Top-Line Results from Phase 3 PALISADE-2 Trial of Fasedienol (PH94B) Nasal Spray in Social Anxiety Disorder

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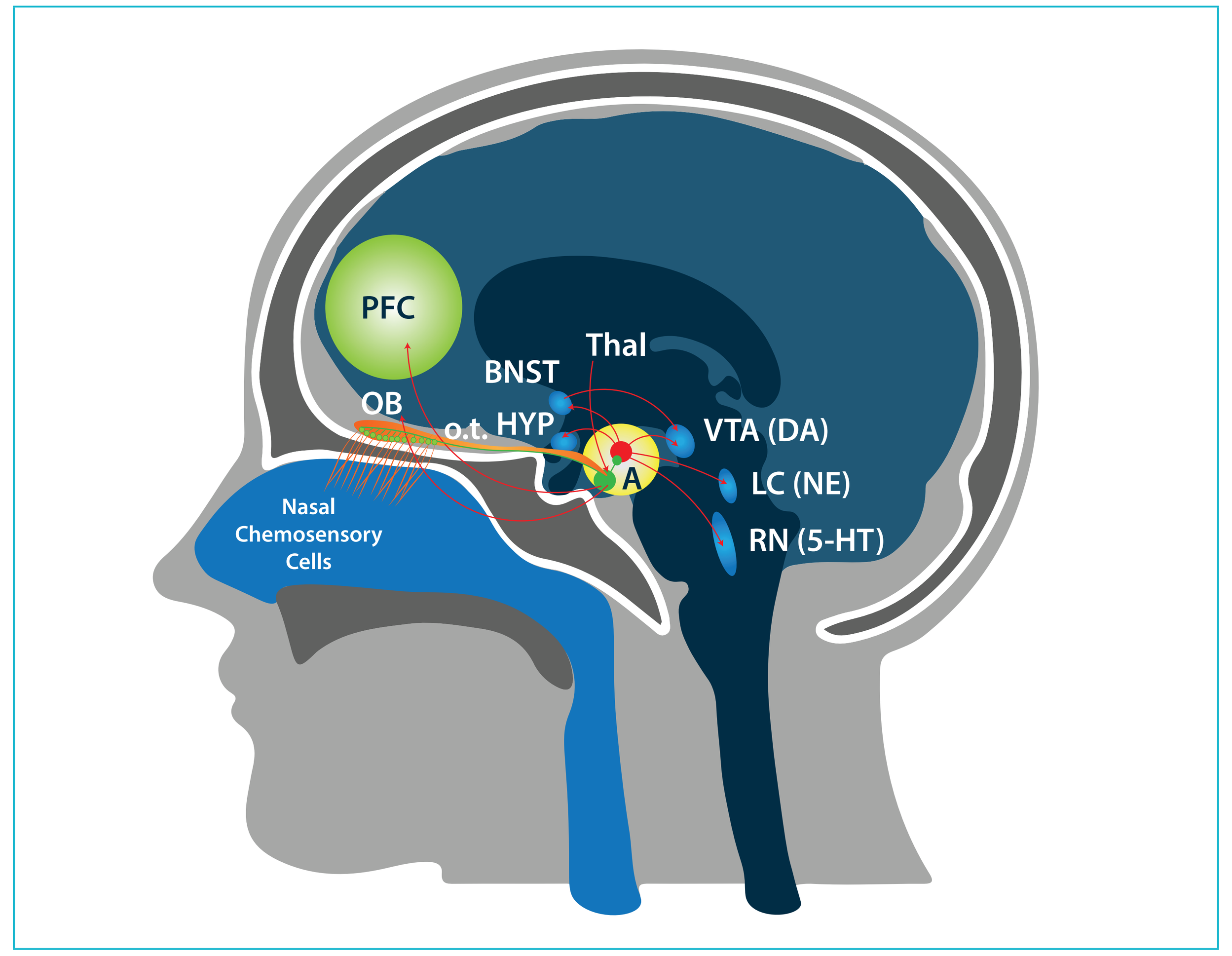
INTRODUCTION

- Anxiety disorders are among the most common psychiatric disorders in the United States, with a prevalence of around 32%, and are a leading cause of disability[1]
- Social anxiety disorder (SAD) is one of the most common anxiety disorder types, with a lifetime prevalence of 12.1%[2,3]; up to 81% of patients with SAD have other comorbid psychiatric or medical conditions[4]
- Individuals with SAD fear the scrutiny of others and experience intense emotional and/or physical discomfort in social situations[3]
  - This discomfort results in avoidance, fear, and/or anxious anticipation that significantly interferes with daily routine, occupational functioning, and social life[4]

Fasedienol

- Fasedienol (PH94B; 3β-androsta-4,16-dien-3-ol) is an investigational synthetic neuroactive nasal spray from the androstane family of pherines
- Intranasal administration of fasedienol activates receptors on peripheral nasal chemosensory neurons connected to subsets of neurons in the olfactory bulbs that in turn are neurally connected to GABAergic forward inhibitory neurons in the limbic amygdala involved in the pathophysiology of SAD (**Figure 1**), regulating fear and anxiety by modulating inhibitory neurotransmission in other brain regions
  - Fasedienol is locally metabolized in the olfactory mucosa without systemic uptake and with minimal distribution to the tissues of the central nervous system (CNS)
  - In vitro experiments indicate that the anxiolytic effects of fasedienol involve neither direct activation of GABA-A receptors nor binding to neuronal receptors in the CNS

Figure 1. Olfactory Connections to the Limbic Amygdala and Related Areas[6]



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

- In a phase 2 clinical study, PH94B nasal spray induced a rapid and significant decrease in public speaking performance anxiety and social interaction anxiety compared with placebo nasal spray, as measured by Subjective Units of Distress Scale (SUDS) scores[5]
  - A subsequent phase 3 investigation (PALISADE-1) failed to meet its primary efficacy endpoint of change from baseline in SUDS scores with PH94B vs placebo, although this study found PH94B to be safe and well tolerated

OBJECTIVE

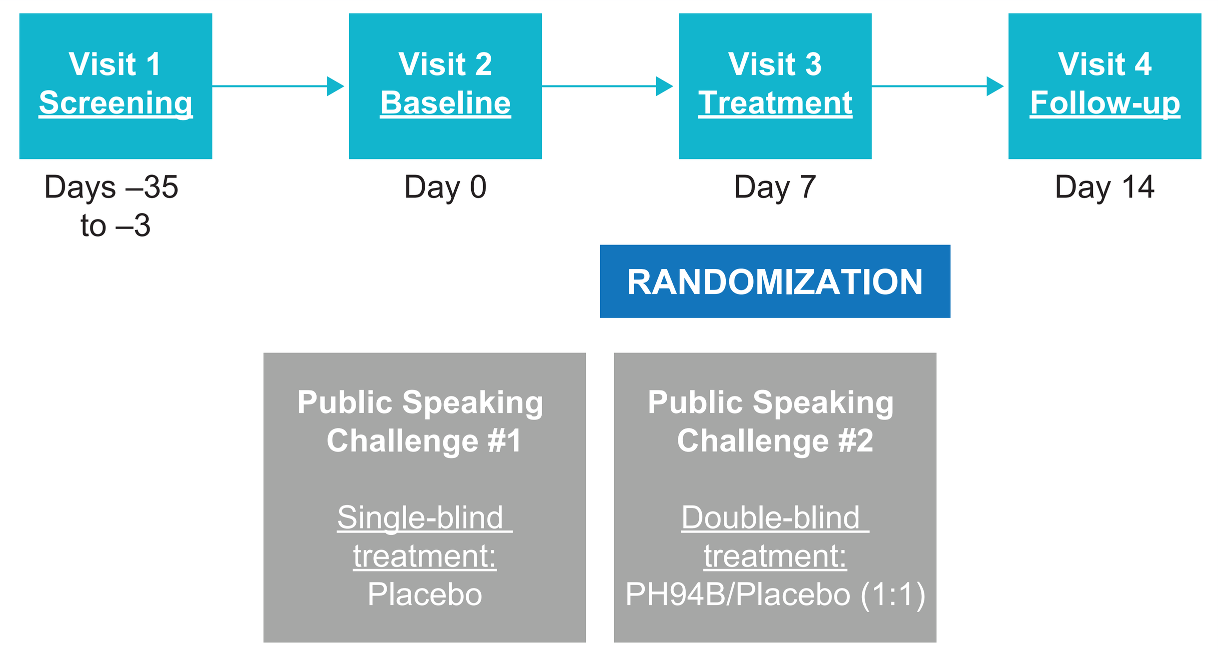
- The primary objective was to evaluate the efficacy of PH94B vs placebo in the relief of acute anxiety induced during a public speaking challenge (PSC) in adults with SAD as measured by SUDS

METHODS

Study Design

- This multicenter, double-blind, randomized, placebo-controlled study included adults with SAD (NCT05011396) (**Figure 2**) as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition and confirmed by the Mini-International Neuropsychiatric Interview

Figure 2. Study Design



- Eligible participants provided signed informed consent, completed visit 1, and entered a screening period of 3 to 35 days
- Participants who continued to meet all eligibility criteria at the end of the screening period were scheduled to return for visit 2
  - At visit 2, participants who continued to meet all eligibility criteria received placebo nasal spray in each nostril and took part in a 5-minute PSC
  - SUDS scores were recorded before and every minute during the PSC
  - Participants who reported SUDS scores ≥75 during the visit 2 PSC were scheduled to return 1 week later for visit 3
- Participants who continued to meet eligibility criteria at visit 3 were randomized to receive fasedienol (3.2 µg intranasally; 1.6 µg in each nostril) or placebo for self-administration and took part in another 5-minute PSC, with SUDS scores recorded before and every minute during the PSC
- Following the PSC at visit 3, trained raters completed a Clinical Global Impression of Improvement (CGI-I) assessment and study participants completed a Patient Global Impression of Change (PGI-C) questionnaire

Participants

Key Inclusion Criteria

- Adults aged ≥18 years
- Current diagnosis of SAD as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition
- Clinician-rated Liebowitz Social Anxiety Scale total score ≥70 at screening (visit 1)
- Clinician-rated Hamilton Rating Scale for Depression total score <18 at screening (visit 1)

Key Exclusion Criteria

- Any history of bipolar I or II disorder, schizophrenia, schizoaffective disorder, psychosis, anorexia or bulimia, premenstrual dysphoric disorder, autism-spectrum disorder, or obsessive-compulsive disorder, or any other current Axis I disorder, other than SAD, which is the primary focus of treatment
- 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
- 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
- A positive urine drug screen at the screening or baseline visit
- History of cancer or malignant tumor not in remission for ≥2 years (participants with basal cell skin cancers are not excluded)

Endpoints

- Primary
  - Difference between the average SUDS score from double-blind visit 3 to the single-blind visit 2 PSC for fasedienol vs placebo
- Secondary
  - CGI-I response (much or very much less anxious) with fasedienol vs placebo at the end of visit 3
  - Safety was assessed via the overall frequency of treatment emergent adverse events (TEAEs), their severity, serious TEAEs, and TEAEs leading to discontinuation
- Exploratory
  - PGI-C response (much or very much less anxious) with fasedienol vs placebo at the end of visit 3
  - SUDS response (≥20-point improvement from visit 2 to visit 3) with fasedienol vs placebo

Statistical Analysis

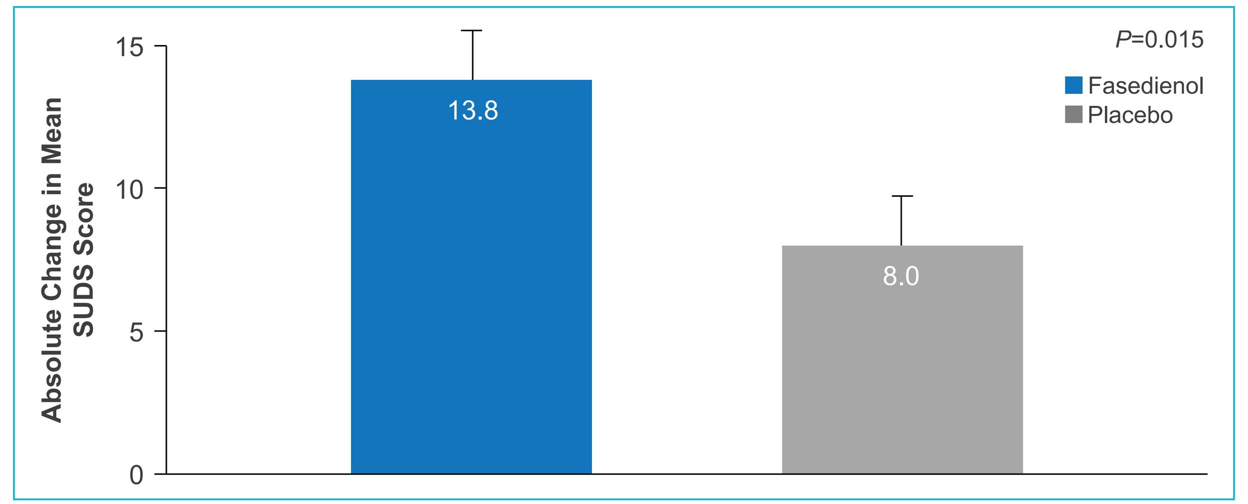
- Efficacy analyses
  - For each participant at each PSC, average SUDS scores were calculated from SUDS scores recorded at 1-minute intervals during each performance
  - An analysis of covariance model was used to test the null hypothesis that average change from baseline in SUDS scores did not differ between fasedienol- and placebo-treated participants
    - Treatment group and site were included as factors; baseline average SUDS score was a covariate
  - The secondary CGI-I efficacy endpoint was analyzed using a normal approximation test for the difference between 2 binomial proportions
    - The null hypothesis was tested that the population proportions were equal
- Safety analysis
  - Descriptive statistics were used to assess safety and tolerability of fasedienol, measured by reports of TEAEs

RESULTS

Primary, Secondary, and Exploratory Efficacy Endpoints

- Fasedienol-treated participants (n=70) demonstrated a significantly greater reduction in mean SUDS score (mean change: −13.8) than placebo-treated participants (n=71; mean change: −8.0), with a mean difference of −5.8 (P=0.015) (**Figure 3**)

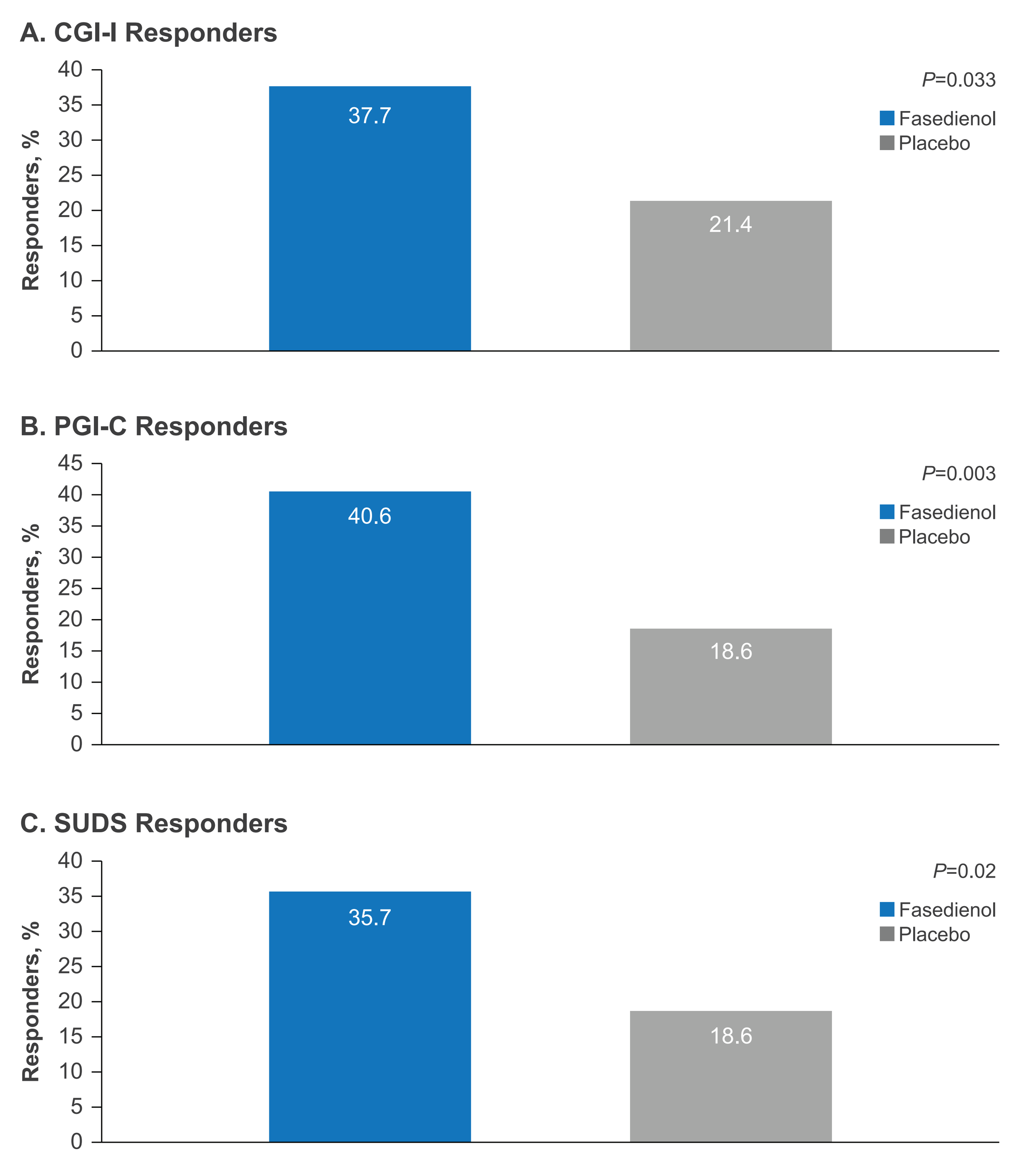
Figure 3. Primary Efficacy: Absolute Change in Mean SUDS (Visit 3 to Visit 2)



SUDS, Subjective Units of Distress Scale.

- CGI-I response significantly favored fasedienol over placebo (37.7% vs 21.4%; P=0.033) (**Figure 4A**)
- PGI-C response significantly favored fasedienol over placebo (40.6% vs 18.6%; P=0.003) (**Figure 4B**)
- Significantly more patients taking fasedienol vs placebo were SUDS responders (35.7% vs. 18.6%; P=0.02) (**Figure 4C**)

Figure 4. Secondary and Exploratory Efficacy Endpoints



CGI-I, Clinical Global Impression of Improvement; PGI-C, Patient Global Impression of Change; SUDS, Subjective Units of Distress Scale.

Safety and Tolerability

- Fasedienol was well tolerated; there were no TEAEs that occurred in more than 1 participant during fasedienol treatment (**Table 1**)

Table 1. Incidence of TEAEs

	During or After Visit 3 Dosing		
Preferred Term	**Fasedienol n (%)**	**Placebo n (%)**	**Overall n (%)**
Subjects with at least 1 TEAE	**8 (11.4)**	**5 (7.1)**	**13 (9.3)**
COVID-19	1 (1.4)	1 (1.4)	2 (1.4)
Dizziness	1 (1.4)	1 (1.4)	2 (1.4)
Pyrexia	0	2 (2.9)	2 (1.4)
Anxiety	1 (1.4)	0	1 (0.7)
Arthralgia	1 (1.4)	0	1 (0.7)
Aspartate aminotransferase increased	1 (1.4)	0	1 (0.7)
Dysgeusia	1 (1.4)	0	1 (0.7)
Headache	0	1 (1.4)	1 (0.7)
Nasal discomfort	1 (1.4)	0	1 (0.7)
Nasopharyngitis	1 (1.4)	0	1 (0.7)
Pharyngitis streptococcal	0	1 (1.4)	1 (0.7)
Rash	0	1 (1.4)	1 (0.7)
Somnolence	1 (1.4)	0	1 (0.7)

COVID-19, coronavirus disease 2019; TEAE, treatment-emergent adverse event.

- No severe or serious AEs were reported
- There were no discontinuations for AEs following exposure to fasedienol
- AEs were infrequent and mild or moderate in severity

CONCLUSIONS

- The phase 3 PALISADE-2 trial results demonstrated that a single dose of fasedienol prior to a stressful PSC reduced anxiety levels as measured by SUDS scores
- Clinician-rated (CGI-I) and participant-rated (PGI-C and SUDS) response rates supported the primary efficacy findings, significantly favoring fasedienol vs placebo
- The results also confirm the nasal-amygdala neural circuits as a new portal for administration of pharmaceuticals and support the continued development of fasedienol as a first-in-class, rapid-onset, well-tolerated treatment for SAD without addictive properties

References

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Key Contributors

MRL contributed to planning and conducting the trial, planning data analyses, data interpretation, and medical writing. **ES** contributed to the review and organization of the clinical data, interpretation of the results, and medical writing. **RH** contributed to the design and planning of the study, development of the statistical analysis plan, final data analysis/graphics/interpretation, and medical writing. **BR** contributed to the review and interpretation of safety data, medical monitoring of the trial, and medical writing. **RAB** contributed to the data analysis, critical input, and medical writing. **LM** contributed to the study design and execution, data interpretation, and medical writing.

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Disclosures

Michael R. Liebowitz: Managing Director and owner of The Medical Research Network, LLC; owner of stock and stock options in Vistagen Therapeutics, Inc.; and holds the copyright to the Liebowitz Social Anxiety Scale (LSAS) and has licensed it to Vistagen Therapeutics, Inc., for use in clinical trials. **Louis Monti, Ester Salmán, Rita Hanover, Brittney Reed,** and **Ross A. Baker:** Employees and owners of stock or stock options in Vistagen Therapeutics, Inc.

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