be signed by the Investigator with an electronic signature. A copy of the final eCRFs will be provided to the Investigator after Study closure to be kept in the Investigator's Study files.

9.2.4 Retention of Study Documents

It is the Investigator's responsibility to retain Study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country 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 if required by an agreement with the Sponsor. In such an instance, it is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

9.3 CONFIDENTIALITY

Information about Study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in the Study.
- Who will have access to that information and why.
- Who will use or disclose that information.
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled Study period.

9.3.1 Data

The Investigator must keep all information confidential about the nature of the proposed investigation provided by the Sponsor or Study monitor to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the subject, or the appropriate regulatory authority).

9.3.2 Subject Anonymity

The anonymity of participating subjects must be maintained. Subjects will be identified by an assigned subject number on eCRFs and other documents retrieved from the site or sent to the Study monitor, Sponsor, regulatory agencies, central laboratories, or blinded reviewers. Documents that identify the subject (e.g., the signed informed consent form) must be maintained in strict confidence by the Investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the Study monitor, or Sponsor representatives.

9.4 PROTOCOL COMPLIANCE

A protocol deviation is any noncompliance with the Protocol or Good Clinical Practice (GCP). Noncompliance may be on the part of the subject, the Investigator, or the Study site staff. As a result of major deviations as determined by the Study monitor, corrective actions are to be developed by the site and implemented promptly. Documentation of the deviation and corrective actions will be included in the data quality assessment during blinded review.

9.5 STUDY MONITOR FUNCTIONS AND RESPONSIBILITY

The Study monitor, in accordance with the Sponsor's requirements, will ensure that the Study is conducted and documented properly by carrying out the activities outlined in International Council for Harmonisation E6, Section 5.18.4.

9.5.1 Clinical Monitoring

The conduct of the Study will be closely monitored by representatives (Clinical Research Associates "CRAs" or study monitors) of the Sponsor, to verify adherence to the Protocol, ICH GCP guidelines, and applicable regulations. The CRA will verify eCRF entries by comparing them with hospital, clinical, office and/or Study records which will be made available for this purpose. CRAs will monitor the Study as outlined in the Monitoring Plan prepared for the Study.

During the Study, CRAs will contact the clinical site on a regular basis to assess and assure satisfactory enrollment rate, data recording, maintenance of required regulatory documentation, IP accountability, and compliance with the Protocol. The Investigator will ensure that all requested materials, including subject charts, eCRFs, source documents, laboratory records, and drug inventory records, will be available to the CRA if needed. At the end of the Study, a close-out visit will be performed.

Reports of all monitoring visits will be archived in the Trial Master File. The Investigator will allow the Sponsor's representatives, designee and/or any regulatory agency to have direct access to all Study records, eCRFs, corresponding subject medical records, IP dispensing records, and IP storage area, and any other documents considered source documentation. The Investigator also agrees to assist the representative, if required.

9.5.2 Quality Assurance, Auditing and Inspection

The Study is conducted under the sponsorship of VistaGen in compliance with the applicable international and local regulatory requirements as well as applicable ICH guidelines, Helsinki (1964, 1975, 1983, 1989 and 1996) and in respect of the VistaGen or its designee's SOPs for Study conduct and monitoring.

The Investigator will permit Study-related monitoring, audits, and inspections by the IRB, the Sponsor, and government regulatory bodies of all Study related documents (e.g., source documents, regulatory documents, data collection instruments, study data, etc.).

Participation as an Investigator in this Study implies acceptance of potential inspection by government regulatory authorities.

9.6 GENERAL INFORMATION

The Investigator should refer to the Investigator's Brochure, Study Procedures Manual, and any other information provided about this IP and details of the procedures to be followed during the Study.

9.7 PUBLICATION PLAN

Neither the partial, complete or any part of the results of the Study carried out under this protocol, nor any of the information provided by the Sponsor for the purposes of performing the Study, may be published or passed on by Investigator or any member of the Study site's staff to any third party without the prior written consent of VistaGen. Any Investigator involved with this Study is obligated to provide VistaGen with complete test results and all data derived from the Study in an efficient and timely manner. For multi-center studies, the first publication or disclosure shall be a complete, joint multi-center publication or disclosure.

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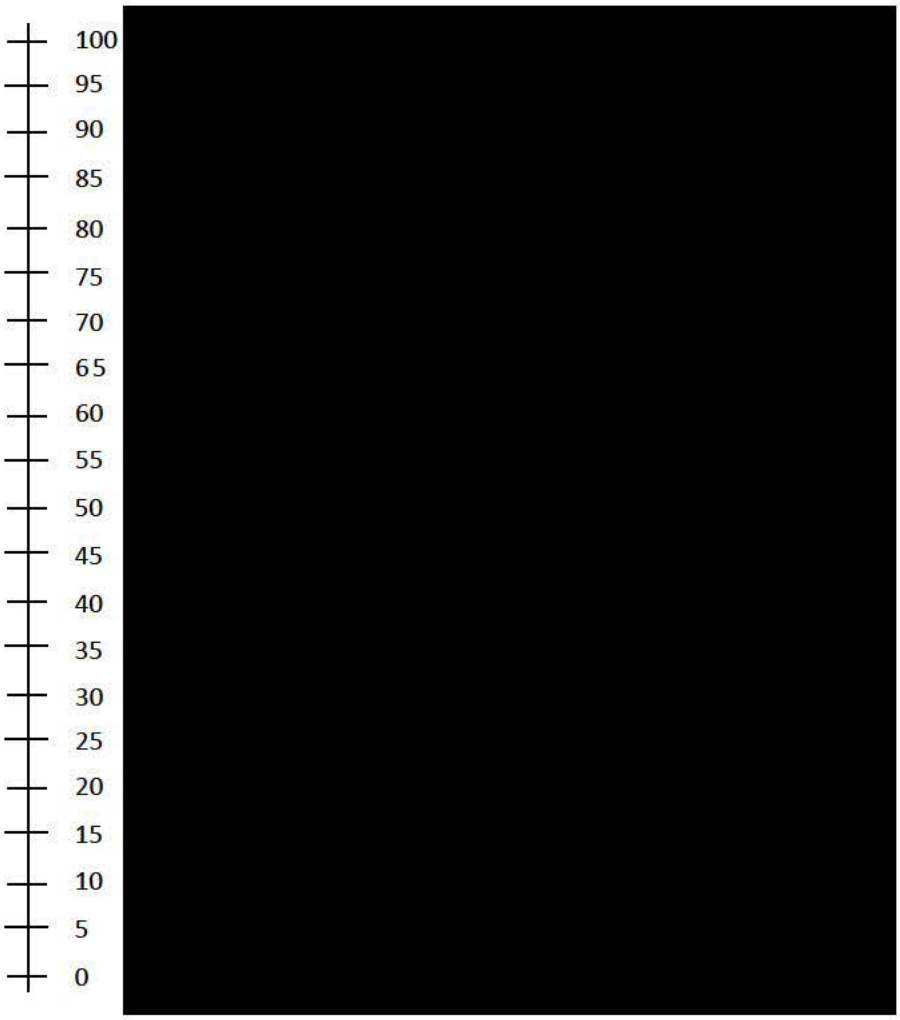
APPENDICES

APPENDIX A

SUBJECTIVE UNIT OF DISTRESS SCALE

Subjective Units of Distress Scale (SUDS) Thermometer

Using the Subjective Units of Distress Scale (also called the SUDS), you can record how anxious you feel in different situations by picking a number between 0 and 100; zero would mean totally relaxed or no anxiety and 100 is the most distress or anxiety imaginable. [redacted]



[redacted]

[redacted]

[redacted]

[redacted]

APPENDIX D

LIEBOWITZ SOCIAL ANXIETY SCALE

VistaGen® Therapeutics

PALISADE-1 CLINICAL TRIAL

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

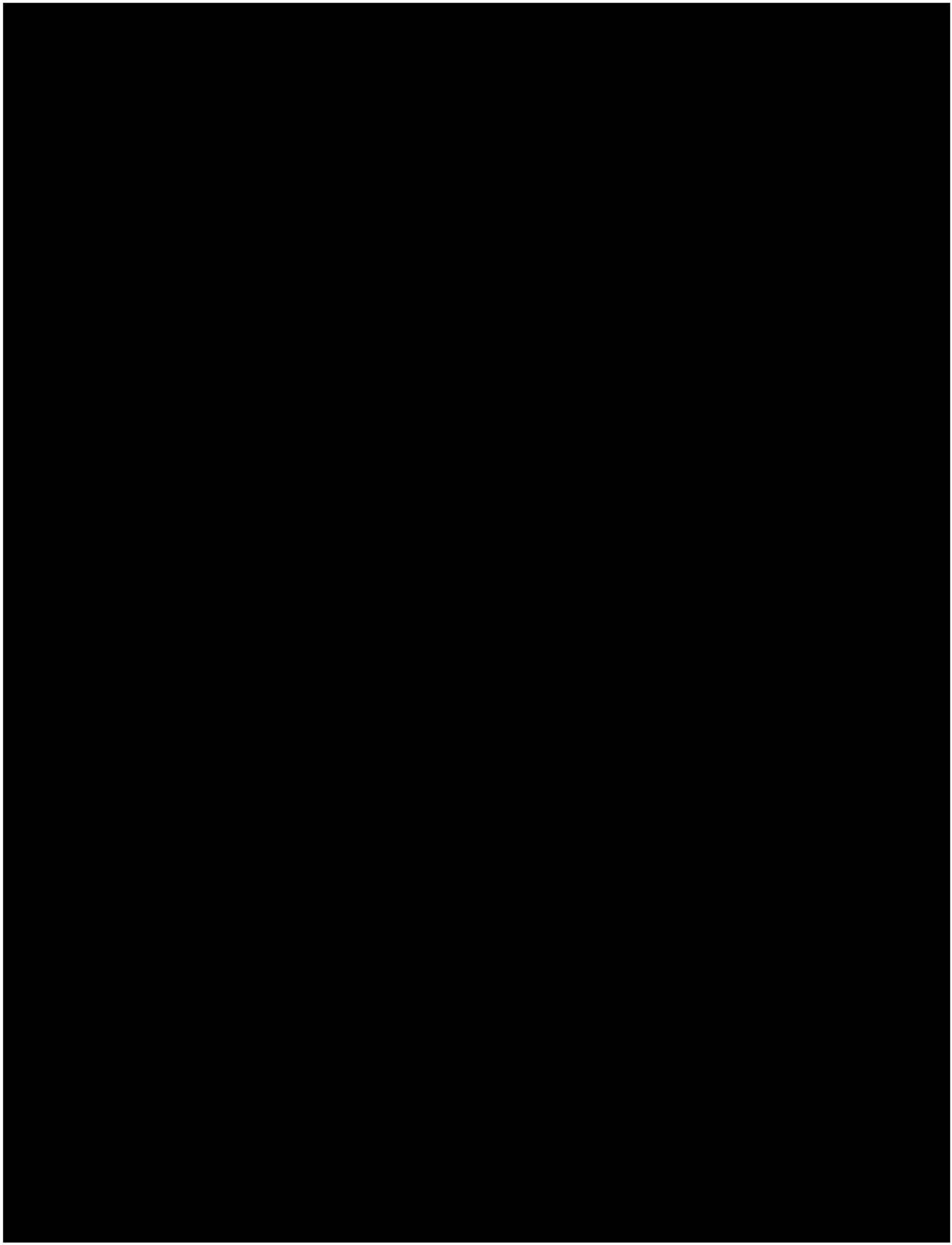
Source Document: Protocol PH94B-CL026

Liebowitz Social Anxiety Scale (LSAS)

Item		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%)	
		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:** _____/_____/_____

[redacted]



[redacted]

APPENDIX G

HAMILTON DEPRESSION RATING SCALE

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

Source Document: Protocol PH94B-CL026

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:** _____/_____/_____

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:** _____/_____/_____

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

Source Document: Protocol PH94B-CL026

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:** _____/_____/_____

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):

APPENDIX H

CLINICAL GLOBAL IMPRESSION IMPROVEMENT SCALE

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

Source Document: Protocol PH94B-CL026

Clinical Global Impression (CGI) Improvement Scale

[redacted]

- ❑ [redacted]
- ❑ [redacted]
- ❑ [redacted]
- ❑ [redacted]
- ❑ [redacted]
- ❑ [redacted]
- ❑ [redacted]

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

[redacted]