Efficacy, Safety, and Tolerability of PH94B in Adjustment Disorder With Anxiety: Design of an Exploratory Phase 2A Clinical Trial

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INTRODUCTION

- Anxiety disorders are the most prevalent psychiatric disorders and are leading causes of disability[1]
- People react differently to stress, even though everyone experiences stress as a common everyday experience
- Some people adapt well to stressful life events while others respond with excessive emotional or behavioral responses that are out of proportion with the severity of the stressor, impacting their functional abilities
  - Individuals who respond disproportionately to a stressor and have consequent functional impairment may receive a diagnosis of adjustment disorder, which is now subsumed within DSM-5's section on trauma- and stress-related disorders (**Figure 1**)

Figure 1. DSM-5 Adjustment Disorder Criteria[2]

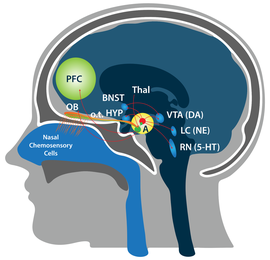
DSM-5
A. Onset of emotional or behavioral symptoms must occur in response to identifiable stressor, and within 3 months of the stressor.
B. These symptoms are clinically significant, marked by: – Distress that is disproportionate to the severity or intensity of the stressor, taking into account contextual and cultural factors, or – Significant impairments in social, occupational or other domains of functioning.
C. The disturbance does not meet the diagnostic criteria for another mental disorder, and is not an exacerbation of a pre-existing disorder.
D. The symptoms do not represent normal bereavement.
E. Symptoms do not last for more than six additional months after the stressor or its consequences have been resolved.

- DSM-5 adjustment disorders may be accompanied by additional features including anxiety, depression, conduct disturbance, or a combination of these symptoms
  - The prevalence of adjustment disorders has been rising, especially since the beginning of the COVID-19 pandemic[3,4]
- A recent claims analysis showed that adjustment disorder with anxiety (AjDA) accounted for 17% (7.7 million of 46.4 million) of all diagnosed anxiety disorders between 2016 and 2021 (IQVIA LAAD Anxiety & Depression Dataset 2016-2021), underscoring the high unmet need for pharmacologic treatment options in this disorder with no current FDA-approved treatment
- Although adjustment disorders are predominantly diagnosed in children and adolescents, they can also affect adults (https://www.hopkinsmedicine.org/health/conditions-and-diseases/adjustment-disorders)
- In AjDA, a stressful event (eg, loss of work, divorce, health setback) causes excessive nervousness, worry, jitteriness, or separation anxiety that significantly impairs the person's ability to function in social, occupational, and/or other situations
- Unlike posttraumatic stress disorder, AjDA resolves within 6 months after the stressful event terminates

PH94B (3β-androsta-4,16-dien-3-ol)

- PH94B is a first-in-class, odorless, tasteless, rapid-onset (10-15 minutes) investigational pherine nasal spray with a novel mechanism of action (MOA) that regulates the olfactory-amygdala neural circuits of fear and anxiety and attenuates the tone of the sympathetic autonomic nervous system. It is currently being evaluated in two phase 3 clinical studies in the United States, PALISADE-1 and PALISADE-2, and a long-term safety study, for the acute treatment of anxiety in adults with social anxiety disorder (SAD)
- Administration of radiolabeled PH94B ([^{14}C]PH94B) nasal spray to rats resulted in no evidence of systemic absorption
  - Central nervous system penetration of [^{14}C]PH94B was minimal in the first 15 minutes after administration but was below the limit of quantification thereafter
- Designed to be administered intranasally at microgram doses, PH94B has a unique potential MOA that is fundamentally differentiated from all current antianxiety medications, including benzodiazepines
  - In vitro experiments indicate that the anxiolytic effects of PH94B do not involve either direct activation of GABA-A receptors or binding to neuronal receptors in the central nervous system[5]
- Despite the lack of systemic absorption and penetration of the blood–brain barrier, PH94B treatment provides rapid onset of anxiolytic effects in patients with SAD and is under phase 3 investigation for that indication[6]
- The MOA of PH94B is still being studied
  - Evidence suggests that despite very limited systemic exposure, PH94B engages peripheral neurons in the nasal passages that activate subsets of olfactory bulb neurons projecting to GABAergic forward inhibitory neurons in the limbic amygdala, regulating fear and anxiety by modulating inhibitory neurotransmission in other brain regions (**Figure 2**)
- Taken together, both preclinical and clinical data suggest that PH94B has the potential to achieve rapid-onset antianxiety effects without systemic uptake or transport into the brain, reducing the risk of benzodiazepine-like side effects and other safety concerns
- The FDA has granted PH94B a Fast-Track designation for its development as a potential treatment for SAD

Figure 2. Olfactory Connections to the Limbic Amygdala and Related Areas[5]



5-HT, serotonin; A, amygdala; BNST, bed nucleus of the stria terminalis; DA, dopamine; LC, locus coeruleus; HYP, hypothalamus; NE, norepinephrine; OB, olfactory bulb; o.t., olfactory tract; PFC, prefrontal cortex; RN, raphe nucleus; Thal, thalamus; VTA, ventral tegmental area.

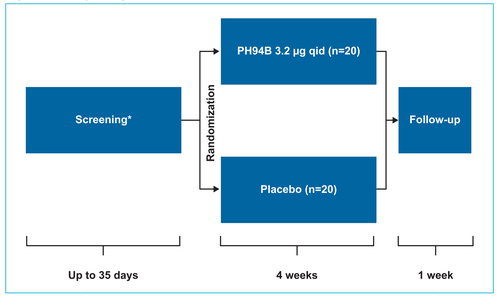
OBJECTIVE

- In this poster, details of a study designed to evaluate the efficacy, safety, and tolerability of administration of PH94B nasal spray 4 times per day as a treatment of AjDA in adults are presented

STUDY DESIGN

- This is a phase 2, randomized, double-blind, placebo-controlled, parallel group, 4-week study in adults with AjDA (NCT04404192) per DSM-5 (**Figure 3**)

Figure 3. Study Design



*All patients must provide written informed consent before any study-related procedures are initiated, including cessation and taper of prohibited concomitant therapy.
qid, 4 times per day.

- PH94B will be dosed as one 100 µL spray (1.6 µg) in each nostril 4 times per day
  - PH94B dosing is targeted for morning, noon, early evening, and at bedtime, with at least 2 hours between doses

Key Inclusion Criteria

- Adults aged ≥18 years
- Current diagnosis of AjDA per DSM-5
- Clinician-rated Hamilton Anxiety Scale (HAM-A) score ≥20 at screening with no more than a 15% decrease from baseline
- Clinician-rated Montgomery-Asberg Depression Rating Scale total score <20 at screening and baseline
- Clinical Global Impression of Severity Scale score ≥4 at both screening and baseline
- 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

Key Exclusion Criteria

- Any history of schizophrenia, schizoaffective disorder, or any other current Axis I disorder that is poorly controlled and the primary focus of treatment
- A diagnosis of SAD with a score >60 on the Liebowitz Social Anxiety Scale
- Subjects who meet criteria for moderate or severe alcohol or substance use disorder within 1 year prior to study entry
- Significant risk for suicidal behavior during the study
- 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
- Acute or chronic condition, including 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
- Any clinically significant abnormality, medical condition, or 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
  - Including use of over-the-counter or prescription treatments for anxiety within 30 days of baseline
- A positive urine drug screen at either the screening or baseline visit
- History of cancer or malignant tumor not in remission for ≥2 years (subjects with basal cell skin cancers are not excluded)

Endpoints

- Primary endpoints
  - Change from baseline to week 4 in HAM-A score
  - Adverse events will be monitored throughout and coded using the most recent version of Medical Dictionary for Regulatory Activities
- Secondary endpoints
  - Change from baseline to week 4 in the Adjustment Disorder–New Module (ADNM-20) 20-item assessment scale (**Figure 4**) and the International Adjustment Disorder Questionnaire (IADQ) scale (**Figure 5**)[7,8]
    - The ADNM-20 and IADQ scales are validated measures of the core diagnostic features of adjustment disorder according to ICD-11 criteria based on stressful events experienced, timing of the event, and their potential functional impact
    - The ADNM-20 scale has also been validated as sensitive to change[9]
  - Clinical Global Impression of Improvement (CGI-I) response ("much" or "very much" improved) at week 4
  - Patient Global Impression of Change (PGI-C) response ("much" or "very much" improved) at week 4
- Exploratory endpoints
  - Change from baseline in HAM-A score at weeks 1, 2, and 3
  - Change from baseline in ADNM-20 subscales at week 4
  - CGI-I and PGI-C scores each week during the study

Figure 4. ADNM-20 Assessment

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 your well-being and behavior. Please indicate what 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	sometimes	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.	☐	☐	☐	☐	☐	☐	☐

The ADNM-20 consists of 6 subscales: preoccupation (4 items), failure to adapt (4 items), avoidance (4 items), depressive mood (3 items), anxiety (2 items), and impulse disturbance (3 items). Participants rate each item of the ADNM-20 on a 4-point Likert scale ranging from 1 (never) to 4 (often) based on their experience over the previous 2 weeks. A high risk of adjustment disorder is found if if 1 item of the core symptoms (preoccupation or failure to adapt) is rated ≥3 and ≥2 items in both core symptom clusters are rated ≥2, and a rating of ≥3 is reported on the impairment criterion. In addition, a score of ≥48 on the ADNM-20 total score indicates a very high likelihood of adjustment disorder.

Figure 5. IADQ

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 problems 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	
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

Statistical Analysis

- Primary analysis
  - Analysis of change from baseline in HAM-A score to week 4 will be conducted using an analysis of covariance model with treatment group as a factor and baseline HAM-A score as a covariate
  - Change from baseline to week 4 in ADNM-20 total score and IADQ total score will be analyzed similarly to the primary endpoint
- Secondary analysis
  - CGI-I and PGI-C will be analyzed using a normal approximation test
- All analyses will be conducted using SAS version 9.4 (SAS Institute, Cary, NC)

RESULTS

- This phase 2 study evaluating the efficacy and safety of PH94B for the treatment of AjDA is currently recruiting, with a planned enrollment of 40 adult patients
- Completion of the study is expected in Fall 2022

CONCLUSIONS

- Stress-related anxiety disorders, such as AjDA, are especially relevant during the current COVID-19 pandemic, as many people's lives have been disrupted, whether due to stressors related to caring for COVID-19 patients (eg, healthcare workers, first responders, family caregivers) or due to the stress of seeing loved ones suffer or die from the virus; children and adolescents are especially vulnerable
- No pharmacologic treatment is currently approved for the highly prevalent adjustment disorder, so new FDA-approved treatments are very much needed
- PH94B, a pherine nasal spray with a unique MOA, is currently under investigation for treatment of AjDA using both standard anxiety measures (HAM-A) and newly developed diagnostic scales (ADNM-20 and IADQ)
- The sensitivity of ADNM-20 and IADQ to change over time could help to standardize research and stimulate further investigation of new treatments for adjustment disorder

References

1. Garakani A et al. *Front Psychiatry*. 2020;11:595584.
2. Agnew-Blais JC et al. *JAMA Psychiatry*. 2016;73:713-20.
3. Li Y et al. *PLoS One*. 2021;16:e0246454.
4. Mahamid M et al. *Omega*. 2021:30222821034372.
5. Monti L et al. *CNS Spectr*. 2022;27:66-72.
6. Liebowitz MR et al. *Am J Psychiatry*. 2014;171:675-82.
7. Lorenz L et al. *Intl J Occup Environ Med*. 2016;7:215-20.
8. Shevlin M et al. *Acta Psychiatr Scand*. 2020;141:265-74.
9. Bachem R et al. *Int J Methods Psychiatr Res*. 2017;26(4):e1545.

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Disclosures

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Michael R. Liebowitz: Managing Director and owner of The Medical Research Network, LLC.; owner of stock and stock options in VistaGen Therapeutics, Inc.; holds the copyright to the Liebowitz Social Anxiety Scale (LSAS) and has licensed it to VistaGen Therapeutics, Inc. for use in clinical trials.

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