PROTOCOL AMENDMENT 3

PRODUCT NAME/NUMBER:	PH94B Nasal Spray
PROTOCOL NUMBER:	PH94B-CL032
IND NUMBER:	[redacted]
DEVELOPMENT PHASE:	3
NCT	05011396
PROTOCOL TITLE:	A US, 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-2)
PROTOCOL DATE:	Version 1.0, 02-Aug-2021
AMENDMENT 1 DATE:	Version 2.0, 25-Aug-2021
AMENDMENT 2 DATE:	Version 3.0, 25-Jan-2022
AMENDMENT 3 DATE:	Version 4.0, 12-Aug-2022
SPONSORED BY:	VistaGen Therapeutics, Inc. 343 Allerton Avenue South San Francisco, CA 94080, USA
CONTRACT RESEARCH ORGANIZATION:	Premier Research 3800 Paramount Parkway, Suite 400 Morrisville, NC 27560, USA

1. APPROVAL SIGNATURES

PROTOCOL NUMBER: PH94B-CL032

PROTOCOL TITLE: A US, 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-2)

AMENDMENT 3 DATE: Version 4.0, 12-Aug-2022

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

SIGNATURE **DATE:**

[redacted]

[redacted]
VistaGen Therapeutics, Inc.

[redacted]

[redacted]
VistaGen Therapeutics, Inc.

[redacted]

[redacted]
VistaGen Therapeutics, Inc.

SIGNATURE **DATE:**

DocuSigned by:
Michael Liebowitz
Signer Name: Michael Liebowitz
Signing Reason: I approve this document
Signing Time: 8/16/2022 | 9:18:23 AM PDT
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2. PROTOCOL SUMMARY

2.1. Synopsis

PRODUCT NAME/NUMBER	PH94B Nasal Spray
PROTOCOL NUMBER	PH94B-CL032
DEVELOPMENT PHASE	3
PROTOCOL TITLE	A US, 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-2)
INDICATION	Social anxiety disorder
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	Primary: 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 of placebo as measured by the Subjective Units of Distress Scale (SUDS). Secondary: The secondary efficacy objective of the study is to compare clinician-observed changes in subject response to an anxiety-provoking situation from Visit 2 to Visit 3 between PH94B-treated subjects and placebo-treated subjects, as measured by Clinical Global Impression Scale of Improvement (CGI-I). The safety objective of the study is to determine safety and tolerability of PH94B compared to placebo in adult subjects with SAD from reported adverse events (AEs) and changes in vital signs, 12-lead electrocardiograms (ECGs), laboratory parameters, suicidality, level of depression, and physical examinations. Exploratory: Exploratory efficacy objectives of the study are to compare PH94B-treated subjects with placebo-treated subjects with regard to the following: • Subject self-evaluation of change in response to the anxiety-provoking situation between Visit 2 (Baseline) and Visit 3 (Treatment) as measured by Patient Global Impression of Change (PGI-C) [redacted] • To compare the proportion of subjects in each group with an improvement of 20 or more points from Baseline (Visit 2) SUDS scores at Visit 3 (Treatment) ("responders").

	• [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 a diagnosis of SAD, confirmed by Mini International Neuropsychiatric Interview (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 form, 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), including participation in a 5-minute public speaking challenge after receiving a single-blind dose of [redacted] in each nostril. [redacted] At Visit 3 (Treatment), the subject will be randomly allocated to receive treatment with either [redacted] or [redacted] The subject will self-administer randomly allocated study treatment and will then undergo a 5-minute public speaking challenge [redacted] At the end of the Visit 3 public speaking challenge, the subject will complete the PGI-C questionnaire, 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), which 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, suicidality and level of depression, ECGs, physical examinations, and vital sign assessments following exposure to PH94B, as well as by comparison of AEs 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 (SAEs) and no AEs occurring with statistically greater frequency for the PH94B group than the placebo group.
PLANNED NUMBER OF SUBJECTS	An estimated 400 subjects will be screened to randomize 208 subjects in a 1:1 manner to PH94B or placebo.
STUDY ENTRY CRITERIA	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 SAD as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, and confirmed by the MINI. 4. Clinician-rated LSAS total score ≥70 at Screening (Visit 1). 5. Clinician-rated Hamilton Depression Score 17-items total score <18 at Screening (Visit 1). 6. Women of childbearing-potential must be able to commit to the consistent and correct use of an effective method of birth control throughout the study and must also have a negative urine pregnancy test result at both Screening (Visit 1) 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 for subjects with COVID-19 symptoms or those who have had direct exposure to someone with a positive COVID-19 test, and/or completion of quarantine period consistent with requirements at the study site as determined by the Investigator. **Exclusion criteria:** 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 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 1 or more suicidal attempts with reference to a 2-year period prior to screening; or c. At Baseline (Visit 2): the subject scores "yes" on items 4 or 5 in the Suicidal Ideation section of the C-SSRS with reference to screening; or d. The subject is considered to be an imminent danger to themself or others. 4. Clinically significant nasal pathology or history of significant nasal trauma, nasal surgery, total anosmia, or nasal septum perforation that may have damaged the nasal chemosensory epithelium. 5. An acute or chronic condition, including an infectious illness, uncontrolled seasonal allergies at the time of the study, or significant nasal congestion that potentially could affect drug delivery to the nasal chemosensory epithelium. 6. Two or more documented failed treatment trials with a registered medication approved for SAD, at any time during the lifetime of the subject, whereby an adequate treatment trial is defined as that described 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 medication permitted for insomnia: eszopiclone, ramelteon, melatonin, zaleplon, zolpidem, or antihistamines). 8. Use of any anxiolytics, such as benzodiazepines or unapproved treatments such as beta blockers, within 30 days before study entry; concomitant use is prohibited during the study. Subjects who have been taking benzodiazepines daily for 1 month or longer at the time of Visit 1 are not eligible to participate. 9. Use of any over-the-counter product, prescription product, or herbal preparation for treatment of the symptoms of anxiety or social anxiety within 30 days before study entry; concomitant use is prohibited during the study. 10. Prior participation in a clinical trial involving PH94B. 11. Women who have a positive 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 Screening (Visit 1) or Baseline (Visit 2) ([redacted]). 14. Any current clinically significant and/or uncontrolled medical condition, based on medical history or as evidenced in screening assessments, such as COVID-19, HIV, cancer, stroke, congestive heart failure, uncontrolled diabetes mellitus, or any other medical condition or disease that, in the clinical judgment of the Investigator, could place the subject at undue risk, interfere with study participation, or confound the results of the study. 15. History of cancer or malignant tumor not in remission for at least 2 years. Basal cell skin cancers are not exclusionary.
TEST PRODUCT	Name: PH94B Nasal Spray Dose, route, frequency: 3.2 µg administered as an intranasal (i n.) solution (a 1.6 µg spray to each nostril per dose).
CONTROL PRODUCT	Name: Placebo Dose, route, frequency: Administered via i n. route, 1 spray to each nostril per dose.
TREATMENT REGIMENS	Subjects will receive a single dose of [redacted] at Visit 2 (Baseline) and a single dose of [redacted] at Visit 3 (Treatment).
PLANNED STUDY SITES	The study is designed as a multi-center trial and it is projected that up to approximately 15 to 18 centers will be involved, with each center providing up to approximately 10 to 20 randomized subjects.
CRITERIA FOR EVALUATION	Efficacy endpoints: • Primary efficacy endpoint: The primary endpoint for the study is the difference in average SUDS score during the [redacted] Visit 3 public speaking challenge versus the average SUDS scores during the [redacted] Visit 2 public speaking challenge for PH94B compared to placebo. • Secondary efficacy endpoint: The secondary efficacy endpoint in the study is the difference between proportions of PH94B- and placebo-treated groups in CGI-I scores of 1 [redacted] or 2 [redacted] recorded at the end of Visit 3 (Treatment). • Exploratory efficacy endpoints: o Difference between proportions of PH94B- and placebo-treated groups in PGI-C scores of 1 [redacted] or 2 [redacted] recorded at the end of Visit 3 (Treatment) o Difference in mean Visit 2 (Baseline) and Visit 3 (Treatment) [redacted] o Proportion of subjects in each treatment group with 20-point improvement in SUDS scores from Visit 2 (Baseline) at Visit 3 (Treatment)

	○ [redacted] Safety endpoints: • Incidence and severity of AEs • Changes in vital signs results • Changes in clinical laboratory evaluation (hematology, chemistry, and urinalysis) results • Changes in 12-lead ECG results • Changes in physical examination findings • Mean HAM-D scores • Incidence of treatment-emergent suicidal ideation and behavior
STATISTICAL METHODS	Analysis Populations: Intent-to-Treat (ITT) Population: The Intent-to-Treat Population in the Study includes all subjects who are randomized. Safety Population: All subjects who receive IP. Efficacy Analyses: For each subject at each public speaking challenge, average SUDS scores will be calculated from SUDS scores recorded at 1-minute intervals during each performance. Change from Visit 2 to Visit 3 in average SUDS scores between PH94B- and placebo-treated subjects will be used. An analysis of covariance (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. The secondary efficacy endpoint will be analyzed using a normal approximation test for the difference between 2 binomial proportions. The null hypothesis to be tested is that the population proportions are equal. Exploratory endpoint analyses will be summarized, and all p-values reported for descriptive purposes. Safety Analyses: Descriptive statistics will be used to present safety and tolerability of PH94B (3.2 µg) as measured by reports of AEs and SAEs, changes in laboratory values, suicidality and level of depression, vital signs, ECGs, and physical examination. Interim Analysis An interim analysis will be conducted using all SUDS data from the first 140 subjects who complete Visit 3, with the goal to assess the study for futility, and if warranted, to conduct a sample size re-estimation.
SAMPLE SIZE DETERMINATION	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]

	[redacted] Based on these considerations, 208 subjects (104 in each arm) will be included in the study.
STUDY AND TREATMENT DURATION	The sequence and maximum duration of the study periods will be as follows: 1. Screening and washout: From 3 to 35 days 2. Eight-day treatment period, with [redacted] treatment at Baseline (Day 0) and [redacted] treatment with [redacted] on Day 7 3. 7-day follow-up period (follow-up visit on Day 14) The maximum study duration for each subject is approximately 7 weeks. The maximum treatment duration for each subject is approximately 8 days (including [redacted] treatment).

2.2. Schedule of Events

Table 2-1: Schedule of Events

Assessment	Screening *Day -35 to -3* Visit 1	Baseline *Day 0* Visit 2	Treatment *Day 7 (± 2 days)* Visit 3	Follow-up *Day 14 (± 2 days)* Visit 4
Written Informed Consent	X			
Subject Demographics	X			
Urine Drug Screen (Instant Exam, on site)	X	X	X	X
Urine Pregnancy Test	X	X	X	X
MINI	X			
Medical and Psychiatric History	X			
Prior and Concomitant Medication Recording	X	X	X	X
[redacted]	[redacted]			
LSAS	X			X
Hamilton Depression Scale	X			X
[redacted]	[redacted]			[redacted]
C-SSRS	X	X (end of visit)[c]	X (end of visit)[c]	X
Physical Examination and Examination of Nasal Passages	X			X
Vital Signs	X	X	X	X
Electrocardiogram	X			X
Blood Tests and Urinalysis	X			X
Inclusion/Exclusion Review	X	X		
Investigational Product Administration Training	X			
[redacted]		[redacted]		
Investigational Product Administration		X	X	
Public Speaking Challenge[b]		X	X	
Randomization			X	
PGI-C Scale			X	
CGI-I Scale			X	
Adverse Events Recording		X	X	X
[redacted]				[redacted]

Abbreviations: C-SSRS = Columbia Suicide Severity Rating Scale; CGI-I = Clinical Global Impression of Improvement; LSAS = Liebowitz Social Anxiety Scale; [redacted]
PGI-C= Patient Global Impression of Change; [redacted]

3. TABLE OF CONTENTS

3.1. List of In-Text Tables

3.2. List of In-Text Figures

REASONS FOR AMENDMENT

1. The purpose is to add a futility interim analysis, based on the recent topline results from the similar Phase 3 study (PALISADE-1; Study PH94B-CL026), for which the study did not meet its primary endpoint.

SUMMARY OF AMENDED SECTIONS

SYNOPSIS — STATISTICAL METHODS

Now reads:

Interim Analysis

An interim analysis will be conducted using all SUDS data from the first 140 subjects who complete Visit 3, with the goal to assess the study for futility and to conduct a sample size re-estimation.

Section 13.1.6 — Interim Analysis

Text formerly read: No interim analyses are planned.

Now reads:

An interim analysis will be conducted using all SUDS data from the first 140 subjects who complete Visit 3, with the goal to assess the study for futility, and if warranted, to provide a sample size re-estimation. To maintain integrity of this double-blind study, an independent, unblinded, external statistician will evaluate conditional power and communicate only one of the following recommendations to VistaGen:

1. the study may be stopped due to futility,
2. the study can continue with no change, or
3. the sample size is recommended to increase.

The sponsor and all study staff will remain blinded, and only the independent biostatistician will have access to unblinded study data. Details of the interim analysis will be provided in an independent interim statistical analysis plan.

The constrained promising zone approach[45] will be used to re-estimate

AMENDED PROTOCOL

The following are the amended protocol and appendices, including all revisions specified above.

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	EXPLANATION
AE	adverse event
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical
C-SSRS	Columbia-Suicide Severity Rating Scale
CGI-I	Clinical Global Impression – Improvement scale
COVID-19	coronavirus 2019
CRA	clinical research associate
CSR	clinical study report
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form
GCP	Good Clinical Practice
[redacted]	[redacted]
HAM-D	Hamilton Depression Scale
IB	investigator brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
i.n.	intranasal
IND	Investigational New Drug
IP	investigational product
IRB	institutional review board
ITT	Intent-to-Treat
IWRS	interactive web response system
LSAS	Liebowitz Social Anxiety Scale
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
PGI-C	Patient Global Impression of Change
SAD	social anxiety disorder
SAE	serious adverse event
SD	standard deviation
SUDS	Subjective Units of Distress Scale
WHO-DD	World Health Organization Drug Dictionary

5. INTRODUCTION

This document is a protocol for a Phase 3 human research study. This study is to be conducted according to United States and international standards of Good Clinical Practice (Food and Drug Administration Title 21 part 312 and International Council for Harmonisation guidelines), applicable government regulations and Institutional research policies and procedures.

5.1. Background and Rationale

5.1.1 Social Anxiety Disorder

The essential features of social anxiety disorder (SAD) are defined as intense, marked, and persistent fear of social or performance situations, in which the subject believes embarrassment, humiliation, 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.

5.1.2 Nasal Chemosensory Systems

In humans, as in other mammals, the olfactory system is a rostral projection of the telencephalon and it is the only sensory system with direct neural connections to the limbic system without a previous 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, odorless chemosensory cues also engage nasal chemosensory receptors and induce behavioral and neuroendocrine responses, without olfactory awareness.[11-16]

In most mammals, odorless chemosignals induce activation of accessory olfactory neural circuits.[17-22]

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

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

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

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

5.1.3 PH94B

PH94B (3β-androsta-4,16-dien-3-ol) is a synthetic neuroactive steroid discovered and initially developed at Pherin Pharmaceuticals that targets human nasal chemosensory cells[11,36] and has been demonstrated in Phase 2 clinical 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 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] In institutional review board (IRB)-approved studies, pulsatile intranasal (i.n.) administration of nanogram quantities of airborne PH94B to human subjects induced dose-dependent depolarization of the electrogram recorded from the surface nasal chemosensory mucosa, which is a measure of the local mass receptor potential response.

[redacted] PH94B exerts its activity by stimulation of neural circuits involving the limbic amygdala, and it does not require systemic uptake and distribution to produce its anxiolytic pharmacological effect. PH94B is being investigated as a potential acute treatment for the alleviation of anxiety symptoms in adult patients with SAD. While PH94B may regulate gamma aminobutyric acid circuits in the limbic amygdala, electrophysiological experiments in vitro showed that PH94B does not directly bind to or modulate gamma aminobutyric acid receptors at concentrations of 10 µM or lower, which differentiates its mechanism of action from benzodiazepines.[44]

5.2. Clinical Experience

5.2.1 Phase 1 Studies

[redacted]

5.2.2 Phase 2 Studies

Two previously completed Phase 2 clinical studies have enrolled similar populations and had similar efficacy endpoints to Protocol PH94B-CL026. These double-blind, randomized, placebo-controlled Phase 2 clinical studies ([redacted]) included a total of

91 female subjects who met criteria for SAD (generalized subtype) as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. PH94B (1.6 µg) was administered i.n. in spray form [redacted] 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). The SUDS scores range from 0 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.

5.3. Summary of Potential Risks and Benefits

There are no direct benefits to participation for subjects in this study. Subjects will receive a single i.n. dose of PH94B or placebo at the study site. PH94B is intended for acute treatment of SAD, and the activity is not expected to last long beyond the subjects' study visit.

Based on previous clinical studies conducted with PH94B, it is believed to be safe and well tolerated, and risks to subjects are considered minimal. Intranasal administration of PH94B may increase the risk of local site reactions including itching, burning, runny nose, sneezing and soreness inside the nose. In completed clinical studies, the most commonly reported AE was headache. None of these effects was reported in more subjects receiving PH94B than in subjects receiving placebo.

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

6. OBJECTIVES

6.1. Primary Objective

The primary 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 of placebo as measured by the SUDS.

6.2. Secondary Objectives

The secondary efficacy objective of the study is to compare clinician-observed changes in subject response to an anxiety-provoking situation from Visit 2 to Visit 3 between PH94B-treated subjects and placebo-treated subjects, as measured by Clinical Global Impression - Improvement (CGI-I) scale.

The safety objective of the study is to determine safety and tolerability of PH94B compared to placebo in adult subjects with SAD from reported AEs and changes in vital signs, 12-lead electrocardiograms (ECGs), laboratory parameters, suicidality, level of depression, and physical examinations.

6.3. [redacted]

[redacted]

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

6.4. Endpoint Mapping

Endpoints are mapped to study objectives as follows:

Objectives	Endpoints
Primary	
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 of placebo as measured by the SUDS.	The primary endpoint for the study is the difference in average SUDS score during the [redacted] Visit 3 public speaking challenge versus the average SUDS scores during the [redacted] Visit 2 public speaking challenge for PH94B compared to placebo.
Secondary	
The secondary efficacy objective of the study is to compare clinician-observed changes in subject response to an anxiety-provoking situation from Visit 2 to Visit 3 between PH94B-treated subjects and placebo-treated subjects, as measured by CGI-I.	The secondary efficacy endpoint in the study is the difference between proportions of PH94B- and placebo-treated groups in CGI-I scores of 1 [redacted] or 2 [redacted] recorded at the end of Visit 3 (Treatment).
The safety objective of the study is to determine safety and tolerability of PH94B compared to placebo in adult subjects with SAD from reported AEs and changes in vital signs, 12-lead ECGs, laboratory parameters, suicidality, level of depression, and physical examinations.	Incidence and severity of AEs Changes in vital signs results Changes in clinical laboratory evaluation (hematology, chemistry, and urinalysis) results Changes in 12-lead ECG results Changes in physical examination findings Mean HAM-D scores Incidence of treatment-emergent suicidal ideation and behavior
[redacted]	
[redacted]	[redacted]
[redacted]	
[redacted]	
[redacted]	

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

7. STUDY DESIGN

7.1. Overall Study Design and Plan

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

Subject participation in the study will last a total of 3 to 7 weeks, depending on the duration of the screening period and intervals between visits. Upon signing an informed consent form (ICF), 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), including participation 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 allocated to receive treatment with [redacted] The subject will self-administer randomly allocated 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, the subject will complete the PGI-C questionnaire, and the site personnel will complete the CGI-I assessment. One week (±2 days) after the completion of Visit 3, the subject will come back for Visit 4 (Follow-up), which will involve a repeat of the safety and psychiatric assessments conducted at Screening, [redacted]

[redacted]

7.2. Rationale and Discussion of Study Design

The present study employs a randomized, double-blind, placebo-controlled, parallel design, which is generally considered to be the gold-standard for clinical trials. The use of a placebo for the study comparator is based on the absence of an active comparator that could be delivered by the i.n. route, which is essential for maintaining the study blind.

The study will use a public speaking challenge to provoke anxiety in participating subjects, who will rate their anxiety subjectively using the SUDS, which are both commonly used in clinical studies of SAD. Additional subjective evaluations include the PGI-C scale and [redacted] Other evaluations include the CGI-I, performed by the Investigator and a trained observer. [redacted]

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

7.3. Selection of Doses in the Study

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. A [redacted] formulation has been used with the i.n. administration route in Phase 1 and Phase 2 clinical studies. 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] 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 levels 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, and in particular on the observations made in study [redacted] The IP (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.

7.4. Study Sites

The study will take place at approximately 15 to 18 sites in the United States. Each site is anticipated to screen a sufficient number of subjects to randomize approximately 14 subjects. A study site with a high recruitment rate may be allowed to recruit more subjects if other sites have slow enrollment.

7.5. End of Study Definition

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

8. SUBJECT POPULATION

8.1. Selection of Study Population

Eligibility for participation in the study will be determined from demographic information, medical and psychiatric history, physical and psychiatric examination, ECG, clinical laboratory findings, and clinical rating scale assessments performed at Screening (Visit 1). Subjects may be recruited from the Investigator or sub-Investigator clinical practices, the 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 IRB prior to use and implementation.

8.2. Study Entry Criteria

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

8.2.1 Inclusion Criteria

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

1. Written informed consent provided prior to conducting any study-specific assessment.
2. Male and female adults, 18 through 65 years of age, inclusive.
3. Current diagnosis of SAD as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, and confirmed by the MINI.
4. Clinician-rated LSAS total score ≥70 at Screening (Visit 1).
5. Clinician-rated Hamilton Depression Score 17-items total score <18 at Screening (Visit 1).
6. Women of childbearing-potential must be able to commit to the consistent and correct use of an effective method of birth control throughout the study and must also have a negative urine pregnancy test result at both Screening (Visit 1) 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 for subjects with COVID-19 symptoms or those who have had direct exposure to someone with a positive COVID-19 test, and/or completion of quarantine period consistent with requirements at the study site as determined by the Investigator.

8.2.2 Exclusion Criteria

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

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 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 1 or more suicidal attempts with reference to a 2-year period prior to screening; or

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

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

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

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

6. Two or more documented failed treatment trials with a registered medication approved for SAD, at any time during the lifetime of the subject, whereby an adequate treatment trial is defined as that described 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 medication permitted for insomnia: eszopiclone, ramelteon, melatonin, zaleplon, zolpidem, or antihistamines).

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

9. Use of any over-the-counter product, prescription product, or herbal preparation for treatment of the symptoms of anxiety or social anxiety within 30 days before study entry; concomitant use is prohibited during the study.
10. Prior participation in a clinical trial involving PH94B.
11. Women who have a positive 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 Screening (Visit 1) or Baseline (Visit 2) ([redacted]).
14. Any current clinically significant and/or uncontrolled medical condition, based on medical history or as evidenced in screening assessments, such as COVID-19, HIV, cancer, stroke, congestive heart failure, uncontrolled diabetes mellitus, or any other medical condition or disease that, in the clinical judgment of the Investigator, could place the subject at undue risk, interfere with study participation, or confound the results of the study.
15. History of cancer or malignant tumor not in remission for at least 2 years. Basal cell skin cancers are not exclusionary.

8.3. Premature Subject Withdrawal

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

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

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

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

- 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
- Pregnancy

If a subject is withdrawn before completing the study, the reason for withdrawal and the date of discontinuation will be recorded on the appropriate page of the electronic case report form (eCRF). Whenever possible and reasonable, the evaluations that were to be conducted at the completion of the study should be performed at the time of premature discontinuation.

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.

Subjects who sign the ICF and are subsequently withdrawn will not be replaced.

8.4. Subject Replacement Criteria

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

Enrolled subjects who are withdrawn from the study may not re-enter. The subject number for a withdrawn subject will not be reassigned to another subject.

9. TREATMENTS

All IP should [redacted] prior to use but [redacted].

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

9.1. Identification of Investigational Products

PH94B nasal spray solution [redacted]

The placebo [redacted] and contains the identical excipients without PH94B.

PH94B nasal spray solution and placebo nasal spray solution are similar in appearance.

Drug and placebo will be supplied in [redacted] Each spray delivers 1.6 µg PH94B per 100 µL spray.

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

PH94B and placebo will be supplied by [redacted]

9.2. Selection of Timing of Dose for Each Subject

The 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. Each nasal spray delivers 100 µL containing 1.6 µg PH94B. [redacted]

One dose of IP is defined as one 1.6 µg spray (100 µL) administered to each nostril, thus 2 sprays total per dose provides a total dose of 3.2 µg of PH94B.

Twenty minutes prior to each public speaking challenge, the subject will be instructed to administer the IP as described above.

9.3. Dose Adjustment Criteria

Dose adjustment is not allowed in this study.

9.4. Treatment Compliance

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.

Before dispensing the IP to a subject, the Investigator or study staff will ensure the study drug is at room temperature and prime the spray vial.

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.

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.

9.5. Method of Assigning Subjects to Treatment Groups

In this parallel-group randomized study, subjects who meet study entry criteria, and who complete the Visit 2 public speaking challenge, will be randomly assigned in a 1:1 ratio to [redacted] The randomization schedule will be computer generated using a permuted block algorithm and will randomly allocate IP to randomization numbers. The randomization numbers will be assigned sequentially through a central interactive web response system (IWRS) as subjects are entered into the study. Randomization will be stratified by study site; blocks will be allocated to sites by IWRS in real-time.

The randomization schedule will be prepared by Premier Research before the start of the study. No one involved in the study performance will have access to the randomization schedule before official unblinding of treatment assignment. No subject will be randomized into this study more than once.

9.6. Blinding and Unblinding Treatment Assignment

Each study site will be provided with a supply of blinded IP, each vial individually numbered with a unique identification code. For Visit 2 and Visit 3, the IWRS 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 eCRF.

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

All subjects, investigators, and study personnel involved in the conduct of the study, including data management, will be blinded to treatment assignment with the exception of a specified unblinded statistician and a member of the Interactive Response Technology team from Premier Research who will have access to the randomization code. The unblinded study personnel will not participate in study procedures or data analysis prior to unblinding of the study data to all study-related personnel. If an interim analysis is to be conducted, then unblinded personnel who are not otherwise involved in the study will prepare the data for review.

Study personnel will make every effort to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment.

Unblinding should be discussed in advance with the medical monitor, if possible. For emergency unblinding, study personnel will use the IWRS. If the investigator is not able to discuss treatment unblinding in advance, then he/she must notify the medical monitor as soon as possible about the unblinding incident without revealing the subject's treatment assignment.

The investigator or designee must record the date and reason for treatment unblinding on the appropriate eCRF for that subject. In all cases that are not emergencies, the investigator must discuss the event with the medical monitor prior to unblinding the subject's treatment assignment.

If treatment assignment is unblinded for an individual subject, study personnel will be notified of that subject's treatment assignment without unblinding the treatment assignments for the remaining subjects in the study. Thus, the overall study blind will not be compromised. If a subject's treatment assignment is unblinded, he/she may or may not be asked to withdraw from the study. The investigator will make this decision after consultation with the medical monitor.

Overall unblinding will take place at the end of the study only after database lock has been achieved.

9.7. Permitted and Prohibited Therapies

All medications taken by or administered to the subject during the month prior to Screening (Visit 1) should be recorded in the eCRF.

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

9.7.1 Permitted Therapies

With the exception of those noted in Section 9.7.2, all medications (prescription or over-the-counter) that were started prior to Screening may be continued during the course of the 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 Section 9.7.2.

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

[redacted]

9.7.2 Prohibited Therapies

With the exception of concomitant medications for the treatment of insomnia described in Section 9.7.1, 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.

Prior use of PH94B is not permitted.

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 pharmacokinetics of the medication being discontinued. The subject must be consented before any tapering is started.

9.7.3 Restrictions

Subjects who meet criteria for moderate or severe alcohol or substance use disorder (including cannabinoids) within the 1 year prior to Study entry will be excluded from the study.

9.8. Treatment After End of Study

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

9.9. Dispensing and Storage

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

All IP supplied to each site by the Sponsor will be maintained in a safe and secure (locked) area, stored [redacted], until dispensed, and [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.

The key to the storage area is to be kept by the investigator or designee responsible for the IP. The store will be accessible only to those persons authorized by the investigator to dispense the IP.

9.10. Drug Accountability

Upon receipt of each IP shipment, an inventory must be performed, and a drug receipt log filled out and signed by the person accepting the shipment. 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.

9.11. Labeling and Packaging

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

9.11.1 Labeling

The vials will have a label affixed that meets the applicable regulatory requirements and may include the following: protocol number, unique vial identifier, caution statement ("New Drug – Limited by United States Law to Investigational Use"), a storage statement, and "FOR NASAL USE ONLY".

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

9.11.2 Packaging

PH94B and placebo will be packaged so as to be blinded to the investigator, the study clinic personnel, and subjects.

10. STUDY PROCEDURES

Subjects must provide written informed consent and/or assent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

For the timing of assessments and procedures throughout the study, refer to the schedule of events (Table 2-1). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the schedule of events for each subject. If a subject misses a study visit for any reason, the visit should be rescheduled as soon as possible.

10.1. Study Duration

The study comprises a [redacted] phase on Day 0, followed by a double-blind exposure for 1 day approximately 1 week later.

Following participation in the PALISADE-2 study, subjects will have the option to participate in the PALISADE LTS study (PH94B-CL030), pending their provision of consent and confirmation of eligibility. The PALISADE LTS study is an open-label study in which subjects participate for up to 12 months. Participating subjects will self-administer PH94B nasal spray prior to or during anxiety-provoking social situations or events, as needed.

10.2. Study Periods and Visits

A comprehensive schedule of study assessments is presented in Table 2-1 and described in the following sections. Every effort should be made to complete all required procedures and evaluations at the designated visits. For each study visit, a window of ±2 days is permitted.

10.2.1 Screening and Washout

10.2.1.1 Screening (Visit 1)

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 2 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 (APPENDIX B).

Generally, healthy subjects who are thought to meet inclusion and exclusion criteria and express an interest in participating will be informed about the study, the 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 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 4-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.

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

1. ICF will be reviewed and completed before any other assessments. Collect demographic information; and assign subject number
2. Urine sample for drug screen and pregnancy test (if appropriate) will be collected early in the screening visit to determine eligibility and to guide diagnostic interviews, especially with regards to substance use assessment. The urine sampling is to include:
    a. Obtain urine sample for urine drug screen: 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 screen is positive [redacted]
    b. For females of child-bearing potential, obtain urine sample and complete on-site urine pregnancy test
3. Medical and psychiatric history and diagnosis (usually starting with MINI) to include:
    a. Administer MINI (7.0.2)
    b. Obtain medical history (including nicotine, alcohol use, and menstrual information on women of childbearing potential) and psychiatric history
    c. Record prior and concomitant treatment and medication use (medication name, dose, and frequency)
    d. [redacted]
4. Standardized assessments (usually starting with LSAS but per investigator judgement based on the MINI) to include:
    a. Administer LSAS

b. Administer HAM-D

c. [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 10.3.2.1.1 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)

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

10.2.1.2 Washout Period

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

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 pharmacokinetics of the medication being discontinued. The subject must be consented before any tapering is started.

10.2.2 Visit 2 (Baseline): [redacted] Public Speaking Challenge

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 screen 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 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]
- [redacted]

- The subject will be escorted [redacted] into a room to give a 5-minute speech in front of [redacted] after the last SUDS anticipatory anxiety score is collected. [redacted] At these timepoints, [redacted]

- [redacted] the subject will be given information on attending the next visit (Visit 3) - otherwise, 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 during the performance phase 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

- Administer C-SSRS (Since Last Visit) as the last part of Visit 2

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

[redacted]

10.2.3 Visit 3 (Treatment): [redacted] Public Speaking Challenge

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
- Perform urine drug screen (Instant Exam, to be performed on site, with results documented in the source)
- For females of child-bearing potential, obtain urine sample and complete on-site urine pregnancy test
- 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 10.2.2 and Figure 10-1) with the same trained observer as in Visit 2; the subject will record SUDS accordingly

After the completion of the Visit 3 public speaking challenge:

- Complete the PGI-C (by the subject)
- Complete the CGI-I (by the trained observer of the public speaking challenge)
- Review and record AEs
- Administer C-SSRS (Since Last Visit) as the last part of the visit

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

10.2.4 Follow-up (or Early Termination) Evaluation

At Visit 4, 1 week (±2 days) after Visit 3, the following procedures will be performed:

- Obtain 12-lead ECG in supine position after the subject has rested for 5 minutes
- Obtain blood and urine samples for evaluation by the central clinical laboratory, including hematology, chemistry, thyroid functioning, and urinalysis (refer to Section 10.3.2.1.1 for complete list)

- Perform physical examination, including height (inches) and body weight (pounds). The physical examination also includes an examination of the nasal passages
- Measure vital signs after the subject has rested for 5 minutes: seated systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (°F)
- 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 screen is positive [redacted]
- For females of child-bearing potential, obtain urine sample and complete on-site urine pregnancy test
- [redacted]
- Administer HAM-D
- [redacted]
- Administer C-SSRS (Since Last Visit)
- Record concomitant medication use
- Review and record AEs
- [redacted]

10.3. Assessments

10.3.1 Efficacy Variables

10.3.1.1 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]

10.3.1.2 Subjective Units of Distress Scale

The 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 subjects in this study as 0=totally relaxed or no anxiety, and 100=most distress or anxiety imaginable). It is a standard instrument for rating social and

performance anxiety in patients with SAD during role-playing situations. Additional details on introducing the scale to the subject are presented in APPENDIX A.

[redacted]

10.3.1.3 Liebowitz Social Anxiety Scale

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

10.3.1.4 [redacted]

[redacted]

10.3.1.6 Clinical Global Impression of Improvement

The Clinical Global Impression of Improvement (APPENDIX I) is a clinician-rated instrument that measures the clinician's evaluation of change in subjects' overall improvement with treatment

on a scale where 1 and 7 using the same scale as for the PGI-C (see Section 10.3.1.5).

In this study, the CGI-I will be completed by the trained observer of the public speaking challenge, comparing the subject's anxiety level during the second public speaking challenge to the first public speaking challenge.

10.3.1.7

10.3.2 Safety Variables

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

10.3.2.1 Clinical Laboratory Safety Assessments

10.3.2.1.1 Clinical Laboratory Tests to be Performed

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

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

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

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 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
Urinalysis Macroscopic Panel:	bilirubin, blood, clarity, color, glucose, ketones, leucocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen

Urine Drug Screen:	If on-site urine drug screen is positive, urine sample will be submitted to central laboratory for confirmatory urine drug screens to be performed: antidepressants, opiates, cocaine, benzodiazepines, amphetamines, barbiturates, cannabinoids, methadone, phencyclidine, propoxyphene, methamphetamine, buprenorphine, ecstasy, oxycodone [redacted]
Other:	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)

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

Results and reports from the central laboratory should be filed with the source documents for each subject. The central laboratory will provide laboratory results to the study site as soon as they are available; results will also be provided to 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.

10.3.2.1.2 Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all study personnel involved in the collection of blood and handling of specimens in both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of subject samples, specific regulations exist regarding the shipment of biologic/etiologic samples. Procedures and regulations for the packaging and shipping of infectious samples are outlined in the study procedures manual or other appropriate reference.

The Investigator is responsible for ensuring that all study samples that are to be transported to another location are packed and shipped appropriately according to the applicable regulations.

10.3.2.1.3 Evaluation of Clinical Laboratory Values

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

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

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

All measurements described in this section are recognized standard methods.

10.3.2.2 Clinical Examinations

10.3.2.2.1 Vital Signs

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

10.3.2.2.2 Twelve-lead Electrocardiogram

A standard 12-lead ECG will be performed after the subject has been seated for at least 5 minutes. All ECG recordings will be identified with the subject number, initials, date, and time of the recording and will be attached to the subject's eCRF.

10.3.2.2.3 Physical Examination

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

10.3.2.2.4 Hamilton Depression Scale

The Hamilton Depression scale is a 17-item instrument that evaluates symptoms of expression experienced over the past week (see APPENDIX G). Items are scored on a variety of scales, including 3-, 4-, and 5-point questions. An overall score of 0 to 7 is generally accepted to be within the normal range, while a score of 20 or higher indicates at least moderate severity.

10.3.2.2.5 Columbia-Suicide Severity Rating Scale

The C-SSRS is a semi structured interview that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The interview includes

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

10.3.2.3 Adverse Events

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

11. ADVERSE EVENTS

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

11.1. Definitions

11.1.1 Adverse Events

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

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. (Worsening of a pre-existing condition is considered an AE.)

In this study, AEs will be classified by time of occurrence and Visit 3 group assignment to more clearly identify those arising after exposure to placebo only and those arising after exposure to PH94B.

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

11.1.2 Unexpected Adverse Event

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

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

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

11.1.3 Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- results in death

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

11.1.4 Significant Adverse Events

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

11.1.5 Treatment-emergent Adverse Events

Treatment-emergent AEs are defined as:

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

11.2. Event Assessment and Follow-up of Adverse Events

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

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

AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

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

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

The Investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 days after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

11.2.1 Assessment

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

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

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

11.2.2 Evaluation

11.2.2.1 Severity of Adverse Events

The clinical severity of an AE will be classified as:

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

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

11.2.2.2 Seriousness

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

11.2.2.3 Actions Taken

Actions taken may consist of:

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

11.2.2.4 Outcome at the Time of Last Observation

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

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved
- Fatal*
- Unknown

*Investigators should only select fatal as an outcome when the AE results in death. If more than 1 AE is judged to be possibly related to the subject's death, the outcome of death should be indicated for each such AE. Although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

11.2.2.5 Adverse Event Relationship to Investigational Product

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

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

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

11.2.3 Documentation

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

- AE name or term
- When the AE first occurred (start date and time)

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

11.2.4 Treatment of Adverse Events

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

If AEs occur in a subject that are not tolerable, the investigator must decide whether to stop the subject's involvement in the study and/or treat the subject. Special procedures may be recommended for the specific IP, such as the collection of a serum sample for determining blood concentrations of IP, specific tapering procedures, or treatment regimens, as appropriate.

For double-blinded studies, it is not necessary to unblind a subject's treatment assignment in most circumstances, even if an SAE has occurred. If unblinding is necessary, see Section 9.6 for a description of the unblinding procedures.

11.2.5 Follow-up

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

11.2.6 Reporting

11.2.6.1 Serious Adverse Events

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

Email: PVDS-NA@premier-research.com

Fax number (back-up): +1 215 972 8765

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

- Protocol number
- Reporter (study site and investigator)
- Subject's study number
- Subject's date of birth
- Subject's gender
- Date of first dose of IP
- Date of last dose of IP, if applicable
- Adverse event term
- Date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria(on) that were met
- Concomitant medication at onset of the event
- Relevant medical history information
- Relevant laboratory test findings
- Investigator's opinion of the relationship to IP ("Is there a reasonable possibility that the IP caused the SAE? Yes or No?")
- Whether and when the investigator was unblinded as to the subject's treatment assignment

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

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

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

11.2.6.2 Nonserious Adverse Events

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

11.3. Special Considerations

11.3.1 Pregnancy

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

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

A woman who becomes pregnant during IP treatment or within 7 days of discontinuing the IP will be immediately discontinued from study participation. The investigator must report the pregnancy within 48 hours of learning of the pregnancy, to Premier Research Pharmacovigilance using the Pregnancy Data Collection Form via the same fax number and/or email address as for SAE reporting. The investigator should contact the designated individual(s) who receive SAE notification and record information related to the pregnancy on an Exposure in Utero form provided by the sponsor or its designee.

Early Termination Visit assessments are required as soon as possible after learning of the pregnancy. The investigator is also responsible for following the pregnancy until delivery or termination. These findings must be reported on the Exposure in Utero form and forwarded to the designated individual(s). The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly.

11.3.2 Overdose

The maximal dose of PH94B should not be exceeded during the study. Overdose that occurs during the study will be treated and documented as an AE/UAE/SAE if it fulfills the criteria. The information contained therein should include study site identification, reporter identification, subject identification, IP, dose, action taken (e.g., supportive measures or therapy), and any comments. If the overdose does not result in an AE, it should be reported in the eCRF.

12. DATA SAFETY MONITORING BOARD

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

13. STATISTICS

13.1. Statistical Analysis

This section presents a summary of the planned statistical analyses.

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

Unless otherwise indicated, all testing of statistical significance will be 2-sided, and a difference resulting in a p value of < 0.05 will be considered statistically significant.

For analyses involving study site, if the number of subjects per site is small, sites may be pooled for analysis (see Section 13.1.4.2). The final determination will be made prior to database lock.

The data will be summarized in tables, as appropriate, showing the number of subjects with non-missing data (n), mean, standard deviation (SD), 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.

13.1.1 Analysis Populations

The following 2 analysis populations are planned for this study:

- Intent-to-treat (ITT): The Intent-to-Treat Population in the Study includes all subjects who are randomized
- Safety: All subjects who receive IP

Inclusion in the analysis populations will be determined prior to database lock.

If a subject is randomized incorrectly or is administered the incorrect IP, analyses of the ITT population will be based on the assigned treatment whereas all other analyses will be based on the actual treatment.

13.1.2 Study Subjects and Demographics

13.1.2.1 Disposition and Withdrawals

The numbers of subjects randomized, completing, and withdrawing, along with reasons for withdrawal, will be tabulated overall and by treatment group. The number of subjects in each analysis population will be reported.

13.1.2.2 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

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

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

13.1.2.3 Demographics and Other Baseline Characteristics

These analyses will be conducted for all analysis populations.

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

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

13.1.3 Exposure and Compliance

Investigational product administration will be summarized in terms of number of doses received (PH94B and placebo). Descriptive statistics for categorical data will be provided by treatment group.

13.1.4 Efficacy Analysis

Efficacy variables will be summarized and analyzed using the ITT population, unless otherwise specified.

13.1.4.1 Efficacy Endpoints

Primary Endpoint

The primary endpoint for the study is the difference in average SUDS score during the [redacted] Visit 3 public speaking challenge versus the average SUDS scores during the [redacted] Visit 2 public speaking challenge for PH94B compared to placebo.

For each subject at each public speaking challenge, average SUDS scores will be calculated from SUDS scores recorded at 1-minute intervals during each performance. Change from Visit 2 to Visit 3 in average SUDS scores between PH94B- and placebo-treated subjects will be used.

Secondary Endpoint

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

Exploratory Endpoints

The exploratory efficacy endpoints are as follows:

- Difference between proportions of PH94B- and placebo-treated groups in PGI-C scores of 1 [redacted] or 2 [redacted] recorded at the end of Visit 3 (Treatment)
- [redacted]
- [redacted]
- [redacted]
- Proportion of subjects in each treatment group with 20-point improvement in SUDS scores from Visit 2 (Baseline) at Visit 3 (Treatment)
- [redacted]

13.1.4.2 Primary Analysis

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 the [redacted] Visit 2 public speaking challenge for PH94B compared to placebo.

[redacted] Change from Visit 2 (Baseline) to Visit 3 (Treatment) in average SUDS scores between PH94B- and placebo-treated subjects will be used.

An analysis of covariance (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.

13.1.4.3 Secondary Analyses

The secondary efficacy endpoint in the study is the difference between proportions of PH94B- and placebo-treated groups in CGI-I scores of 1 [redacted] or 2 [redacted] at the end of Visit 3 (Treatment).

This secondary endpoint will be analyzed using a normal approximation test for the difference between 2 binomial proportions. The null hypothesis to be tested is that the population proportions are equal.

13.1.4.4 Exploratory Analyses

A by-group comparison of the proportions of PH94B- and placebo-treated groups in PGI-C scores of 1 [redacted] or 2 [redacted] recorded at the end of Visit 3 (Treatment) will be conducted.

[redacted]

A by-group comparison of responder rates (proportion of subjects with 20-point improvement in SUDS scores at Visit 3 [Treatment]) will be conducted.

A by-group comparison of the change in SUDS scores between Visit 2 (Baseline) and Visit 3 [redacted]

13.1.4.5 [redacted]

[redacted]

13.1.4.6 Estimand Framework and Sensitivity Analyses

13.1.4.6.1 Primary Estimand

The treatment of interest is PH94B, 3.2 µg administered as an i.n. solution (a 1.6-µg spray to each nostril per dose). The population of interest is adult patients with SAD as defined by the protocol inclusion and exclusion criteria (Section 8.2). [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.

Mapping of endpoints to study objectives is presented in Section 6.4.

13.1.4.6.2 Secondary Estimand

The treatment of interest is PH94B, 3.2 µg administered as an i.n. solution (a 1.6-µg spray to each nostril per dose). The population of interest is adult patients with SAD as defined by the protocol inclusion and exclusion criteria (Section 8.2). 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 (Very much less anxious) or 2 (Much less anxious) for PH94B will be compared to placebo using a comparison of binomial proportions.

13.1.4.6.3 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.

13.1.4.6.4 Missing Data and Imputation

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

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 methods and sensitivity analyses will be applied. Details on the treatment of missing data will be described in the final Statistical Analysis Plan.

13.1.5 Safety and Tolerability Analyses

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 Events (Table 2-1). Details of clinical laboratory tests are provided in Section 10.3.2.1.1.

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

Safety analyses will be conducted using data from the safety population (as defined in Section 13.1.1).

13.1.5.1 Adverse Events

All AEs will be coded using the most recent version of MedDRA.

Treatment-emergent AEs are defined as:

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

Adverse events will be classified by time of occurrence and Visit 3 group assignment to more clearly identify those arising after exposure to placebo only and those arising after exposure to PH94B.

The number and percentage of subjects with AEs will be displayed for each treatment group by system organ class and preferred term. Summaries of AEs by severity and relationship to IP will also be provided. Serious adverse events and AEs resulting in discontinuation of IP will be summarized separately in a similar manner. Subject listings of AEs, SAEs, and AEs causing discontinuation of IP will be produced.

13.1.5.2 Clinical Laboratory Evaluations

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

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

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

13.1.5.3 Vital Signs

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

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

13.1.5.4 Twelve-lead Electrocardiograms

The number and percentage of subjects with normal and abnormal ECG findings will be summarized for each treatment group at each time point. Abnormal results will be grouped as clinically significant and not clinically significant.

A comparison of QT results will be presented. Summary statistics for baseline values at Screening, and at Visit 4 (Follow-up) will be displayed by treatment group for QT and the QT interval corrected for heart rate (QTc). In addition, the number and percent of subjects in each treatment group who experienced a change >30 ms or a change >60 ms will be presented.

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

13.1.5.5 Physical Examination Findings

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

13.1.5.6 Hamilton Depression Scale

Results of HAM-D evaluations will be summarized with descriptive statistics, by treatment group and overall, for each assessment.

13.1.5.7 Columbia-Suicide Severity Rating Scale

The number and percentage of subjects reporting "Yes" for any of the 5 suicidal ideation questions (Categories 1 to 5) or any of the 5 suicidal behavior questions (Categories 6 to 10) will be displayed for each treatment group, along with the number and percentage reporting suicidal ideation OR behavior (Categories 1 to 10).

Treatment-emergent suicidal ideation and behavior (an increase in maximum score during treatment) will also be presented.

13.1.6 Interim Analysis

An interim analysis will be conducted using all SUDS data from the first 140 subjects who complete Visit 3, with the goal to assess the study for futility, and if warranted, to provide a sample size re-estimation. To maintain integrity of this double-blind study, an independent, unblinded, external statistician will evaluate conditional power and communicate only one of the following recommendations to VistaGen:

1. the study may be stopped due to futility,
2. the study can continue with no change, or
3. the sample size is recommended to increase

The sponsor and all study staff will remain blinded, and only the independent biostatistician will have access to unblinded study data. Details of the interim analysis will be provided in an independent interim statistical analysis plan.

[redacted]

[redacted]

13.2. [redacted]

[redacted]

14. STUDY CONDUCT

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

14.1. Sponsor and Investigator Responsibilities

14.1.1 Sponsor Responsibilities

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

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

14.1.2 Investigator Responsibilities

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

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

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

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

14.1.3 Confidentiality and Privacy

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

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

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

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

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

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

14.2. Site Initiation

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

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

14.3. Screen Failures

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

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

14.4. Study Documents

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

14.4.1 Informed Consent

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

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

14.4.2 Investigator's Regulatory Documents

The regulatory documents are listed in the Premier Research study plans.

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

14.4.3 Case Report Forms

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

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

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

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

14.4.4 Source Documents

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

14.5. Data Quality Control

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

14.5.1 Monitoring Procedures

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

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

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

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

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

14.5.2 Data Management

VistaGen Therapeutics, Inc. or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and Premier Research's standard operating procedures. A comprehensive data

management plan will be developed, including a data management overview, description of database contents, annotated eCRF, and consistency checks.

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

14.5.3 Quality Assurance/Audit

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

- site audits
- Trial Master File audits
- database audits
- document audits (e.g., protocol and/or clinical study report [CSR])

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

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

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

14.6. Study Termination

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

14.6.1 Premature Study Termination

The study may be temporarily suspended or terminated prematurely is there is sufficient reasonable cause at any time by VistaGen Therapeutics, Inc., IRBs, regulatory authorities, respective steering committees, or the coordinating investigator.

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

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

- Determination of unexpected, significant, or unacceptable risk to subjects

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

Study sites may be asked to have all subjects currently participating in the study complete all of the assessments for the Follow-up Visit (Visit 4).

The Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

14.7. Study Site Closure

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

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

14.7.1 Record Retention

The investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including, but not limited to, those defined by GCP as essential until:

- At least 2 years after the last marketing authorization for the IP has been approved or the sponsor has discontinued its research with the IP, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of the IP.

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

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

14.7.2 Sample Retention

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

14.8. Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of VistaGen Therapeutics, Inc. The protocol amendment must be signed by the investigator and approved by the IRB before it may be implemented. Protocol

amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

14.9. Use of Information and Publication

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

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

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

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

15. FINAL CLINICAL STUDY REPORT

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

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

The final CSR may be submitted to the regulatory authorities.

16. ETHICAL AND LEGAL CONSIDERATIONS

16.1. Good Clinical Practice

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

16.2. Subject Information and Informed Consent

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

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

16.3. Approval by Institutional Review Board

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

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

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

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

16.4. Finance and Insurance

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

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18. ATTACHMENTS

18.1. Investigator's Agreement

PROTOCOL NUMBER:	PH94B-CL032
PROTOCOL TITLE:	A US, 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-2)
FINAL PROTOCOL:	02-Aug-2021
AMENDMENT 1:	25-Aug-2021
AMENDMENT 2:	25-Jan-2022
AMENDMENT 3:	12-Aug-2022

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

Principal Investigator:

Printed Name:

_____

Signature:

_____

Date:

_____

APPENDICES

A. Subjective Unit of Distress Scale
B. [redacted]
C. [redacted]
D. Liebowitz Social Anxiety Scale
E. [redacted]
F. [redacted]
G. Hamilton Depression Rating Scale
[redacted]
I. Clinical Global Impression of Improvement
J. Regulations and Good Clinical Practice Guidelines

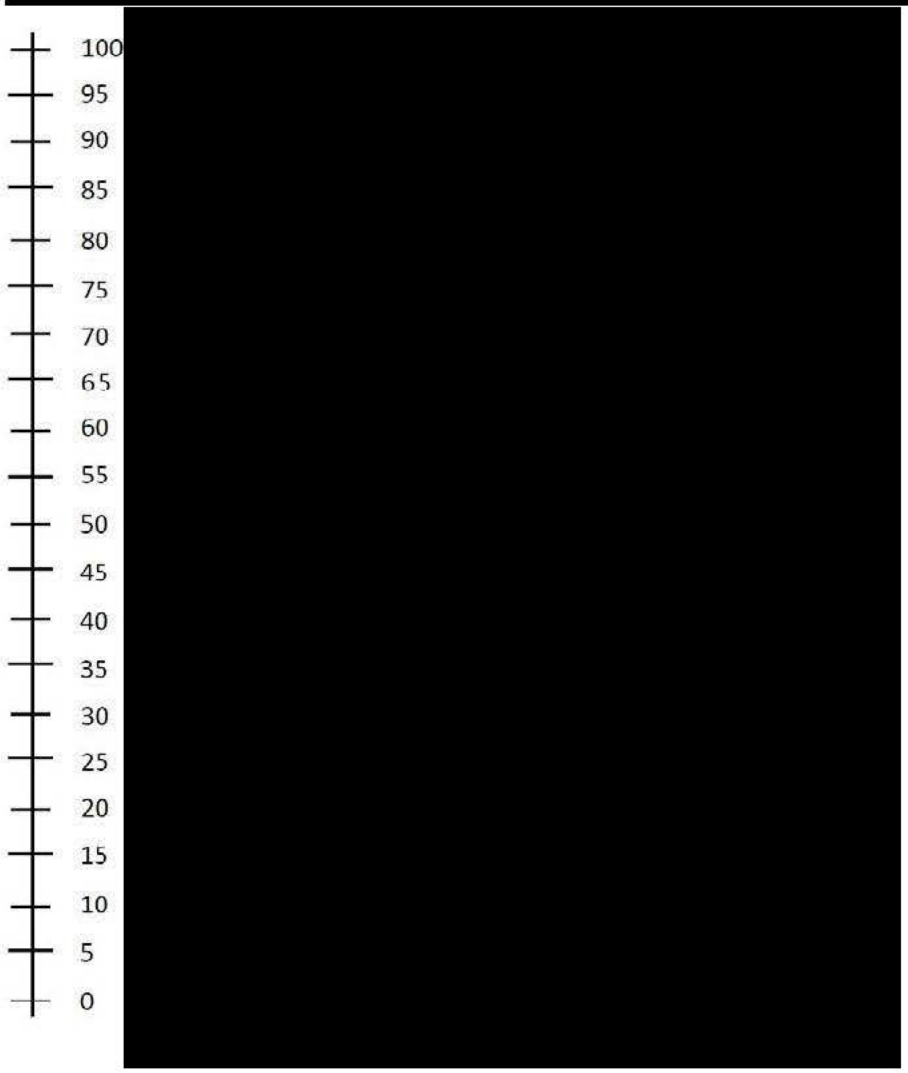
A. Subjective Units of Distress Scale

SUBJECTIVE UNITS OF DISTRESS SCALE

Subjective Units of Distress Scale (SUDS) Thermometer

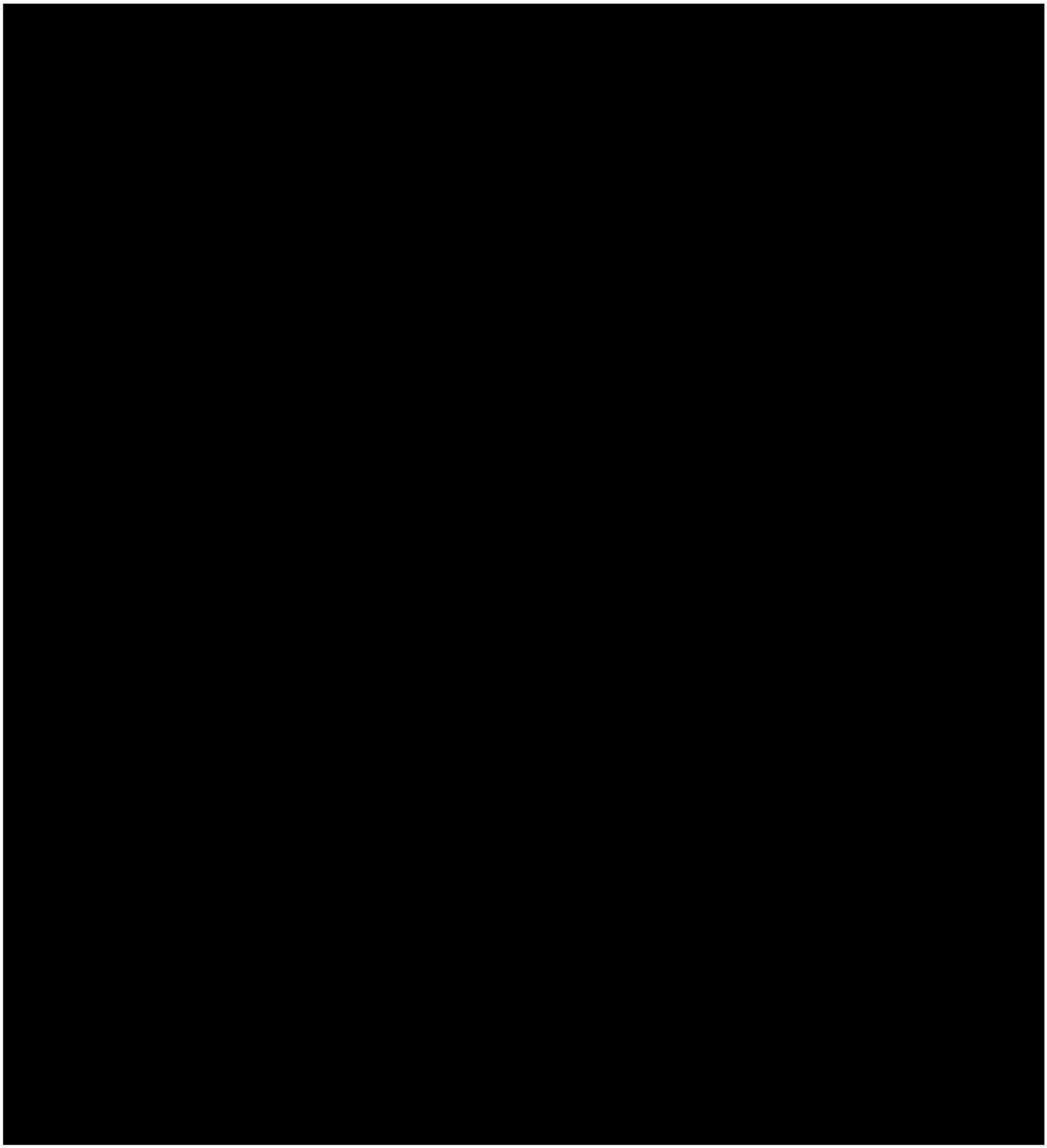
Using the Subjective Units of Distress Scale (also called the SUDS), you can record how anxious you feel in different situations by picking a number between 0 and 100; zero would mean totally relaxed or no anxiety and 100 is the most distress or anxiety imaginable.

[redacted]



B. [redacted]

[redacted]



C. [redacted]

[redacted]

D. Liebowitz Social Anxiety Scale

VistaGen Therapeutics

PALISADE-2 CLINICAL TRIAL

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

Source Document: Protocol PH94B-CL032

Liebowitz Social Anxiety Scale (LSAS)

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

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

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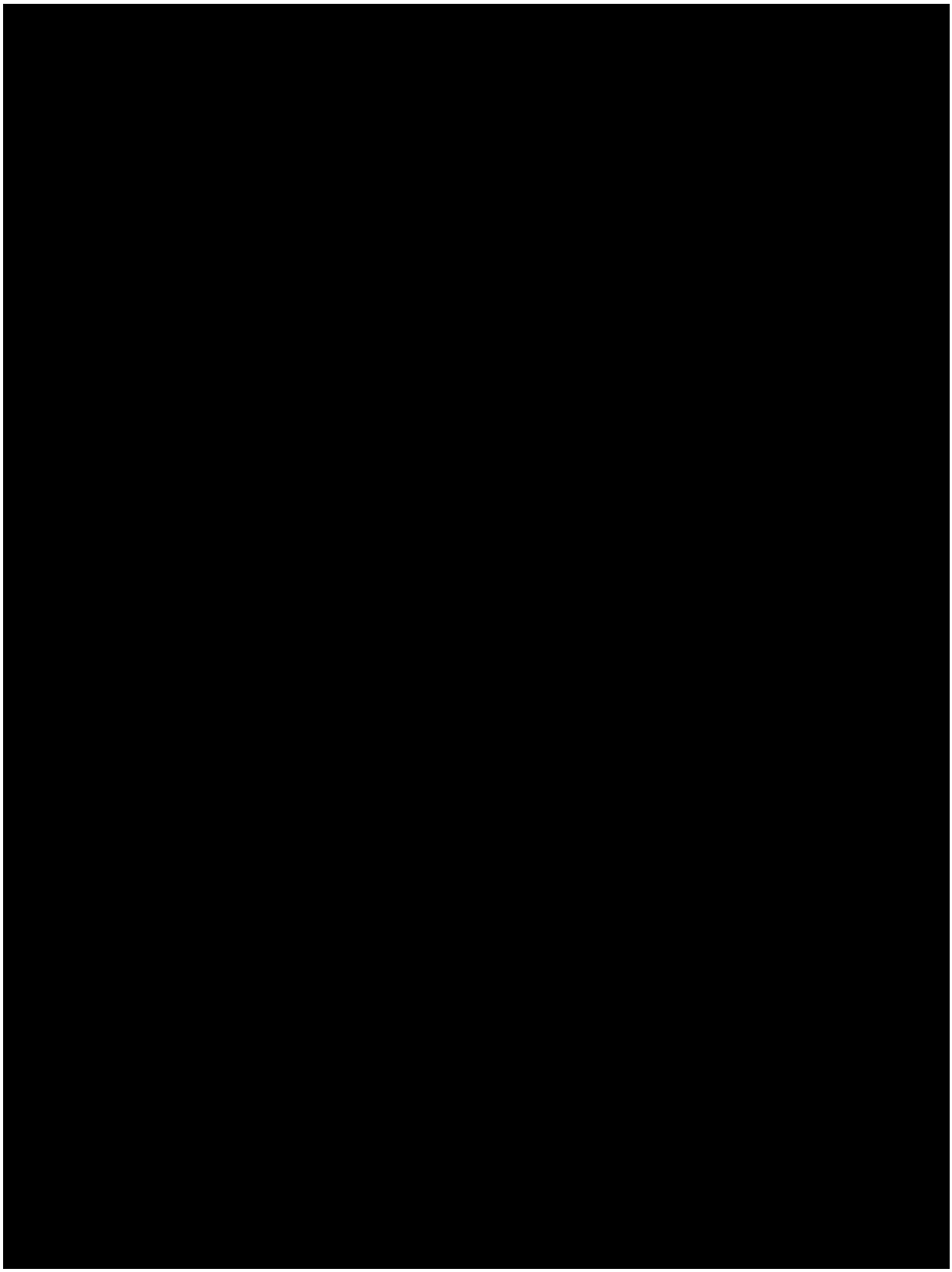
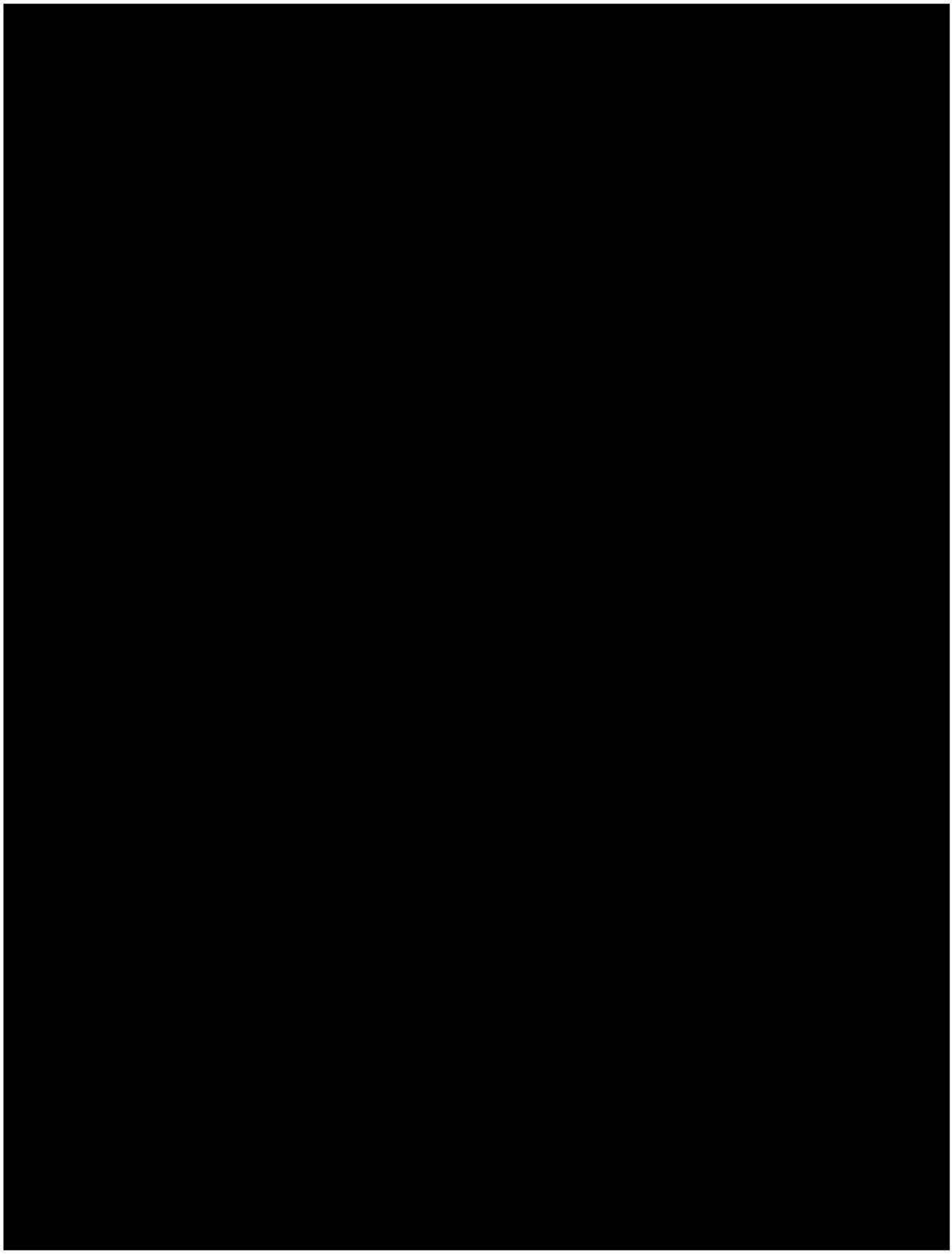
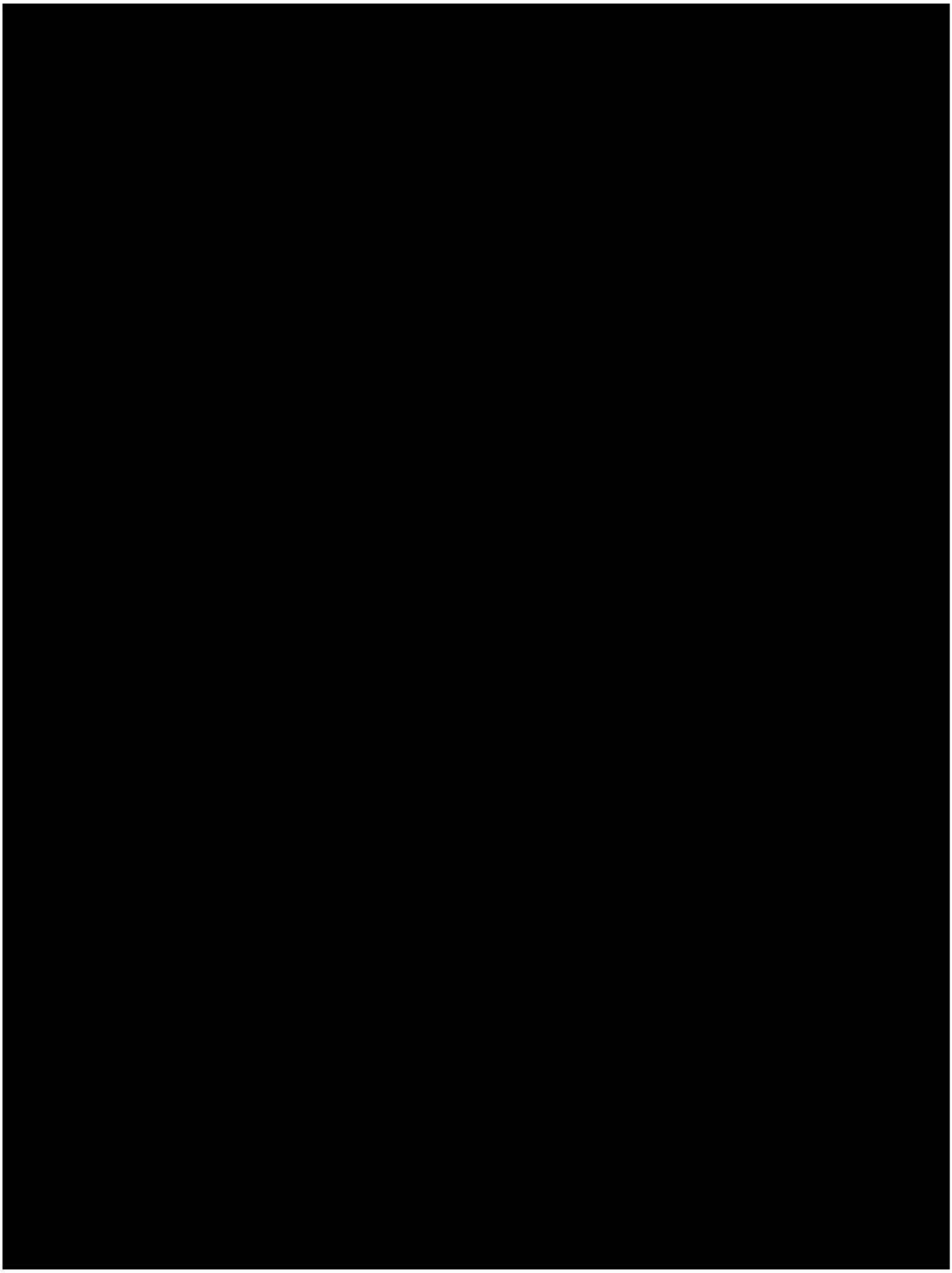
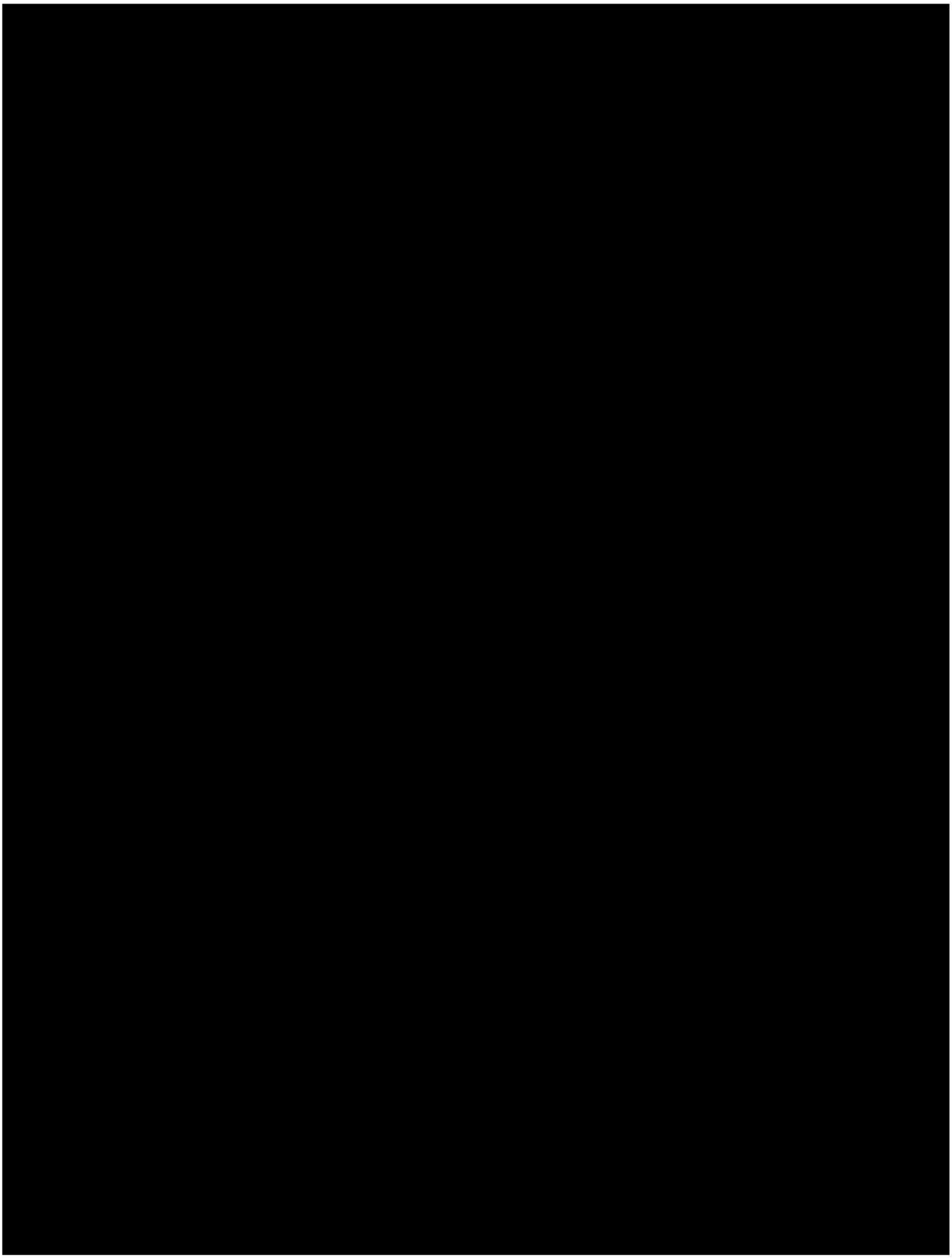
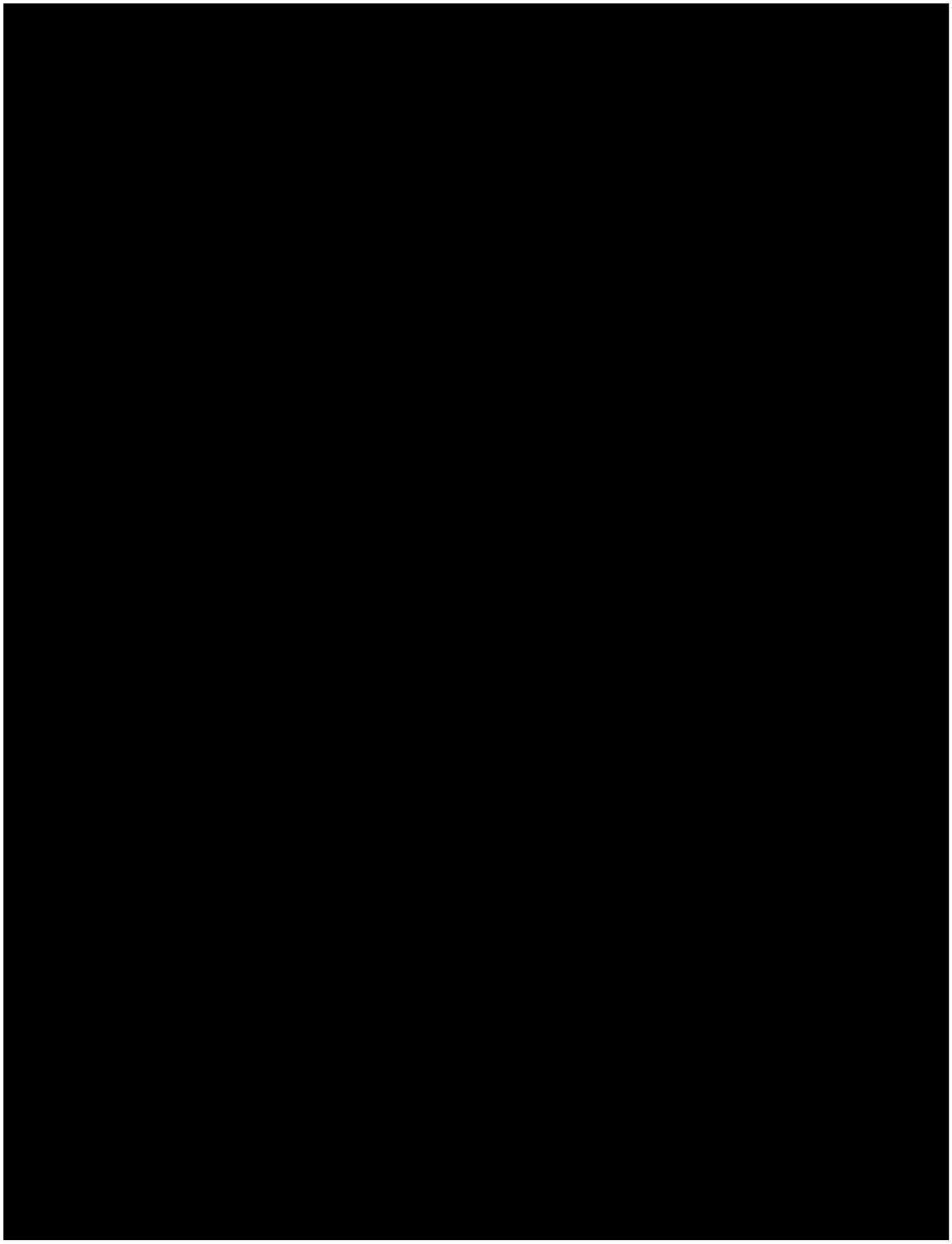
E. [redacted] Type text here











F. [redacted]

[redacted]

G. Hamilton Depression Scale

VistaGen® Therapeutics

PALISADE-2 CLINICAL TRIAL

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

Source Document: Protocol PH94B-CL032

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:** _____/_____/_____

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VistaGen® Therapeutics

PALISADE-2 CLINICAL TRIAL

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

Source Document: Protocol PH94B-CL032

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:** ____/____/____

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VistaGen Therapeutics

PALISADE-2 CLINICAL TRIAL

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

Source Document: Protocol PH94B-CL032

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:** _____/_____/_____

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

Source Document: Protocol PH94B-CL032

Hamilton Depression Rating Scale (HAM-D)

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

17. **INSIGHT**
    - ❑ 0 Acknowledges being depressed and ill.
    - ❑ 1 Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
    - ❑ 2 Denies being ill at all.

Total (17 Items):

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

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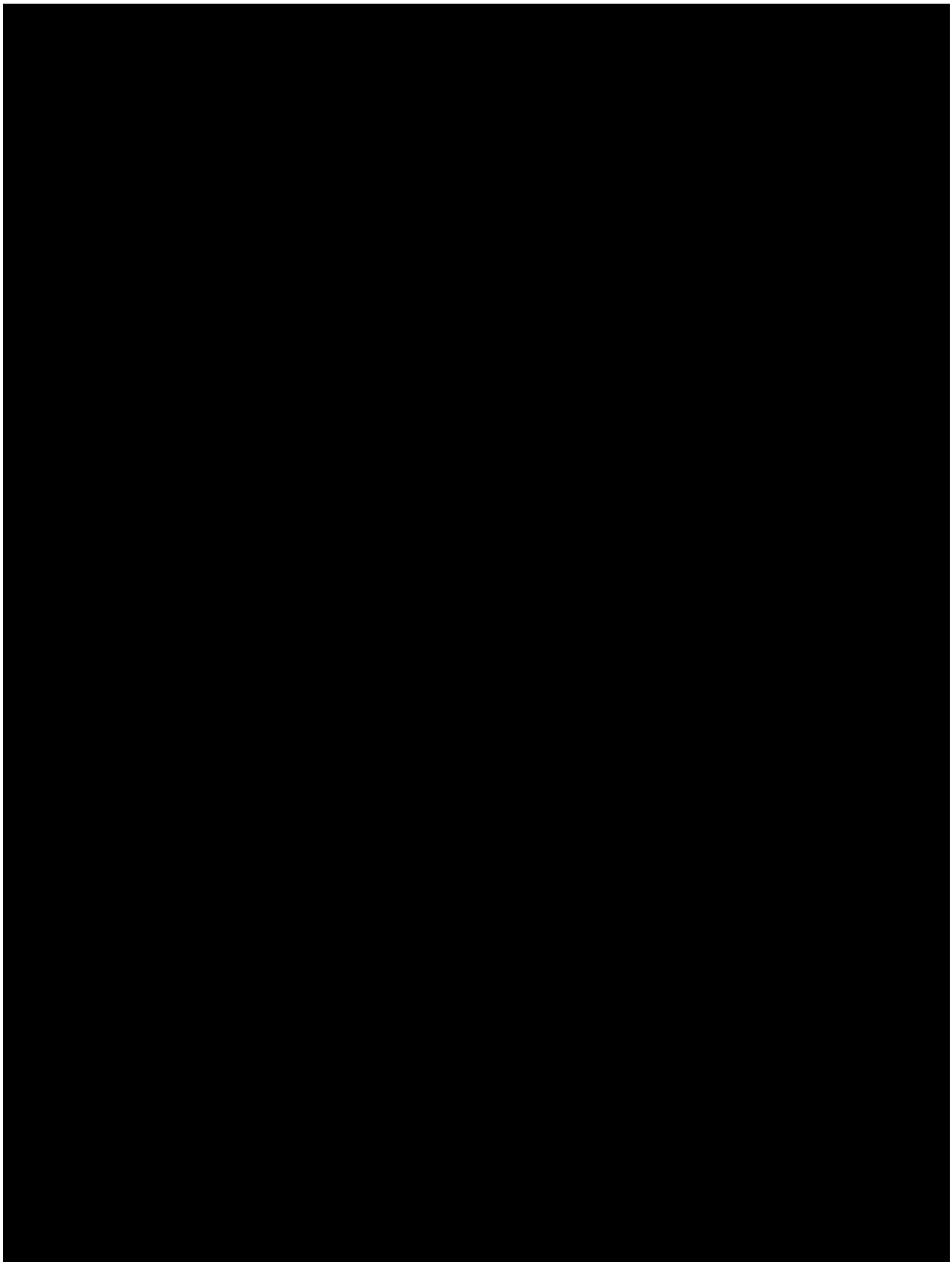

I. Clinical Global Impression of Improvement

VistaGen Therapeutics

PALISADE-2 CLINICAL TRIAL

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

Source Document: Protocol PH94B-CL032

Clinical Global Impression (CGI) Improvement Scale

[redacted]

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

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J. Regulations and Good Clinical Practice Guidelines

1. Regulations

Refer to the following United States Code of Federal Regulations (CFR):

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

2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URLs:

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

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