PROTOCOL

PRODUCT NAME/NUMBER:	PH94B Nasal Spray
PROTOCOL NUMBER:	PH94B-CL029
[redacted]	[redacted]
NCT NUMBER:	NCT04404192
DEVELOPMENT PHASE:	2a
PROTOCOL TITLE:	A Phase 2a Double-blind, Placebo-controlled, Parallel Study of PH94B Nasal Spray in the Treatment of Anxiety in Adults with Adjustment Disorder with Anxiety
PROTOCOL DATE:	Final, Version 2.0, 30-Aug-2021
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-CL029

PROTOCOL TITLE: A Phase 2a Double-blind, Placebo-controlled, Parallel Study of PH94B Nasal Spray in the Treatment of Anxiety in Adults with Adjustment Disorder with Anxiety

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

SIGNATURE **DATE:**

[redacted]

[redacted]

[redacted]

[redacted]

Sponsor:	VistaGen Therapeutics, Inc., a Nevada corporation (VistaGen) 343 Allerton Avenue South San Francisco, CA 94080
Sponsor Contact:	[redacted] VistaGen Therapeutics, Inc. [redacted]
Medical Monitor:	[redacted] VistaGen Therapeutics, Inc [redacted]

2. PROTOCOL SUMMARY

2.1. Synopsis

PRODUCT NAME/NUMBER	PH94B Nasal Spray
PROTOCOL NUMBER	PH94B-CL029
DEVELOPMENT PHASE	2a
PROTOCOL TITLE	A Phase 2a Double-blind, Placebo-controlled, Parallel Study of PH94B Nasal Spray in the Treatment of Anxiety in Adults with Adjustment Disorder with Anxiety
INDICATION	Adjustment disorder with anxiety
OBJECTIVES	Primary: The primary objective of the study is to evaluate the efficacy of PH94B Nasal Spray (PH94B) administered 4 times per day over 4 weeks for the treatment of anxiety in adult subjects with adjustment disorder with anxiety (AjDA). Secondary: The secondary objective of the study is to evaluate the safety and tolerability of PH94B. Exploratory: The exploratory objective of the study is to evaluate efficacy of PH94B over time during the 4-week treatment period.
RATIONALE	The study is designed to evaluate the safety, tolerability, and efficacy of the administration of PH94B as a treatment for anxiety in adults with AjDA.
STUDY DESIGN	This is a Phase 2a double-blind, placebo-controlled, parallel group clinical study in adult subjects diagnosed with AjDA. Subjects diagnosed with AjDA by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria and have a clinician-rated Hamilton Anxiety Scale (HAM-A) score of 20 or greater are to be enrolled. Experimental procedures: Subject participation in the study will last a total of 6 to 10 weeks, depending on the duration of the screening period and whether they need a washout of concomitant anxiolytics. Upon signing an investigation review board approved informed consent, all subjects will complete Visit 1 (Screening) and enter a screening period lasting 7 to 35 days that could include tapering of concomitant anxiolytics, if necessary. Screening (Visit 1) will consist of safety assessments (medical history, physical examination, laboratory tests [chemistry and blood], electrocardiogram [ECG], urine drug screen, and urine pregnancy test [if appropriate]) and psychiatric assessments (Mini-International Neuropsychiatric Interview [MINI], HAM-A, Montgomery-Asberg Depression Rating Scale [MADRS], Clinical Global Impression - Severity Scale [CGI-S], Columbia-Suicide Severity Rating Scale [C-SSRS], and Liebowitz Social Anxiety Scale [LSAS]) to determine eligibility. Subjects will then return to complete Visit 2 (Baseline). At this visit, subjects will complete all psychiatric assessments (HAM-A, MADRS, C-SSRS, Adjustment Disorder New Module Scale [ADNM], International Adjustment Disorder Questionnaire [IADQ], and CGI-S), vital signs, laboratory tests (chemistry and blood), urine drug screen, and urine pregnancy test (if appropriate). If the subject continues to meet the inclusion criteria and none of the exclusion criteria, the subject will be randomized 1:1 to PH94B or placebo. The subject will be trained on using the

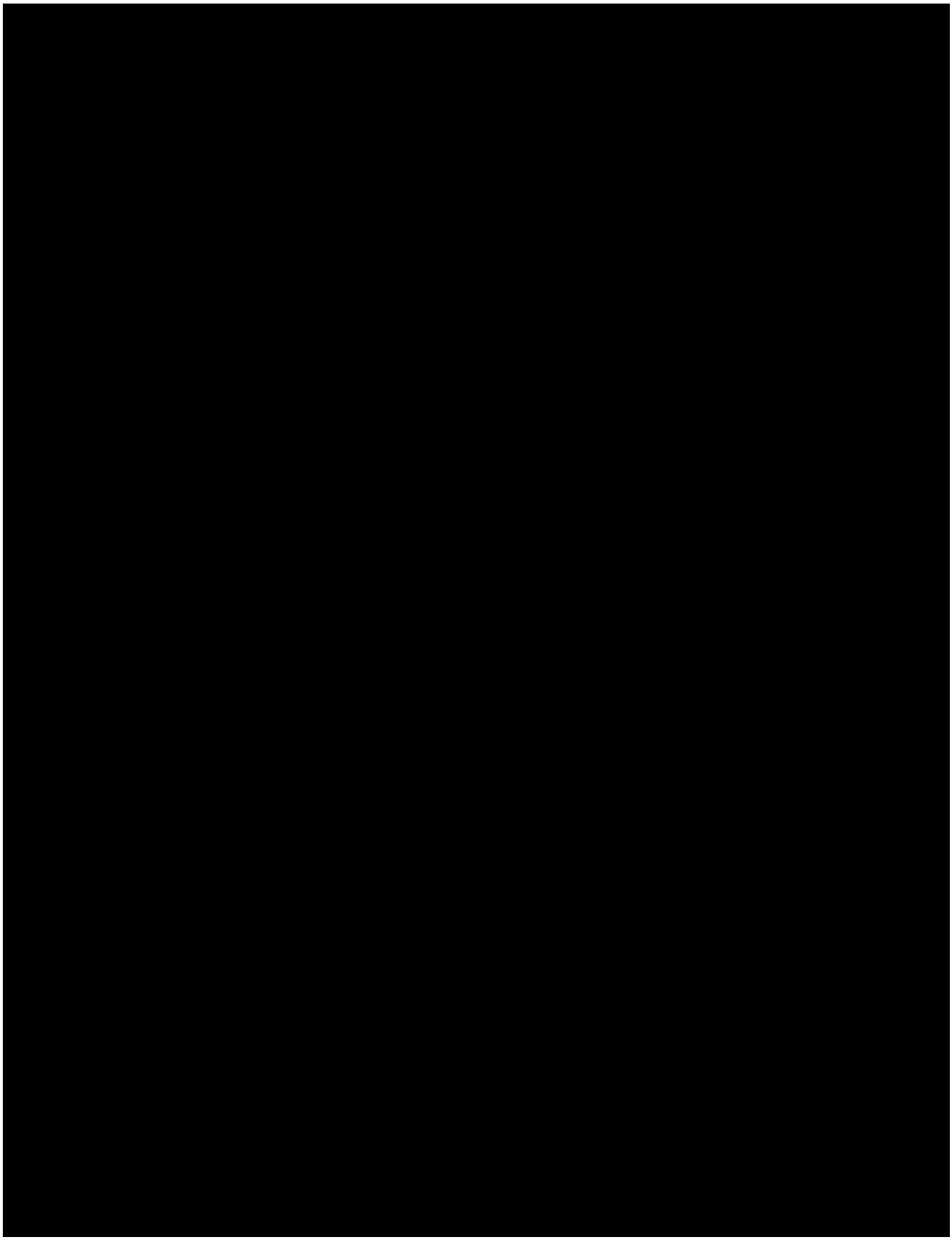
	investigational product (IP) and will be dispensed a 1-week supply of PH94B or placebo. Subjects will then commence 4 weeks of double-blind treatment with the randomized IP 4 times per day. Subjects will return for weekly site visits (Visits 3, 4, and 5), in which the subject will return the IP vials dispensed at the previous visit and receive new vials. Concomitant medications and adverse events (AEs) will be recorded. During these visits, the HAM-A, Patient Global Impression of Change (PGI-C), Clinical Global Impression - Improvement (CGI-I), CGI-S, and C-SSRS will be completed. Vital signs will be collected, and nasal passages will be examined. When the subject returns for Visit 6, besides the assessments completed at Visits 3 through 5, the subjects will complete the MADRS, ADNM, and IADQ; and have a physical examination, ECG, laboratory tests (chemistry and blood), urinalysis, urine drug screen, and urine pregnancy test conducted. Any remaining IP vials will be collected. The subject will then come back after a 1-week washout period for the Follow-up visit (Visit 7). During this visit, AEs and concomitant medications since the last visit will be collected and the HAM-A, C-SSRS, and the 20-item Physician Withdrawal Checklist (PWC-20) will be completed. For each visit following Baseline (Visit 2), a ± 2-day window will be allowed. Safety considerations: Safety and tolerability of PH94B will be assessed and summarized through changes from screening in clinical laboratory values, ECGs, physical examinations, and vital sign assessments following exposure to PH94B, as well as by comparison of AEs reported during treatment with the IP. To date, limited exposure to PH94B (<2 weeks, <4 doses per day) in over 200 subjects has resulted in no serious AEs (SAEs) and no AEs occurring with statistically greater frequency for the PH94B group than for the placebo group. In addition, the PWC-20 will be administered to document any withdrawal effects that may be occurring.
PLANNED NUMBER OF SUBJECTS	Forty adult subjects will be randomized 1:1 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 years of age. 3. Current diagnosis of AjDA as defined in the DSM-5. 4. Clinician-rated HAM-A score ≥20 at Screening (Visit 1) and no greater than 15% decrease at Baseline (Visit 2). 5. Clinician-rated MADRS total score <20 at Screening (Visit 1) and Baseline (Visit 2). 6. Clinical Global Impression - Severity Scale (CGI-S) score ≥4 at Screening (Visit 1) and Baseline (Visit 2). 7. 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. 8. Males whose sexual partners are women of childbearing potential must commit to the consistent and correct use of an effective method of birth control throughout the study.

	9. Negative COVID-19 test for subjects with COVID-19 symptoms or who have had direct exposure to someone with a positive COVID-19 test, as determined by the Investigator. Exclusion criteria: 1. Any history of schizophrenia or schizoaffective disorder. 2. Any other current Axis I disorder, including, but not limited to, major depressive disorder, bipolar disorder, post-traumatic stress disorder, obsessive-compulsive disorder, premenstrual dysphoric disorder, and generalized anxiety disorder, which is in poor control and the primary focus of treatment. 3. A diagnosis of social anxiety disorder. 4. A score >60 on the LSAS at Screening (Visit 1). 5. Subjects who meet criteria for moderate or severe alcohol or substance use disorder within 1 year prior to study entry. 6. In the opinion of the Investigator, the subject has a significant risk for suicidal behavior during their participation in the study, or a. At Screening (Visit 1): the subject scores "yes" on items 4 or 5 in the Suicidal Ideation section of the Columbia-Suicide Rating Scale (C-SSRS) with reference to a 6-month period prior to screening; or b. At Screening (Visit 1): the subject has had one or more suicidal attempts with reference to a 2 -year period prior to screening; or c. At Baseline (Visit 2): the subject scores "yes" on items 4 or 5 in the Suicidal Ideation section of the C-SSRS with reference to screening; or d. The subject is considered to be an imminent danger to themselves or others. 7. 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. 8. 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. The Investigator may allow concomitant use of over-the-counter nasal decongestants as needed, since there is no apparent drug interaction between these and PH94B. 9. Concomitant use of any anxiolytics, such as benzodiazepines, buspirone, or cannabinoids during the study and within 30 days of Baseline (Visit 2). 10. Concomitant use of any over-the-counter, prescription product, or herbal preparation for treatment of the symptoms of anxiety during the study and within 30 days before study entry. Selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, or other approved antidepressants are permitted if the dose has been stable for 30 days prior to Baseline (Visit 2). 11. Women who have a positive urine pregnancy test prior to IP administration or are currently breast feeding. 12. Subjects with clinically significant abnormalities in hematology, blood chemistry, urinalysis, ECG, or physical examination identified at the Screening 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). 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. Use of a concomitant medication 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. 16. 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 [redacted], 4 times per day separated by at least 2 hours (target morning, noon, early evening, and bedtime).
CONTROL PRODUCT	Name: Placebo Dose, route, frequency: placebo as an i.n. solution administered as 1 spray to each nostril per dose, 4 times per day separated by at least 2 hours (target morning, noon, early evening, and bedtime).
TREATMENT REGIMENS	Treatment will be administered 4 times per day from Visit 2 (Baseline) to Visit 6 (End of Treatment). [redacted]
PRINCIPAL INVESTIGATOR	[redacted]
PLANNED STUDY SITES	It is projected that up to 2 centers will participate.
CRITERIA FOR EVALUATION	<u>Efficacy endpoints</u>: Primary efficacy endpoint: • Change from baseline in anxiety level as measured by the HAM-A at the end of the 4-week treatment period. Secondary efficacy endpoints: • Individual subject improvement as assessed by the CGI-I. Values for comparison will be the proportion of "responders" in each group, defined as subjects receiving scores of 1 (Very much improved) or 2 (Much improved) at the end of treatment. • Individual subject improvement as assessed by the subject's self-assessment of improvement (by PGI-C) at the end of treatment compared to baseline. Values for comparison will be the proportion of "responders" in each group, defined as subjects receiving scores of 1 (Very much improved) or 2 (Much improved) at the end of treatment. • Individual subject improvement on the ADNM scale at the end of treatment compared to baseline. • Individual subject improvement on the IADQ at the end of treatment compared to baseline. Exploratory efficacy endpoints: • Summaries and changes from baseline in HAM-A at Weeks 1, 2, and 3. • Summaries and changes from baseline in ADNM subscales at Week 4. • Summaries of CGI-I and PGI-C at Weeks 1, 2, 3, and 4 (each week).

	Safety endpoints: • Incidence and severity of AEs, AEs leading to discontinuation, and SAEs. • Changes in clinical laboratory (hematology, chemistry, and urinalysis) values. • Changes in 12-lead ECG results. • Changes in physical examination findings. • Changes in vital signs results. • Changes in MADRS scores. • Changes in suicidal ideation scores.
STATISTICAL METHODS	Analysis Populations: Intent-to-treat (ITT) population: All subjects who are randomized and have documented one dose of IP at Visit 2 will be included in the ITT population. All efficacy analyses will be performed using the ITT population. Safety population: All subjects who are dispensed IP and reported administering at least one dose of IP will be included in the safety population. All safety analyses will be performed using the safety population. Efficacy Analyses: Primary Efficacy Analyses: An analysis of covariance model with treatment group as factor and baseline HAM-A as covariate will be used to test the null hypothesis that there is no difference between PH94B- and placebo-treated subjects in change from baseline to end of treatment in HAM-A scores. Secondary Efficacy Analyses: CGI-I and PGI-C at the end of treatment will be analyzed using a normal approximation test for the difference between 2 binomial proportions. The null hypothesis to be tested is that there is no difference between PH94B- and placebo-treated subjects. Change from baseline to Week 4 in ADNM total and in IADQ total score will be analyzed analogously to the primary endpoint. Safety Analyses: Descriptive statistics will be used to summarize safety and tolerability of PH94B (3.2 µg) as measured by reports of AEs and SAEs, changes in clinical laboratory values, ECGs, vital signs, and physical examinations, MADRS scores, as well as suicidal ideation (as documented using the C-SSRS), and withdrawal effects (PWC-20). Estimand Framework: The target of estimation to address the scientific question of interest (posed by the primary objective for this study): *In adults with AjDA, is the difference in mean change from baseline anxiety severity (as measured by HAM-A total score) greater for PH94B-treated subjects compared to placebo-treated subjects, after 4 weeks of treatment?* is defined by the following attributes: 1. Population: Adults with AjDA (as defined by inclusion and exclusion criteria) 2. Treatment: PH94B compared to placebo control 3. Variable of interest: Change in subject reported severity of anxiety as measured by the change from baseline in HAM-A total score using the Structured

	Interview Guide for the HAM-A (SIGH-A), after 4 weeks of randomized treatment with the study medication 4. Population-level summary measure: Difference in mean HAM-A total score between PH94B-treated and placebo-treated subjects after 4 weeks of treatment 5. Anticipated intercurrent event: Treatment discontinuation prior to the planned assessment time frame
SAMPLE SIZE DETERMINATION	A sample size of 40 subjects was selected based on information from published studies on treatments for adjustment disorder suggesting that a clinically meaningful effect size could be estimated using a sample size of 40.
STUDY AND TREATMENT DURATION	The sequence and maximum duration of the study periods will be as follows: 1. Screening and washout: [redacted] 2. Treatment period: From Visit 2 (Baseline) through Visit 6 (End of Treatment) 3. Follow-up period: Follow-up visit (Visit 7) conducted approximately 1 week after last treatment The maximum study duration for each subject is approximately 10 weeks. The maximum treatment duration for each subject is 4 weeks.



3. TABLE OF CONTENTS

3.1. List of In-Text Tables

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	EXPLANATION
ADNM	Adjustment Disorder New Module Scale
AE	adverse event
AjD	adjustment disorder
AjDA	adjustment disorder with anxiety symptoms
CFR	Code of Federal Regulations
CRA	clinical research associate
C-SSRS	Columbia-Suicide Severity Rating Scale
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression - Severity Scale
COVID-19	coronavirus disease 2019
ECG	electrocardiogram
EDC	electronic data capture
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAM-A	Hamilton Anxiety Scale
IADQ	International Adjustment Disorder Questionnaire
IB	investigator brochure
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
ID	identification
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
MADRS	Montgomery-Asberg Depression Rating Scale
MINI	Mini-International Neuropsychiatric Interview
PGI-C	Patient Global Impression of Change
PWC-20	Penn Physician Withdrawal Checklist
PH94B	PH94B Nasal Spray
SAD	social anxiety disorder

ABBREVIATION	EXPLANATION
SAE	serious adverse event
SAP	statistical analysis plan
SIGH-A	Structured Interview Guide for the HAM-A
SUDS	Subjective Units of Distress Scale
UAE	unexpected adverse event

5. INTRODUCTION

5.1. Background and Rationale

5.1.1 Adjustment Disorder

Adjustment disorder (AjD) refers to a maladaptive emotional and/or behavioral response to an identifiable stressor occurring within 3 months of the onset of the stressor as evidenced by one or both of the following: (1) marked distress that is out of proportion to the severity or intensity of the stressor, taking into account socially or culturally expected reactions; and/or (2) significant impairment or interference with a person's social, occupational or other important areas of daily functioning. Unlike post-traumatic stress disorder or acute stress disorder, which have clear criteria for what constitutes a traumatic event, adjustment disorder criteria do not specify any requirements for what may be regarded as a stressor giving rise to AjD. However, research has identified that identifiable stressor events may include both traumatic events, such as exposure to actual or threatened death or illness of a loved one, oneself or others (e.g., stress experienced by healthcare workers and first responders related to the coronavirus disease 2019 [COVID-19] pandemic), medical condition, as well as non-traumatic stressful events, such as interpersonal conflict, unemployment, and financial difficulties. Importantly the stress reaction can be so great in AjD that patients attempt suicide. Indeed, patients diagnosed with AjD have a 12-fold increased rate of suicide compared to controls.[1]

According to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), 6 subtypes of AjD feature symptoms of: (i) depressed mood; (ii) anxiety; (iii) mixed anxiety and depressed mood; (iv) disturbance of conduct; (v) mixed disturbance of emotions and conduct; and (vi) unspecified. Because PH94B has been shown to be safe in all clinical studies to date, to have significant clinical efficacy in treating anxiety in subjects with social anxiety disorder (SAD),[2,3] and because PH94B's antidepressant properties are as yet unknown, the present Phase 2a study will be focused on adjustment disorder with anxiety (AjDA).[4]

Current treatments for AjD include both psychosocial and pharmacological measures. Psychosocial treatments include exposure therapy and cognitive behavioral therapy. Pharmacological measures vary widely and include antidepressants (selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors), benzodiazepines, buspirone and natural products such as cannabidiol.[5] Interestingly, the non-benzodiazepine drug etifoxine has shown efficacy in AjD.[6] This may be relevant to the present study of PH94B because etifoxine is known to induce the synthesis of centrally active neurosteroids.[7]

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 access to the limbic system without a relay in the thalamus. Therefore, the limbic amygdala is the only brain structure that receives rapid afferent neural inputs from peripheral nasal chemosensory receptors.[8,9] 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,[10,11] and the development of anxiety and depression in humans with congenital anosmia.[12,13]

Stimulation of human olfactory chemosensory cells with primary odors produces olfactory awareness via the main olfactory neural circuits,[14,15] but in humans there are chemosensory cues that engage nasal chemosensory receptors and induce behavioral and neuroendocrine responses, without olfactory awareness.[16-21] These chemosignals induce activation of accessory olfactory neural circuits.[22-27] Some mammals including humans do not have an accessory olfactory system and neural impulses arising from nasal chemosensory neurons activated by odorless chemosignals trigger subsets of neurons in the main olfactory bulbs which project directly to the cortical and the medial amygdala. This in turn triggers an important contingent of forward inhibitory gamma aminobutyric acid (GABA)ergic neural circuits in the central amygdala involved in the modulation of fear and anxiety.[26-31]

The olfactory-limbic neural circuits play an important role in social behavior and emotions.[16-18,24,32,33] This has been confirmed in molecular biology/behavioral studies, in studies using knockout mouse lines with loss of function in different zones of the olfactory bulbs,[25] in human functional magnetic resonance imaging studies,[17,34] in clinical studies in human subjects with isolated congenital anosmia,[12,35] and in subjects with congenital hypogonadotropic hypogonadism,[36] and in clinical studies in patients with anxiety and depression.[21,37]

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[19,38-40] 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.[17-34] Pherines are odorless, and brain activation by pherines does not produce olfactory awareness[17,19] and can modulate brain autonomic and psychophysiological responses.[2,16,18,20,34,41,42]

5.1.3 PH94B

PH94B (3β-androsta-4,16-dien-3-ol) is a synthetic neuroactive steroid that targets human nasal chemosensory receptor cells[16,40] and has been demonstrated in Phase 2 clinical trials to have benefits for the acute treatment of anxiety in subjects with SAD.[3]

Pherines induce calcium ion entry in human nasal chemosensory neurons.[41,42] Pherines such as PH94B target G-protein-coupled receptors that are expressed in human nasal chemosensory neurons.[38-44]

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.[45] These membrane currents are carried by calcium ions.[42] 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 of the nasal chemosensory epithelium, 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 effects. PH94B is being investigated as a potential acute treatment for the

alleviation of anxiety symptoms in adult patients with SAD. While PH94B may regulate gamma aminobutyric acid circuits in the limbic amygdala, electrophysiological experiments in vitro show that PH94B does not directly bind to or modulate gamma aminobutyric acid receptors at concentration 10 µM or lower, which differentiates its mechanism of action from that of benzodiazepines.[46]

5.2. Clinical Experience

[redacted]

5.2.1 Phase 1 Studies

[redacted]

[redacted]

5.2.2 Phase 2 Studies

For SAD, 2 double-blind, randomized, placebo-controlled Phase 2 clinical studies (PH94B-CL016 and -CL022) included a total of 91 female subjects who met criteria for SAD (generalized subtype) as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. PH94B (1.6 µg) was administered i.n. [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 - Improvement (CGI-I) and the Subjective Units of Distress Scale (SUDS). SUDS scores range from zero to 100, with higher scores indicating greater levels of anxiety. Subjects receiving PH94B were more likely than those who received placebo to show improvement on the CGI-I following treatment. In the PH94B group, 34 of 45 subjects (75.6%) were rated very much improved or much improved 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 SUDS score at Visit 3 (initial treatment visit) as compared to Visit 2 (Baseline, at which all subjects received placebo). In comparison, subjects randomized to placebo ($n = 46$) showed an improvement of only 14.0 points 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

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

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

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

6. OBJECTIVES

6.1. Primary Objective

The primary objective of this Phase 2a study is to evaluate the efficacy of PH94B Nasal Spray (PH94B) administered 4 times per day over 4 weeks for the treatment of anxiety in adult subjects with AjDA.

6.2. Secondary Objectives

The secondary objective of the study is to evaluate the safety and tolerability of PH94B.

6.3. Exploratory Objective

An exploratory objective of the study is to evaluate efficacy PH94B over time during the 4-week treatment period.

6.4. Endpoint Mapping

Objectives	Endpoints
Primary	
The primary objective of this Phase 2a study is to evaluate the efficacy of PH94B administered 4 times per day over 4 weeks for the treatment of anxiety in adult subjects with AjDA.	The primary efficacy endpoint of the study is change from baseline in anxiety level as measured by the HAM-A at the end of the 4-week treatment period. Secondary efficacy endpoints of the study include the following: Individual subject improvement as assessed by the CGI-I. Values for comparison will be the proportion of "responders" in each group, defined as subjects receiving scores of 1 (Very much improved) or 2 (Much improved) at end of treatment with PH94B. Individual subject improvement as assessed by the subject's self-assessment of improvement (by PGI-C) at the end of treatment compared to baseline. Values for comparison will be the proportion of "responders" in each group, defined as subjects receiving scores of 1 (Very much improved) or 2 (Much improved) at end of treatment with PH94B. Individual subject improvement on the ADNM scale at the end of treatment compared to baseline. Individual subject improvement on the IADQ at end of treatment compared to baseline.

Objectives	Endpoints
Secondary	
The secondary objective of the study is to evaluate the safety and tolerability of PH94B.	Incidence and severity of AEs, AEs leading to discontinuation, and SAEs. Changes in clinical laboratory values. Changes in 12-lead ECG results. Changes in physical examination findings. Changes in vital signs results. Changes in MADRS scores. Changes in suicidal ideation, as documented using the C-SSRS.
[redacted]	
[redacted]	[redacted]

7. STUDY DESIGN

7.1. Overall Study Design and Plan

The study is a Phase 2a, double-blind, placebo-controlled, parallel study of i.n. PH94B versus placebo in 40 adult subjects with AjDA as defined by the DSM-5.

Subject participation in the study will last a total of 6 to 10 weeks, depending on the duration of the screening period and intervals between visits. Upon signing an informed consent, all subjects will complete Visit 1 (Screening) and enter a screening period lasting 7 to 35 days and includes a taper of concomitant anxiolytics, if necessary. As this protocol requires patients to be free of benzodiazepine anxiolytics for 30 days prior to baseline, the maximum screening period accounts for both a taper period and a 30 day benzodiazepine-free period if needed. The Screening visit will consist of safety assessments and psychiatric assessments to determine eligibility. After the screening period, eligible subjects will then return to complete Visit 2 (Baseline). If the subject continues to meet inclusion and exclusion criteria after review of psychiatric scales and laboratory results, the subject will be randomized 1:1 to receive 4 weeks of either PH94B or placebo administered 4 times daily. The subject will be trained on using the investigational product (IP) and it will be dispensed in 2 vials.

Subjects will return for weekly site visits (Visits 3, 4, and 5), in which the subject will return the IP vials dispensed at the previous visit and receive 2 new vials. Concomitant medications and AEs will be recorded. During these visits, the Hamilton Anxiety Scale (HAM-A), Patient Global Impression of Change (PGI-C), CGI-I Scale, Clinical Global Impression - Severity (CGI-S), and Columbia-Suicide Severity Rating Scale (C-SSRS) will be completed. Vital signs will be collected, and nasal passages will be examined.

When the subject returns for Visit 6, besides the assessments completed at Visits 3 through 5, the subjects will complete the Adjustment Disorder New Module Scale (ADNM), International Adjustment Disorder Questionnaire (IADQ), and Montgomery-Asberg Depression Rating Scale (MADRS) and have a physical examination, electrocardiogram (ECG), laboratory tests (chemistry and blood), urinalysis, urine drug screen, and urine pregnancy test. Any remaining IP vials will be collected. The subject will then come back after a 1-week washout period for the Follow-up visit (Visit 7). The HAM-A, C-SSRS, and the 20-item Physician Withdrawal Checklist (PWC-20) will be completed and any changes in AEs and concomitant medications from the last visit will be collected.

For each visit following Baseline (Visit 2), a ±2-day window will be allowed.

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.

Subjects will complete the HAM-A, an established scale, to rate their anxiety. Additional evaluations include the PGI-C, ADNM (a newer scale validated for classification of severity of AjDA), and the IADQ (a recently validated questionnaire to identify stressful events subjects have experienced, as well as their potential social impact). Objective evaluations, performed by the Investigator and a trained observer, include the CGI-I and CGI-S.

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, 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 AjDA, the C-SSRS will be used at each study visit as a precautionary measure.

7.3. Selection of Doses in the Study

The i.n. route of administration is required for the small quantities of PH94B to engage directly with nasal chemosensory neurons interspersed in the nasal olfactory epithelium.

Nonclinical and clinical studies with PH94B are summarized in the IB. Nonclinical 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, but the magnitude of effect is slightly reduced for males at the 1.6 µg dose. This study proposes that [redacted] of PH94B or placebo [redacted], be self-administered i.n. by the subjects 4 times per day, separated by at least 2 hours (target morning, noon, early evening, and bedtime). This is based on Phase 1 and Phase 2 study outcomes in general, and in particular on the observations made in study PH94B-CL019. Subjects will be randomly assigned to treatment with either PH94B or placebo.

7.4. Study Sites

It is projected that up to 2 centers will participate.

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 the Screening (Visit 1) and Baseline (Visit 2). 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 Therapeutics, Inc. and by the central 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 inclusion criteria listed below:

1. Written informed consent provided prior to conducting any study-specific assessment.
2. Male and female adults, ≥18 years of age.
3. Current diagnosis of AjDA as defined in the DSM-5.
4. Clinician-rated HAM-A score ≥20 at Screening (Visit 1) and no greater than 15% decrease at Baseline (Visit 2).
5. Clinician-rated MADRS total score <20 at Screening (Visit 1) and Baseline (Visit 2).
6. Clinical Global Impression - Severity Scale score ≥4 at Screening (Visit 1) and Baseline (Visit 2).
7. 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.
8. Males whose sexual partners are women of childbearing potential must commit to the consistent and correct use of an effective method of birth control throughout the study.
9. Negative COVID-19 test for subjects with COVID-19 symptoms or who have had direct exposure to someone with a positive COVID-19 test, 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 schizophrenia or schizoaffective disorder.

2. Any other current Axis I disorder, including, but not limited to, major depressive disorder, bipolar disorder, post-traumatic stress disorder, obsessive-compulsive disorder, premenstrual dysphoric disorder, and generalized anxiety disorder, which is in poor control and the primary focus of treatment.
3. A diagnosis of SAD.
4. A score >60 on the Liebowitz Social Anxiety Scale (LSAS).
5. Subjects who meet criteria for moderate or severe alcohol or substance use disorder within 1 year prior to study entry.
6. In the opinion of the Investigator, the subject has a significant risk for suicidal behavior during their participation in the study, or
    a. At Screening (Visit 1): the subject scores "yes" on items 4 or 5 in the Suicidal Ideation section of the C-SSRS with reference to a 6-month period prior to screening; or
    b. At Screening (Visit 1): the subject has had one or more suicidal attempts with reference to a 2 year period prior to screening; or
    c. At Baseline (Visit 2): the subject scores "yes" on items 4 or 5 in the Suicidal Ideation section of the C-SSRS with reference to screening; or
    d. The subject is considered to be an imminent danger to themselves or others.
7. 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.
8. 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. The Investigator may allow concomitant use of over-the-counter nasal decongestants as needed, since there is no apparent drug interaction between these and PH94B.
9. Concomitant use of any anxiolytics, such as benzodiazepines, buspirone, or cannabinoids during the study and within 30 days of Baseline (Visit 2).
10. Concomitant use of any over-the-counter, prescription product, or herbal preparation for treatment of the symptoms of anxiety during the study and within 30 days before study entry. Selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, or other approved antidepressants are permitted if the dose has been stable for 30 days prior to Baseline (Visit 2).
11. Women who have a positive urine pregnancy test prior to IP administration or are currently breast feeding.
12. Subjects with clinically significant abnormalities in hematology, blood chemistry, urinalysis, electrocardiogram, or physical examination identified at Screening (Visit 1) 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).

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. Use of a concomitant medication 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.
16. 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

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 complete all of the scheduled weekly assessments; with the exception of subjects who withdraw consent to participate in the study. 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 misses ≥2 consecutive scheduled visits during the 4-week treatment period
- The subject is unable to tolerate study medication based on the Investigator's judgment
- Subject requires PH94B administration more than 4 times per day
- The subject requires a medication prohibited by the protocol (Section 9.7.2)
- Termination of the study by VistaGen Therapeutics, Inc.
- At the discretion of the Investigator or VistaGen Therapeutics, Inc.

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.

Subjects who discontinue early from the study will be asked to return for originally scheduled weekly assessments. If this is not possible, all attempts will be made to have subjects return to the study center to complete the assessments listed for Visit 6 (see Section 10.2.4) as soon as possible. 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. No tapering of IP is required in the event of early withdrawal.

Subjects who sign the informed consent form (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.

Randomized 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] at the site [redacted] The first dose will be administered at the study site.

Site personnel will instruct the subject to prime, then self-administer the IP by [redacted]

9.1. Identification of Investigational Product

The IP is defined as the spray delivery device containing PH94B or placebo.

PH94B [redacted]

The placebo is odorless and contains the identical excipients without PH94B.

PH94B and placebo are similar in appearance.

PH94B and placebo will be supplied [redacted]

The spray delivery device consists of an actuator and a 10-mL amber glass vial which contains 8 mL of IP.

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

PH94B and placebo will be supplied by [redacted]

9.2. Selection of Timing of Dose for Each Subject

Before initiation of treatment with the IP at Baseline (Visit 2), subjects will be trained by the Investigator or delegated staff in the proper technique for priming and self-administration of IP as outlined in the Study Manual.

The IP is to be delivered i.n. with the nozzle of the applicator positioned in the nasal vestibule and directed toward the midline (lower anterior part or nasal septum). To administer study medication, the actuator (pusher) should be depressed completely.

Prior to the use of a new IP vial, subjects will prime the spray pump by depressing the actuator 4 times. [redacted] After the new IP vial has been primed for the first administration, only one priming spray is required for subsequent doses.

Subjects will be instructed to administer [redacted] The administration will be done during waking hours and the suggested spacing is at morning, noon, early evening, and bedtime.

[redacted] Placebo IP is one 100 µL spray per nostril for a total

of 200 µL. Study drug will be self-administered 4 times a day. The spacing between doses needs to be at least 2 hours.

9.3. Dose Adjustment Criteria

Dose adjustment is not allowed in this study.

9.4. Treatment Compliance

At Visits 2, 3, 4 and 5; subjects will be dispensed 2 vials of the appropriate IP. Subjects will take home the vials and store and use the IP at room temperature.

Before dispensing the vial(s) to a subject, the Investigator or study site staff will proceed as follows: (a) identify/mark the 2 vials as vial #1 and vial #2, (b) weigh the vials and record, registering the vial number and weight in the source document, c) instruct the subject to prime (4 sprays) the initial (#1) spray vial, and (d) have the subject self-administer the initial IP dose in the clinic office.

In the event a subject loses a vial of IP and requires a replacement vial to be dispensed, the Investigator or study coordinator must contact VistaGen Therapeutics, Inc. or its designee for replacement instructions. Study site staff will not be allowed to deviate from the dispensation order listed above for any reason.

The Investigator or study site staff will instruct the subject to return the used spray vials during the following visit to the clinic. At that time, the study personnel will weigh the returned vials and record the vial numbers and weights in the source document for compliance check.

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.

Compliance with dosing instructions will be reasonably ascertained by weighing the vials as detailed in the Study Manual. The weight of the returned vials will be recorded in the source documents. Additional instructions will be provided in the Study Manual, including the estimated compliance calculation.

In the event the subject fails to return the IP vial(s) that was dispensed at the prior visit, site staff should ask the subject to return the vials to the site as soon as possible, preferably within 24 hours, but at the very least at the next scheduled study visit. The Investigator will also explicitly and thoroughly instruct the subject not to administer any further doses from the previously dispensed vial.

9.5. Method of Assigning Subjects to Treatment Groups

In this parallel group, randomized study, subjects who meet study entry criteria will be randomly assigned in a 1:1 ratio to PH94B or placebo. 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. The randomization schedule will be stratified by site. Study center will not be a blocking factor in the randomization schedule.

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

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. All IP containers will be provided with a code that will unblind the contents in an emergency (details are provided in the Study Manual).

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 concomitant medications used (including over-the-counter medications and herbal supplements) will be recorded in the source document and on the appropriate eCRF.

All medications taken by or administered to the subject during the month prior to Screening (Visit 1) should be recorded in the eCRF. With the exception of those noted in Section 8.2.2, all medications (prescription or over-the-counter) that were started prior to Screening (Visit 1) may be continued during the course of the trial. During the study, subjects should stay on stable doses of their usual allowable medication regimens. Medications for treatment of minor concurrent illnesses unrelated to AjDA that arise after Screening (Visit 1) may be allowed at the discretion of the Investigator, except for the prohibited therapies specified in the protocol.

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 consider 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 (Visit 1) 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 (Visit 1) 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, low-dose doxepin or anti-histamines for the treatment of insomnia is permitted.

PH94B has no apparent pharmacodynamic drug interaction with phenylephrine and oxymetazoline in vitro. Investigator may allow concomitant use of over-the-counter nasal decongestants as needed. If the subject is taking nasal formulations, they should be spaced 15 minutes from IP administration.

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 7). Prohibited psychotropic medications include centrally acting medications used to treat pain and muscle spasms, such as gabapentin and cyclobenzaprine.

Prior use of PH94B is not permitted.

Where washout of prohibited medications is required before randomization, 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. If the washout of the anti-anxiety medications makes the subject clinically unstable, the Investigator has the discretion to not to proceed with the subject in the study.

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.

The Investigator must confirm the receipt of the IP with his or her signature. A copy of this receipt must be kept by the Investigator and another copy will be stored at VistaGen Therapeutics, Inc. and at Premier Research.

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) must be documented in the study files and reported immediately to the monitor.

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: subject identifier, IP name, dosage strength, lot number, protocol number, specified volume of contents, caution statement ("New Drug – Limited by United States Law to Investigational Use" and "Keep out of reach of children"), storage, and sponsor identification.

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

9.11.2 Packaging

IP will be supplied in amber glass vials. The spray delivery device consists of an actuator and a 10-mL amber glass vial.

10. STUDY PROCEDURES

Subjects must provide written informed consent before any study-related procedures are initiated, including the cessation and taper 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. The same trained rater should complete the appropriate assessment with the subject for all visits.

10.1. Study Duration

The study comprises a screening period of up to 35 days, a double-blind phase of 4 weeks, followed by a follow-up visit approximately 1 week later.

10.2. Study Periods and Visits

10.2.1 Screening and Washout

10.2.1.1 Screening (Visit 1)

Screening begins after the written informed consent has been obtained from the subject. 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

To meet these objectives, the duration of screening can be up to 35 days if taper of prohibited medication is required. Subjects continuing to meet all eligibility requirements at Baseline (Visit 2) will be randomized and dispensed double-blinded IP.

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.

The following procedures will be performed at Screening (Visit 1), which is to occur at least 7 days, but no more than 35 days prior to Baseline (Visit 2):

- Obtain informed consent
- Collect demographic information
- Assign subject number, as described above

- Obtain medical history (including nicotine, alcohol and cannabis use, and menstrual information on women of childbearing potential) and psychiatric history
- Record prior and concomitant treatment and medication use (medication name, dose, and frequency)
- Administer MINI 7.0.2
- Perform physical examination, including height (inches), body weight (pounds), body temperature (°F), and clinical examination of both 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
- Obtain 12-lead ECG
- Obtain blood and urine samples for clinical laboratory examination, including hematology, chemistry, prolactin, thyroid functioning, and urinalysis (refer to Section 10.3.2.1.1 for complete list)
- Obtain urine sample for urine drug screen: Instant Exam to be performed on site, with results thoroughly documented in the source
- For females of childbearing potential, obtain urine sample and complete on-site urine pregnancy test. If positive, a serum pregnancy test should be conducted
- Administer LSAS
- Administer MADRS
- Administer HAM-A
- Administer C-SSRS
- Administer CGI-S
- Review all inclusion and exclusion criteria

10.2.1.2 Washout Period

Subjects requiring washout of prohibited concomitant medications such as benzodiazepines must have stopped taking these medications 30 days prior to Baseline (Visit 2). Selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and other antidepressants are allowed so long as the dose has been stable for 30 days prior to Baseline (Visit 2).

Refer to Section 9.7.2 for more information concerning washout procedures.

10.2.2 Baseline (Visit 2)

For subjects continuing to meet all eligibility criteria, the following assessments will be completed at Baseline (Visit 2):

- Subject to fill out ADNM
- Administer MADRS
- Administer HAM-A

- Administer C-SSRS (since last visit)
- Administer CGI-S
- Administer IADQ
- 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 blood and urine samples for clinical laboratory examination, including hematology, chemistry, prolactin, thyroid functioning, and urinalysis (refer to Section 10.3.2.1.1 for complete list)
- Obtain urine sample for urine drug screen: Instant Exam to be performed on site, with results thoroughly documented in the source
- For females of childbearing 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, (after review of the assessments above) the following Visit 2 procedures will be performed:

- Randomize the subject and obtain first IP vial
- Train subjects on use of IP and dosing
- Prior to giving a vial(s) to the subject, site staff will identify/mark the vials as vial #1 and vial #2. Staff will then instruct the subject on initial priming and ongoing priming, as outlined in the Study Manual
- Both IP vials will be weighed (as per instructions in the Study Manual). The subject will then complete the initial priming and self-administer the first dose in the presence of site personnel
- Record any AEs reported after IP administration

The next visit (Visit 3) will be scheduled 1 week (±2 days) after the date of Baseline (Visit 2).

10.2.3 Treatment Period (Visits 3, 4, and 5)

At Visits 3, 4, and 5 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 clinical examination of both nasal passages
- Administer HAM-A
- Administer C-SSRS (since last visit)
- Administer CGI-S
- Administer CGI-I

- Administer PGI-C
- Returned vials dispensed at the previous visit and new vials will be weighed and dispensed (all weights will be documented in source documents and the eCRF)
- Record concomitant medication use
- Review and record AEs

10.2.4 End of Treatment Period (Visit 6)

At Visit 6, subjects should return to the site with IP vials dispensed at Visit 5. The following assessments will be completed:

- Subject to fill out ADNM
- Administer MADRS
- Administer HAM-A
- Administer IADQ
- Administer C-SSRS (since last visit)
- Administer CGI-S and CGI-I
- Administer PGI-C
- Measure vital signs after the subject has rested for 5 minutes: seated systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature, and ECG
- Perform clinical examination of both nasal passages
- Obtain blood and urine samples for clinical laboratory examination, including hematology, chemistry, prolactin, thyroid functioning, and urinalysis (refer to Section 10.3.2.1.1 for complete list)
- Obtain urine sample for urine drug screen: Instant Exam to be performed on site, with results thoroughly documented in the source
- For females of childbearing potential, obtain urine sample and complete on-site urine pregnancy test
- Record concomitant medication use
- Review and record AEs

10.2.5 Follow-up (Visit 7)

At Visit 7, the following assessments will be completed:

- Administer HAM-A
- Administer C-SSRS (since last visit)
- Administer PWC-20
- Measure vital signs after the subject has rested for 5 minutes: seated systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature, and ECG

- Record concomitant medication use
- Review and record AEs

10.3. Assessments

10.3.1 Efficacy Variables

10.3.1.1 Hamilton Anxiety Scale

HAM-A is an established scale to measure the severity of a patient's anxiety. It consists of 14 questions rated on a 5-point scale (0 = not present to 5 = severe). It is completed by trained personnel over a 15-to-20-minute period. The Structured Interview Guide for the HAM-A (SIGH-A) will be used. A copy of the HAM-A is present in Appendix A.

10.3.1.2 Clinical Global Impression Scales

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

10.3.1.3 Patient Global Impression of Change

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

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

10.3.1.4 Adjustment Disorder New Module Scale

ADNM is a newer scale that has been validated for classification of severity of AjD.[47] It consists of an 18-item stressful life event checklist and a list of 20 statements about which reactions these types of events can trigger. Subjects are asked to indicate how often the respective statement

applies to them on a 4-point scale ("never" to "often"). For each statement subjects are then asked how long they have been having this reaction (< 1 month, 1-6 months, 6 months-2 years).[48] A copy of the ADNM is present in Appendix B.

10.3.1.5 International Adjustment Disorder Questionnaire

The International Adjustment Disorder Questionnaire is a recently validated questionnaire to measure AjD symptoms defined by the new International Classification of Disorders (ICD-11) definition.[48] The subject completes a 9-item checklist of potential stressful events, and if they have experienced any stressful events they then complete a 7-item list of potential problems suffered over the last month (preoccupation symptom) and 3-item list of potential social impacts from the stressors (failure to adapt). A copy of the IADQ is present in Appendix C.

10.3.2 Safety Variables

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

10.3.2.1 Clinical Laboratory Safety Assessments

10.3.2.1.1 Clinical Laboratory Tests to be Performed

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

All laboratory tests will be performed on site during the study, and include the following:

Chemistry Panel:	alanine aminotransferase, aspartate aminotransferase, albumin, calcium, chloride, alkaline phosphatase, bicarbonate, cholesterol, creatine kinase, creatinine, direct bilirubin, lactate dehydrogenase, magnesium, globulin, glucose, gamma-glutamyl transferase, indirect bilirubin, phosphorous, potassium, sodium, total bilirubin, total protein, triglycerides, urea nitrogen, uric acid
Hematology/ Hemogram Panel:	hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular concentration, mean corpuscular volume, platelets, red blood cell count, white blood cell count, red blood cell morphology
Hematology Differential Panel:	basophils, eosinophils, lymphocytes, monocytes, neutrophils
Urinalysis macroscopic panel:	bilirubin, blood, clarity, color, glucose, ketones, leucocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen
Urine Pregnancy Test:	for all female subjects of childbearing potential
Urine Drug Screen:	tricyclic antidepressants, opiates, cocaine, benzodiazepines, amphetamines, barbiturates, cannabinoids, methadone, methamphetamine, phencyclidine, propoxyphene, buprenorphine, ecstasy, oxycodone

Other:	prolactin
	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 local laboratory should be used for any unscheduled and follow-up labs, if needed. This includes any confirmatory pregnancy or drug screens for positive urine tests. 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 local laboratory should be filed with the source documents for each subject. The local laboratory will provide results to the study site staff as soon as they are available and will be provided to sponsor or designated data manager within agreed timelines.

Any laboratory value outside the normal range will be flagged for the attention of the Investigator, who must indicate whether the value is of clinical significance. If the result of any laboratory test performed during Screening (Visit 1) or Baseline (Visit 2) is clinically significant, the subject should not be randomized at 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 (Visit 1) 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 laboratory manual or other appropriate reference. The Investigator is responsible for ensuring that all study samples that are to be transported to another location are packed and shipped appropriately according to the applicable regulations.

10.3.2.1.3 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 supine 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 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 (Visit 1) [redacted] 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.

10.3.2.4 Penn Physician Withdrawal Checklist

The PWC-20 is a 20-item simple instrument for assessing anxiolytic discontinuation symptoms. It consists of 20 questions related to withdrawal from benzodiazepines or other anti-anxiety compounds. The symptoms measured are based on those that are potentially related to anxiolytic withdrawal: gastrointestinal, mood, sleep, motor, somatic, perception and cognition. The questions will cover any symptoms that might occur during the week following discontinuation of PH94B. The PWC-20 scores will be compared between placebo and PH94B.[49] The PWC-20 is provided in Appendix D.

11. ADVERSE EVENTS

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

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.)

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 Events

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 AE (UAE) is one for which the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved IP 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 patient 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 patient 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

Action(s) taken may consist of:

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

11.2.2.4 Outcome at the Time of Last Observation

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

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

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

11.2.2.5 Adverse Event Relationship to Investigational Product

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

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

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

11.2.3 Documentation

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

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

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

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- or triple-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:

[redacted]

[redacted]

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

- Protocol number
- Reporter (study site and Investigator)
- Subject's study number
- Subject's year of birth
- Subject's gender
- Date of first dose of IP(s)
- Date of last dose of IP(s), 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(s) ("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 on a follow-up SAE Report Form, together with the following minimal information (initial report, AE, date of occurrence, subject identification [ID], study ID, IP, and site number); this will allow the follow-up information to be linked to the initial SAE report.

Specific information may be requested by the [redacted]

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 Screening (Visit 1) 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.

A statistical analysis plan (SAP) 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 two-sided, and a difference resulting in a p value of ≤ 0.05 will be considered statistically significant.

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

13.1.1 Analysis Populations

The following 2 analysis populations are planned for this study:

- Intent-to-treat (ITT) population: All subjects who are randomized and have documented one dose of IP at Visit 2 will be included in the ITT population. All efficacy analyses will be performed using the ITT population.
- Safety population: All subjects who are dispensed IP and reported administering at least one dose of IP will be included in the safety population. All safety analyses will be performed using the safety population.

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.

13.1.1.1 Estimand Framework

The target of estimation to address the scientific question of interest (posed by the primary objective for this study):

> *In adults with AjDA, is the difference in mean change from baseline anxiety severity (as measured by HAM-A total score) greater for PH94B-treated subjects compared to placebo-treated subjects, after 4 weeks of treatment?*

is defined by the following attributes:

1. Population: Adults with AjDA (as defined by inclusion and exclusion criteria).
2. Treatment: PH94B compared to placebo control.

3. Variable of interest: Change in subject reported severity of anxiety as measured by change from baseline in HAM-A total score using the SIGH-A, after 4 weeks of randomized treatment with the study medication.
4. Population-level summary measure: Difference in mean HAM-A total score between PH94B-treated and placebo-treated subjects after 4 weeks of treatment.
5. Anticipated intercurrent event: Treatment discontinuation prior to the planned assessment time frame.

Strategies for handling potential intercurrent events (ICE) are summarized in Table 13-1.

Table 13-1: Strategies for Handling Intercurrent Events

ICE	Strategy for Addressing ICE
Treatment Discontinuation following randomization but prior to Week 4	While on Treatment Strategy The research objectives seek to understand the response to PH94B compared to placebo while subjects are actively using the study medication. Subjects who discontinue will undergo an Early Termination Visit and provide all Visit 6 outcome measures and safety assessments for the efficacy analysis.
Treatment Discontinuation following randomization but prior to Week 4 (subject lost to follow-up)	Hypothetical Strategy Measurement following ICE is unavailable and will be considered missing. Multiple imputation of Visit 6 efficacy measures using important subject variables and treatment assignment will be conducted and subjected to sensitivity analysis. (complete case comparison and assumption of treatment failure using 0 change from baseline HAM-A).
Use of prohibited medication prior to Week 4	Hypothetical Strategy Measurement following ICE is not of interest and will be considered missing. Multiple imputation of Visit 6 efficacy measures using important subject variables and treatment assignment will be conducted and subjected to sensitivity analyses (complete case comparison and assumption of treatment failure using 0 change from baseline HAM-A).

Abbreviations: HAM-A = Hamilton Anxiety Scale; ICE = intercurrent event

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 non-compliance 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 non-compliance 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, 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 Anatomical Therapeutic Chemical 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.

Details of the statistical approach and code for analysis of each endpoint will be provided in the SAP.

13.1.4.1 Efficacy Endpoints

Primary Endpoint

The primary efficacy endpoint of the study is change from baseline in anxiety level as measured by the HAM-A for the PH94B-treated group compared to placebo-treated group at the end of the 4-week treatment period.

Secondary Endpoints

The secondary efficacy endpoints are as follows:

- Individual subject improvement as assessed by the CGI-I. Values for comparison will be the proportion of "responders" in each group, defined as subjects receiving scores of 1 (Very much improved) or 2 (Much improved) at end of treatment
- Individual subject improvement as assessed by the subject's self-assessment of improvement (by PGI-C) at the end of treatment compared to baseline. Values for comparison will be the proportion of "responders" in each group, defined as subjects receiving scores of 1 (Very much improved) or 2 (Much improved) at end of treatment
- Individual subject improvement on the ADNM scale at the end of treatment compared to baseline
- Individual subject improvement on the IADQ at end of treatment compared to baseline

[redacted]

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

13.1.4.2 Primary Analysis

An analysis of covariance model with treatment group as factor and baseline HAM-A as covariate will be used to test the null hypothesis that there is no difference between PH94B- and placebo-treated subjects in change from baseline to end of treatment in HAM-A scores. (SAS PROC MIXED, version 9.4).

13.1.4.3 Secondary Analyses

CGI-I and PGI-C at end of treatment will be analyzed using a normal approximation test for the difference between 2 binomial proportions. The null hypothesis to be tested is that there is no difference between PH94B- and placebo-treated subjects. (SAS PROC FREQ, version 9.4).

Change from baseline to Week 4 in ADNM total score will be analyzed analogously to the primary endpoint.

Change from baseline to Week 4 in IADQ total score will be analyzed analogously to the primary endpoint.

[redacted]

13.1.5 Safety and Tolerability Analyses

Safety in this study will be determined from evaluation of AEs, clinical laboratory assessments, vital signs assessments, 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 summarize safety and tolerability of PH94B (3.2 µg) as measured by reports of AEs and SAEs, changes in clinical laboratory values, ECGs, vital signs, and physical examinations, as well as suicidal ideation (as documented using the C-SSRS and MADRS scores), and withdrawal effects (PWC-20).

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 Medical Dictionary for Regulatory Activities.

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 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 AEs 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 (Visit 1) and 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 (both correction methods), 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.

13.1.6 Interim Analysis

No interim analyses are planned.

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

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

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

14.1.3 Confidentiality and Privacy

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

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

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

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

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

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at 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 not be rescreened for the study.

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials 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 are 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 subjects. 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

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

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

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

To ensure data accuracy, eCRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the 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, a record of obtaining informed consent, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

14.5. Data Quality Control

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

14.5.1 Monitoring Procedures

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

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

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRFs are described in the 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 by VistaGen Therapeutics, Inc.'s discretion at any time and for any reason.

14.6.1 Premature Study Termination

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

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

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

- Determination of unexpected, significant, or unacceptable risk to subjects
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements

- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

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

In the case of study termination, study sites may be asked to have all subjects currently participating in the study complete all of the assessments for Visit 6/Early Termination.

14.7. Study Site Closure

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

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

14.7.1 Record Retention

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

- Notified by VistaGen Therapeutics, Inc. that records no longer need to be retained
- At least 2 years following the date a marketing application for the IP has been approved in this indication (AjDA), 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 and/or Assent

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 and/or assent 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.

17. REFERENCES

1. Gradus JL, Qin P, Lincoln AK, Miller M, Lawler E, Lash TL. The association between adjustment disorder diagnosed at psychiatric treatment facilities and completed suicide. Clin Epidemiol. 2010;2:23-28.
2. Liebowitz MR, Hanover R, Draine A, Lemming R, Careri J, Monti L. Effect of as-needed use of intranasal PH94B on social and performance anxiety in individuals with social anxiety disorder. Depress Anxiety. 2016;33(12):1081-1089.
3. Liebowitz MR, Salman E, Nicolini H, Rosenthal N, Hanover R, Monti L. Effect of an acute intranasal aerosol dose of PH94B on social and performance anxiety in women with social anxiety disorder. Am J Psychiatry. 2014;171(6):675-682.
4. O'Donnell ML, Agathos JA, Metcalf O, Gibson K, Lau W. Adjustment Disorder: Current Developments and Future Directions. Int J Environ Res Public Health. 2019;16(14):2537.
5. Stein DJ. Pharmacotherapy of adjustment disorder: A review. World J Biol Psychiatry. 2018;19(sup1):S46-S52.
6. Stein DJ. Etifoxine versus alprazolam for the treatment of adjustment disorder with anxiety: a randomized controlled trial. Adv Ther. 2015;32(1):57-68.
7. do Rego JL, Vaudry D, Vaudry H. The non-benzodiazepine anxiolytic drug etifoxine causes a rapid, receptor-independent stimulation of neurosteroid biosynthesis. PLoS One. 2015;10(3):e0120473.
8. Papez JW. A proposed mechanism of emotion. Arch Neurol Psychiatry. 1937;38(4):725-743.
9. Maclean PD. The limbic system ("visceral brain") and emotional behavior. AMA Arch Neurol Psychiatry. 1955;73(2):130-134.
10. Cairncross. Olfactory bulbectomy as a model for depression. N.W. Bond ed. In: Animal models in psychophysiology. Academic Press, New York. 1976:99-128.
11. Song C, leonard B. Effects of olfactory bulbectomy in the rat, alone or in combination with antidepressants and endogenous factor, an immune function. Hum Psychopharmacol Clin Exp. 1995;10(1):7-18.
12. Croy I, Nordin S, Hummel T. Olfactory disorders and quality of life--an updated review. Chem Senses. 2014;39(3):185-194.
13. Croy I, Negoias S, Novakova L, Landis BN, Hummel T. Learning about the Functions of the Olfactory System from People without a Sense of Smell. 2012. Plos One.
14. Kevetter GA, Winans SS. Connections of the corticomedial amygdala in the golden hamster. II. Efferents of the "olfactory amygdala". J Comp Neurol. 1981;197(1):99-111.
15. Sosulski DL, Bloom ML, Cutforth T, Axel R, Datta SR. Distinct representations of olfactory information in different cortical centres. Nature. 2011;472(7342):213-216.
16. Monti-Bloch L, Jennings-White C, Dolberg DS, Berliner DL. The human vomeronasal system. Psychoneuroendocrinology. 1994;19(5-7):673-686.

17. Sobel N, Prabhakaran V, Hartley CA, Desmond JE, Glover GH, Sullivan EV, et al. Blind smell: brain activation induced by an undetected air-borne chemical. Brain. 1999;122 (Pt 2):209-217.
18. Grosser BI, Monti-Bloch L, Jennings-White C, Berliner DL. Behavioral and electrophysiological effects of androstadienone, a human pheromone. Psychoneuroendocrinology. 2000;25(3):289-299.
19. Monti-Bloch L, Grosser BI. Effect of putative pheromones on the electrical activity of the human vomeronasal organ and olfactory epithelium. J Steroid Biochem Mol Biol. 1991;39(4B):573-582.
20. Monti-Bloch L, Diaz-Sanchez V, C. J-W, Berliner DL. Modulation of serum testosterone and autonomic function through stimulation of the male human vomeronasal organ (VNO) with pregna-4,20-diene-3,6-dione. J Steroid Biochem Mol Biol. 1998;65(1-6):237-242.
21. Monti L, Liebowitz M. Neural Circuits of Anxiolytic and Antidepressant Pherine Molecules. Epub ahead of print. CNS Spectrums. 2020;23:1-7.
22. Kevetter GA, Winans SS. Connections of the corticomedial amygdala in the golden hamster. I. Efferents of the "vomeronasal amygdala". J Comp Neurol. 1981;197(1):81-98.
23. Swanson LW, Petrovich GD. What is the amygdala? Trends Neurosci. 1998;21(8):323-331.
24. Dorries KM, Adkins-Regan E, Halpern BP. Sensitivity and behavioral responses to the pheromone androstenone are not mediated by the vomeronasal organ in domestic pigs. Brain Behav Evol. 1997;49(1):53-62.
25. Hagino-Yamagishi K. Diverse systems for pheromone perception: multiple receptor families in two olfactory systems. Zoolog Sci. 2008;25(12):1179-1189.
26. Kang N, Baum MJ, Cherry JA. A direct main olfactory bulb projection to the 'vomeronasal' amygdala in female mice selectively responds to volatile pheromones from males. Eur J Neurosci. 2009;29(3):624-634.
27. Pape HC, Jungling K, Seidenbecher T, Lesting J, Reinscheid RK. Neuropeptide S: a transmitter system in the brain regulating fear and anxiety. Neuropharmacology. 2010;58(1):29-34.
28. Pro-Sistiaga P, Mohedano-Moriano A, Ubeda-Banon I, Del Mar Arroyo-Jimenez M, Marcos P, Artacho-Perula E, et al. Convergence of olfactory and vomeronasal projections in the rat basal telencephalon. J Comp Neurol. 2007;504(4):346-362.
29. Mohedano-Moriano A, de la Rosa-Prieto C, Saiz-Sanchez D, Ubeda-Banon I, Pro-Sistiaga P, de Moya-Pinilla M, et al. Centrifugal telencephalic afferent connections to the main and accessory olfactory bulbs. Front Neuroanat. 2012;6:19.
30. Sokolowski K, Corbin JG. Wired for behaviors: from development to function of innate limbic system circuitry. Front Mol Neurosci. 2012;5:55.
31. Tovote P, Fadok JP, Luthi A. Neuronal circuits for fear and anxiety. Nat Rev Neurosci. 2015;16(6):317-331.

32. Schaal B, Coureaud G, Langlois D, Ginies C, Semon E, Perrier G. Chemical and behavioural characterization of the rabbit mammary pheromone. Nature. 2003;424(6944):68-72.
33. Nuss P. Anxiety disorders and GABA neurotransmission: a disturbance of modulation. Neuropsychiatr Dis Treat. 2015;11:165-175.
34. Savic I, Berglund H, Gulyas B, Roland P. Smelling of odorous sex hormone-like compounds causes sex-differentiated hypothalamic activations in humans. Neuron. 2001;31(4):661-668.
35. Smeets MAM, Veldhuizen MG, Galle S, Gouweloos J, de Haan AJA, Vernooij J, et al. Sense of smell disorder and health-related quality of life. Rehabil Psychol. 2009;54(4):404-412.
36. Aydogan U, Aydogdu A, Akbulut H, Sonmez A, Yuksel S, Basaran Y, et al. Increased frequency of anxiety, depression, quality of life and sexual life in young hypogonadotropic hypogonadal males and impacts of testosterone replacement therapy on these conditions. Endocr J. 2012;59(12):1099-1105.
37. Monti L, Nicolini H, Liebowitz MR, Hanover R. A Placebo Controlled Trial of PH10: Test of a New Rapidly Acting Intranasally Administered Antidepressant. Br J Pharm Res. 2020;4(6):2157-2168..
38. Rodriguez I, Greer CA, Mok MY, Mombaerts P. A putative pheromone receptor gene expressed in human olfactory mucosa. Nat Genet. 2000;26(1):18-19.
39. Grus WE, Shi P, Zhang YP, Zhang J. Dramatic variation of the vomeronasal pheromone receptor gene repertoire among five orders of placental and marsupial mammals. Proc Natl Acad Sci U S A. 2005;102(16):5767-5772.
40. Monti-Bloch L. Patch recorded isolated adult human vomeronasal organ cells are electrically excitable and respond to skin steroidal substances androsta-4,16-dien-3-one and estra-1,3,5(10),16-tetraen-3-ol. Chemical Senses. 1995;20(6):745.
41. Monti-Bloch L, Jennings-White C, Berliner DL. The human vomeronasal system. A review. Ann N Y Acad Sci. 1998;855:373-389.
42. Liebowitz MR, Salmán E, Rosenthal N, Nicolini H, Monti L. Evaluation of a Unique Nanogram-Dose Intranasal Aerosol for the Acute Management of the Symptoms of Social Anxiety Disorder. in New Clinical Drug Evaluation Unit Conference. 2011. Boca Raton, FL.
43. Winegar B, Monti L. Pherines increase cytosolic Ca in isolated living human vomeronasal chemosensory neurons. ACHEMS abstract. 2003.
44. Herman R, Monti-Bloch L. Human VNO cDNA libraries: Pertusis toxin blockade of human VNO receptors (R1). Pherin Pharmaceuticals, Inc.; Los Altos, CA: Pherin Report MB 007; 1997.
45. Monti L. Dose dependent effect of pherine PH94B in isolated female human vomeronasal organ cells. Pherin Study Report # CL009; Report date: May 18, 1999.

46. Monti L, Liebowitz M, Smith M. PH94B: A new intranasal neuroactive steroid with rapid onset of anxiolytic activity but a mechanism of action different from benzodiazepines. ADAA, 2021.
47. Lorenz L, Bachem RC, Maercker A. The Adjustment Disorder--New Module 20 as a Screening Instrument: Cluster Analysis and Cut-off Values. Int J Occup Environ Med. 2016;7(4):215-220.
48. Shevlin M, Hyland P, Ben-Ezra M, Karatzias T, Cloitre M, Vallières F, et al. Measuring ICD-11 adjustment disorder: the development and initial validation of the International Adjustment Disorder Questionnaire. Acta Psychiatr Scand. 2020;141(3):265-274.
49. Rickels K, Garcia-Espana F, Mandos LA, Case GW. Physician Withdrawal Checklist (PWC-20). J Clin Psychopharmacol. 2008 Aug;28(4):447-51
50. Bachem R, Perkonigg A, Stein DJ, Maercker A. Measuring the ICD-11 adjustment disorder concept: Validity and sensitivity to change of the Adjustment Disorder - New Module questionnaire in a clinical intervention study. Int J Methods Psychiatr Res. 2017;26(4).

18. ATTACHMENTS

18.1. Investigator's Agreement

PROTOCOL NUMBER: PH94B-CL029

PROTOCOL TITLE: A Phase 2a Double-blind, Placebo-controlled, Parallel Study of PH94B Nasal Spray in the Treatment of Anxiety in Adults with Adjustment Disorder with Anxiety

FINAL PROTOCOL: 30-Aug-2021

I have read this protocol and agree to conduct this clinical study as outlined herein. I will ensure that all subinvestigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with VistaGen Therapeutics, Inc. and 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. Hamilton Anxiety Scale
B. Adjustment Disorder New Module Scale
C. International Adjustment Disorder Questionnaire
D. Penn Physician Withdrawal Checklist
E. Regulations and Good Clinical Practice Guidelines

A. Hamilton Anxiety Scale

Hamilton Anxiety Rating Scale (HAM-A)

Below is a list of phrases that describe certain feeling that people have. Rate the patients by finding the answer which best describes the extent to which he/she has these conditions. Select one of the five responses for each of the fourteen questions.

0 = Not present, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Very severe.

1 Anxious mood [0] [1] [2] [3] [4]

Worries, anticipation of the worst, fearful anticipation, irritability.

2 Tension [0] [1] [2] [3] [4]

Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax.

3 Fears [0] [1] [2] [3] [4]

Of dark, of strangers, of being left alone, of animals, of traffic, of crowds.

4 Insomnia [0] [1] [2] [3] [4]

Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors.

5 Intellectual [0] [1] [2] [3] [4]

Difficulty in concentration, poor memory.

6 Depressed mood [0] [1] [2] [3] [4]

Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing.

7 Somatic (muscular) [0] [1] [2] [3] [4]

Pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone.

8 Somatic (sensory) [0] [1] [2] [3] [4]

Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation.

9 Cardiovascular symptoms [0] [1] [2] [3] [4]

Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat.

10 Respiratory symptoms [0] [1] [2] [3] [4]

Pressure or constriction in chest, choking feelings, sighing, dyspnea.

11 Gastrointestinal symptoms [0] [1] [2] [3] [4]

Difficulty in swallowing, wind abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation.

12 Genitourinary symptoms [0] [1] [2] [3] [4]

Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence.

13 Autonomic symptoms [0] [1] [2] [3] [4]

Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair.

14 Behavior at interview [0] [1] [2] [3] [4]

Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, etc.

B. Adjustment Disorder New Module Scale

Self-report for the assessment of adjustment disorder

ADNM – 20 Questionnaire

Adjustment Disorder – New Module 20

Below is a list of stressful life events. Please indicate those events that happened during the past [*insert time frame*] years and are currently a strong burden to you, or have burdened you in the last six months. You can indicate as many events as applicable.

Yes	
	01. Divorce / separation
	02. Family conflicts
	03. Conflicts in working life
	04. Conflicts with neighbors
	05. Illness of a loved one
	06. Death of a loved one
	07. Adjustment due to retirement
	08. Unemployment
	09. Too much / too little work
	10. Pressure to meet deadlines / time pressure
	11. Moving to a new home
	12. Financial problems
	13. Own serious illness
	14. Serious accident
	15. Assault
	16. Termination of an important leisure activity
	17. Any other stressful event (please indicate)
	18. Any other stressful event (please indicate)

The events you have just indicated can have numerous consequences for our well-being and behavior. Please indicate was the most straining event(s) below:

_____

_____

In the following, you will find various statements about which reactions these types of events can trigger. We ask you first of all to indicate how often the respective statement applies to you ("never" to "often").

In a second step, we would like to ask you to indicate for how long you have been having this reaction. It can be less than one month (< 1 month), for approx. one month to half a year (< 6 months) or longer than 6 months (> 6 months). This will probably not be very easy to estimate, but please try to give a rough classification of the duration of the reaction!

		Frequency during last week				For how long?		
		never	rarely	some-times	often	<1 month	1 – 6 months	6 months – 2 years
1	Since the stressful problem, I feel low and sad.	☐	☐	☐	☐	☐	☐	☐
2	I have to think about the stressful situation repeatedly.	☐	☐	☐	☐	☐	☐	☐
3	I try to avoid talking about the stressful situation wherever possible.	☐	☐	☐	☐	☐	☐	☐
4	I keep having to think about the stressful situation and this is a great burden to me.	☐	☐	☐	☐	☐	☐	☐
5	Nowadays, I do those activities which I used to enjoy much more rarely.	☐	☐	☐	☐	☐	☐	☐
6	If I think about the stressful situation, I find myself in a real state of anxiety.	☐	☐	☐	☐	☐	☐	☐
7	I avoid certain things that might remind me of the stressful situation.	☐	☐	☐	☐	☐	☐	☐
8	I am nervous and restless since the stressful situation.	☐	☐	☐	☐	☐	☐	☐
9	Since the stressful situation, I am much quicker to lose my temper, even over small things.	☐	☐	☐	☐	☐	☐	☐
10	Since the stressful situation, I can only concentrate on certain things with difficulty.	☐	☐	☐	☐	☐	☐	☐
11	I try to abolish the stressful situation from my memory.	☐	☐	☐	☐	☐	☐	☐
12	I have noticed that I am becoming more irritable due to the stressful situation.	☐	☐	☐	☐	☐	☐	☐
13	I get constant memories of the stressful situation and can't do anything to stop them.	☐	☐	☐	☐	☐	☐	☐
14	I try to suppress my feelings because they are a burden to me.	☐	☐	☐	☐	☐	☐	☐
15	My thoughts revolve around anything to do with the stressful situation.	☐	☐	☐	☐	☐	☐	☐
16	Since the stressful situation, I am scared of doing certain things or of getting into certain situations.	☐	☐	☐	☐	☐	☐	☐
17	Since the stressful situation, I don't like going to work or carrying out the necessary tasks in everyday life.	☐	☐	☐	☐	☐	☐	☐
18	I have been feeling dispirited since the stressful situation and have little hope for the future.	☐	☐	☐	☐	☐	☐	☐
19	Since the stressful situation, I can no longer sleep properly.	☐	☐	☐	☐	☐	☐	☐
20	Overall, the situation affected me strongly in my personal relationships, my leisure activities, or other important areas of life	☐	☐	☐	☐	☐	☐	☐

C. International Adjustment Disorder Questionnaire

THE INTERNATIONAL ADJUSTMENT DISORDER QUESTIONNAIRE (IADQ)

Below is a list of stressful life events that you may have experienced. Please indicate any of the following events that are currently applicable to you:

I am currently experiencing…	**Yes**
1. Financial problems (e.g., difficulty paying bills, being in debt).	
2. Work problems (e.g., unemployment, redundancy, retirement, problems/conflicts with colleagues, change of job role).	
3. Educational problems (e.g., difficulty with course work, deadline pressure).	
4. Housing problems (e.g., stressful home move, difficulty finding a secure residence, lack of secure residence).	
5. Relationship problems (e.g., break-up, separation or divorce, conflict with family or friends, intimacy problems).	
6. My own health problems (e.g., illness onset or deterioration, medication issues, injury or disability).	
7. A loved one's health problems (e.g., illness onset or deterioration, medication issues, injury or disability).	
8. Caregiving problems (e.g., emotional stress, time demands).	
9. Some other problem not mentioned above.	

This section should be completed only if you have answered 'Yes' to at least one of the events above. The following statements reflect problem that people sometimes experience in relation to a stressful life event(s). Thinking about the stressful life event(s) you identified above, please indicate **how much you have been bothered by each of the following problems in the past month**:

	Not at all	***A little bit***	***Moderately***	***Quite a bit***	***Extremely***
10. I worry a lot more since the stressful event(s).	0	1	2	3	4
11. I can't stop thinking about the stressful event(s).	0	1	2	3	4
12. I often feel afraid about what might happen in the future since the stressful event(s).	0	1	2	3	4
13. I find it difficult to adapt to life since the stressful event(s).	0	1	2	3	4
14. I find it difficult to relax and feel calm since the stressful event(s).	0	1	2	3	4
15. I find it difficult to achieve a state of inner peace since the stressful event(s).	0	1	2	3	4
16. Did these problems start within one month of the stressful event(s)?	**Yes**			**No**	

	Not at all	*A little bit*	*Moderately*	*Quite a bit*	*Extremely*
In the past month have the above problems:	0	1	2	3	4
17. Affected your relationships or social life?	0	1	2	3	4
18. Affected your ability to work or your educational life?	0	1	2	3	4
19. Affected any other important part of your life?	0	1	2	3	4

D. Penn Physician Withdrawal Checklist

Penn Physician Withdrawal Checklist

Did the patient manifest or describe any of the following symptoms since the last visit?

	0 Not Present	1 Mild	2 Moderate	3 Severe
1. Loss of appetite	☐ 0	☐ 1	☐ 2	☐ 3
2. Nausea–Vomiting	☐ 0	☐ 1	☐ 2	☐ 3
3. Diarrhea	☐ 0	☐ 1	☐ 2	☐ 3
4. Anxiety–Nervousness	☐ 0	☐ 1	☐ 2	☐ 3
5. Irritability	☐ 0	☐ 1	☐ 2	☐ 3
6. Dysphoric mood–Depression	☐ 0	☐ 1	☐ 2	☐ 3
7. Insomnia	☐ 0	☐ 1	☐ 2	☐ 3
8. Fatigue–Lethargy–Lack of energy	☐ 0	☐ 1	☐ 2	☐ 3
9. Poor coordination	☐ 0	☐ 1	☐ 2	☐ 3
10. Restlessness–Agitation	☐ 0	☐ 1	☐ 2	☐ 3
11. Diaphoresis	☐ 0	☐ 1	☐ 2	☐ 3
12. Tremor–Tremulousness	☐ 0	☐ 1	☐ 2	☐ 3
13. Dizziness–Lightheadedness	☐ 0	☐ 1	☐ 2	☐ 3
14. Headaches	☐ 0	☐ 1	☐ 2	☐ 3
15. Muscle aches or stiffness	☐ 0	☐ 1	☐ 2	☐ 3
16. Weakness	☐ 0	☐ 1	☐ 2	☐ 3
17. Increased acuity for sound, smell, touch, or pain	☐ 0	☐ 1	☐ 2	☐ 3
18. Paresthesias	☐ 0	☐ 1	☐ 2	☐ 3
19. Difficulty concentrating, remembering	☐ 0	☐ 1	☐ 2	☐ 3
20. Depersonalization–derealization	☐ 0	☐ 1	☐ 2	☐ 3

E. Regulations and Good Clinical Practice Guidelines

1. Regulations

Refer to the following United States CFR:

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

2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URLs:

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

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