A Phase 3 Open-label Safety Trial of Fasedienol (PH94B) Nasal Spray in the Treatment of Anxiety in Adults With Social Anxiety Disorder (SAD)

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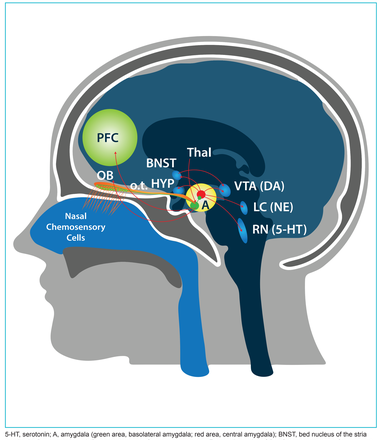
INTRODUCTION

- Social anxiety disorder (SAD) is characterized by intense and persistent fear of embarrassment or humiliation in social or performance situations that markedly impacts occupational functioning and social life
- Fasedienol (PH94B; 3β-androsta-4,16-dien-3-ol) is a synthetic neuroactive steroid from the androstane family of pherines that is administered intranasally and is under phase 3 development in SAD
- Fasedienol is proposed to activate nasal chemosensory neurons in the periphery that in turn connect with a subset of olfactory bulb neurons that directly project to GABAergic forward inhibitory neurons in the amygdala regulating fear and anxiety (**Figure 1**)[1]
- In a phase 2 study (NCT01217788), fasedienol was well tolerated and significantly reduced anxiety during public speaking and social interaction challenges vs placebo as evaluated by the Subjective Units of Distress Scale score reduction[2]
- A similarly designed follow-on phase 3 study (PALISADE-1; NCT04754802) failed to meet its primary endpoint and is still under internal review
- Fasedienol exerts its anxiolytic effects without systemic distribution, potentiation of GABA-A receptors, or direct activity on central nervous system neurons in the brain[3,4]

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



5-HT, serotonin; A, amygdala (green area, basolateral amygdala; red area, central 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 nuclei; Thal, thalamus; VTA, ventral tegmental area.

OBJECTIVES

- The primary objective was to evaluate the safety and tolerability of repeated dosing of fasedienol over a period of up to 12 months
- Exploratory objectives included the evaluation of change in behavior assessment scores and the pattern of PH94B use in patients with SAD from baseline through the end of treatment
  - Efficacy results were calculated based on observed cases

METHODS

Study Design

- This phase 3, open-label study (NCT05030350) assessed the as-needed intranasal administration of fasedienol 3.2 µg (e.g., 1.6 µg in each nostril), up to 4 times/day for up to 12 months
- The study comprised a 7- to 35-day screening period, a treatment period of up to 12 months, and a follow-up visit at 2 weeks after the last visit
- Patients provided written informed consent before any study-related procedures were initiated, including the cessation of prohibited concomitant therapy

Study Participants

- Adults aged 18–65 years with SAD who either completed the PALISADE-1 (NCT04754802) or PALISADE-2 (NCT05011396) acute SAD studies or enrolled de novo
- Included patients who had a Hamilton Depression Rating Scale-17 (HAMD-17) score <18
- Patients were excluded in the presence of other Axis I disorders that were the primary focus of treatment; any clinically significant findings putting the patient at risk; a history of nasal pathology/surgery/trauma or other conditions compromising intranasal drug delivery; alcohol use disorder; benzodiazepine (BZD) or beta-blocker use within 30 days; daily BZD use of >1 month duration at visit 1; or an increased risk for suicide

Assessments

- Primary outcome assessments included the incidence and severity of treatment-emergent adverse events (TEAEs), TEAEs leading to discontinuation, and serious TEAEs; change from baseline in physical examination, vital signs, clinical chemistry, hematology, suicidality (Columbia Suicide Severity Rating Scale [C-SSRS]), level of depression (HAMD-17) and 12-lead electrocardiogram [ECG] assessed monthly)
- Exploratory outcome assessments included changes over time on the Liebowitz Social Anxiety Scale (LSAS), Clinical Global Impression of Severity and Improvement (CGI-S, CGI-I), Patient Global Impression of Change (PGI-C), Hamilton Anxiety Scale (HAM-A), and change in pattern of fasedienol use over time, assessed monthly

Statistics

- Safety, tolerability, and efficacy variables were summarized using descriptive statistics
- Descriptive summaries for categorical variables included count and percentage; for continuous variables, these included number of patients (n), mean, standard deviation (SD), median, minimum, and maximum. Where appropriate, 95% confidence intervals (CIs) were reported
- Summary statistics were reported based on observed data

RESULTS

- Of 482 patients enrolled, 481 received ≥1 dose of study medication and made up the safety population; patient details are presented in **Table 1**
- The study was closed early for business reasons unrelated to clinical results or safety findings
- At the time of closure, study participants had a mean (SD) duration of participation of 121.4 (71.4) days, with a maximum duration of 320 days

Table 1. Baseline Demographics and Patient Characteristics

Parameter	Fasedienol (N=481)
Age, mean (SD), years	36.4 (12.3)
18–35, n (%)	249 (51.8)
36–55, n (%)	198 (41.2)
≥56, n (%)	34 (7.1)
Race, n (%)	
White	318 (66.1)
Black	87 (18.1)
Asian	41 (8.5)
More than one race	13 (2.7)
Not reported	9 (1.9)
American Indian/Alaska Native	6 (1.2)
Other	5 (1.0)
Sex, n (%)	
Female	300 (62.4)
Male	181 (37.6)
Ethnicity, n (%)	
Hispanic or Latino	73 (15.2)
Not Hispanic or Latino	398 (82.7)
Not reported	10 (2.1)
Age of SAD onset, mean (SD), years	13.9 (7.6)
HAMD-17 total score, mean (SD)	6.5 (4.2)
LSAS total score, mean (SD)	93.4 (18.8)
HAM-A total score, mean (SD)	9.5 (6.4)
CGI-S total score >4, n (%)	242 (50.3)
C-SSRS, n (%)	
Suicidal ideation in last 6 months	17 (3.5)
Suicidal behavior in last 2 years	1 (0.2)

CGI-S, Clinical Global Impression-Severity; C-SSRS, Columbia Suicide Severity Rating Scale; HAM-A, Hamilton Anxiety Scale; HAMD-17, Hamilton Depression Rating Scale-17; LSAS, Liebowitz Social Anxiety Scale; PWC-20, Penn Physician Withdrawal Checklist-20; SAD, social anxiety disorder; SD, standard deviation.

Safety and Tolerability

- Long-term intranasal fasedienol 3.2 µg, up to 4x daily prn, was safe and well tolerated in adults with SAD
- In total, 273 (56.8%) patients had ≥1 TEAE; 108 (22.5%) of TEAEs were considered related to treatment
- Headache (82 [17.0%]) and COVID-19 infection (55 [11.4%]) were the only TEAEs that occurred in >5% of patients (**Table 2**); 42 (8.7%) headaches and none of the COVID TEAEs were considered treatment related
- Overall, 186 (38.7%) TEAEs were mild, 78 (16.2%) were moderate, and 9 (1.9%) were severe; none of the severe TEAEs were considered treatment related by the investigator

Table 2. TEAEs Occurring in ≥2% of Patients Treated With Fasedienol

TEAE	Fasedienol (N=481) n (%)
Headache	82 (17.0)
COVID-19 infection	55 (11.4)
Dizziness	22 (4.6)
Epistaxis	18 (3.7)
Nausea	15 (3.1)
Oropharyngeal pain	15 (3.1)
Nasopharyngitis	13 (2.7)
Urinary tract infection	13 (2.7)
Nasal congestion	12 (2.5)
Upper respiratory tract infection	12 (2.5)

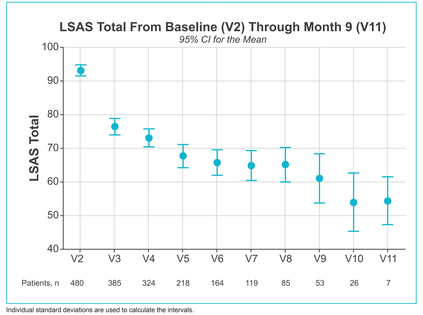
TEAE, treatment-emergent adverse event.

- Fourteen patients (2.9%) experienced a TEAE leading to discontinuation
  - Nasal congestion, rhinalgia, and headache were the cause in 2 patients each; no other TEAE led to discontinuation in >1 patient
- Six patients (1.2%) experienced a treatment-emergent serious adverse event; none were considered related to fasedienol
- One death occurred (0.2%) in a patient diagnosed with gall bladder and lung cancer
- There were no relevant changes in ECGs, laboratory, or clinical findings observed
- At baseline, 18 (3.7%) patients endorsed suicidal ideation (n=17, 3.5%) or suicidal behavior (n=1, 0.2%) based on the C-SSRS
  - At the end of treatment, 6 (1.4%) endorsed suicidal ideation but none endorsed suicidal behavior based on the C-SSRS
- Mean (SD) baseline HAMD-17 total score of 6.5 (4.2) improved to 5.8 (4.9) at the end of treatment

Exploratory Outcomes

- In patients who remained on treatment, mean (SD) LSAS total scores decreased from 93.4 (18.8) at baseline to 54.4 (7.8) at month 9 (**Figure 2**)

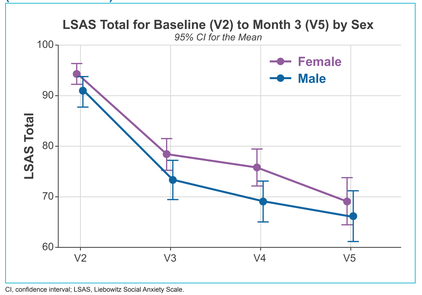
Figure 2. LSAS Total Score Change Over Time (Observed Cases)



Individual standard deviations are used to calculate the intervals.
CI, confidence interval; LSAS, Liebowitz Social Anxiety Scale.

- In patients who remained on treatment through month 3, fasedienol was associated with similar LSAS total score reductions (i.e., improvement) in both males and females (**Figure 3**)

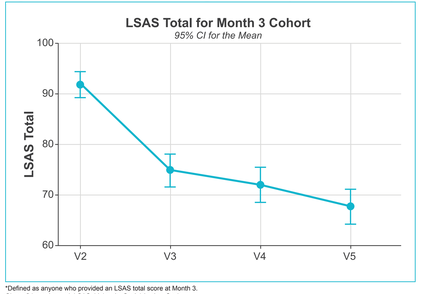
Figure 3. LSAS Total Scores, Baseline to Month 3 by Sex (Observed Cases)



CI, confidence interval; LSAS, Liebowitz Social Anxiety Scale.

- In an analysis of 218 patients who completed treatment through month 3, mean (SD) LSAS scores decreased (i.e., improved) from 91.72 (19.1) at baseline to 67.59 (25.6) at month 3 (**Figure 4**)

Figure 4. LSAS Total Score Change Over Time (Month 3 Cohort*)



*Defined as anyone who provided an LSAS total score at Month 3.
CI, confidence interval; LSAS, Liebowitz Social Anxiety Scale.

- In 385 patients who provided LSAS data at visit 2, the mean (SD) baseline LSAS total score of 93.4 (18.8) declined (i.e., improved) to 72.3 (25.3) by month 3 when analyzed according to last observation carried forward; these results were similar to those from the observed case analysis noted above
- Treatment with fasedienol was associated with decreased illness severity and increased frequency of CGI-I and PGI-C response over time (**Table 3**)
  - There was congruence between clinician and patient assessments of improvement throughout most of the trial

Table 3. CGI-S, CGI-I, and PGI-C Response Over Time (Observed Cases)

Visit	n	CGI-S (% >4)	CGI-I (% Response)	PGI-C (% Response)
Baseline (V2)	481	50.3	N/A	N/A
Month 1 (V3)	385	21.8	28.6	26.8
Month 2 (V4)	326	17.2	33.7	35.6
Month 3 (V5)	218	12.4	42.7	43.6
Month 4 (V6)	165	12.1	48.5	44.2
Month 5 (V7)	119	15.1	44.5	42.0
Month 6 (V8)	85	17.6	48.2	48.2
Month 7 (V9)	53	17.0	58.5	47.2
Month 8 (V10)	26	3.8	69.2	50.0
Month 9 (V11)	7	0.0	71.4	42.9

For each visit, the percent of patients remaining above a clinician-rated illness severity level of 4 (moderately ill) or achieving the level of "responder" (much or very much clinician or patient-rated improvement) reflects the number who meet the criteria divided by the number with non-missing data for CGI-S, CGI-I, and PGI-C at that visit multiplied by 100.
CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; PGI-C, Patient Global Impression of Change.

- Mean (SD) HAM-A total scores decreased (i.e., improved) from 9.5 (6.4) at baseline to 7.5 (6.0) at end of treatment based on observed cases
- The number of doses taken by each patient over the course of the study was not predictive of the number of AEs: shared variance (r = .107) was estimated at 1.2% (r^2 = .011449)
- The number of doses taken by each patient over the course of the study was not predictive of the total LSAS change from baseline over 1 month. At visit 3 (month 1), the shared variance (r = .177) was estimated at 3.1% (r^2 = .03133)

CONCLUSIONS

- Long-term, open-label treatment data from ~500 patients suggest that repeated, as-needed administration of fasedienol 3.2 µg was safe and well tolerated and provided improved overall symptom control in adults with SAD

References

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Key Contributors

JL contributed to the review and organization of the clinical data, interpretation of the results, and medical writing. **ES** contributed to the review and organization of the clinical data, interpretation of the results, and medical writing. **RH** contributed to conception and design of the study, development of the statistical analysis plan, final data analysis/graphics, 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. **MAS** contributed to the design and management of the trial and medical writing. **MRL** contributed to study design and execution, data interpretation, and medical writing.

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Disclosures

JL, ES, RH, BR, RAB, and **MAS:** Employees and owners of stock or stock options in Vistagen Therapeutics, Inc.

MRL: 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.

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