Age of Onset of Social Anxiety Disorder (SAD) in Trials of Fasedienol (PH94B) Nasal Spray

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INTRODUCTION

- Social anxiety disorder (SAD) is a prevalent and impactful psychiatric disorder associated with intense emotional or physical discomfort in social and/or performance situations[1]
- SAD can manifest early in childhood,[2,3] and early onset of SAD has been associated with severity of symptoms, poorer social functioning, poor treatment outcomes, and an elevated risk of comorbid disorders such as depression and suicide attempts[2-4]
  - However, the association between early onset of SAD and poorer outcomes has not been observed in all study populations[5]
- Fasedienol (PH94B; 3β-androsta-4,16-dien-3-ol) is an investigational synthetic pherine nasal spray from the androstane family of pherines currently in development for the treatment of SAD[6,7]
  - In a phase 2 study, treatment with fasedienol rapidly and significantly improved scores from baseline on the Subjective Units of Distress Scale (SUDS) in subjects with SAD during a public speaking challenge (PSC) task[7]
  - Significant improvement in mean peak SUDS score also was observed in another phase 2 study in which subjects with SAD received fasedienol or placebo up to 4 times daily as needed before feared social or performance events in daily life[8]
- The efficacy and safety of fasedienol were assessed using the PSC task in two phase 3 studies, PALISADE-1 (NCT04754802) and PALISADE-2 (NCT05011396)
  - Subjects who completed PALISADE-1 and PALISADE-2 were eligible to enroll in an open-label long-term safety study (LTSS; NCT05030350), which also enrolled subjects de novo

OBJECTIVE

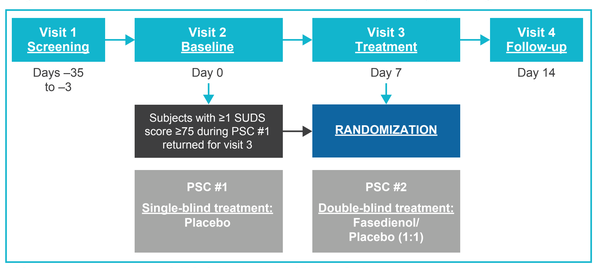
- The objective of this post hoc analysis was to assess the age of onset of SAD in PALISADE-1, PALISADE-2, and the LTSS and to describe the baseline characteristics of subjects with early (≤10 years of age) vs adolescent/adult (≥11 years) onset of SAD
  - Efficacy and safety results from PALISADE-1 and PALISADE-2 are reported to provide context

METHODS

Data Source

- This analysis included data from subjects enrolled in PALISADE-1 and PALISADE-2, which were similarly designed, multicenter, double-blind, randomized, placebo-controlled studies of fasedienol for the treatment of SAD (**Figure 1**). All subjects who enrolled in PALISADE-1 and PALISADE-2 were eligible to enter the LTSS
- Subjects who enrolled de novo in the LTSS were also included in the current analysis
- Data from the 3 studies were pooled for analysis

Figure 1. PALISADE-1 and PALISADE-2 Study Design



PSC, public speaking challenge; SUDS, Subjective Units of Distress Scale.

Participants

Key Inclusion Criteria

- PALISADE-1 and PALISADE-2
  - Adults aged ≥18 to ≤65 years
  - Current diagnosis of SAD as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*) and confirmed by the Mini-International Neuropsychiatric Interview (MINI)
  - Clinician-rated Liebowitz Social Anxiety Scale[9] (LSAS) total score ≥70 at screening
  - Clinician-rated 17-item Hamilton Depression Rating Scale[10] (HAMD-17) total score <18 at screening
- LTSS
  - Adults aged ≥18 to ≤65 years
  - Participation in PALISADE-1 or PALISADE-2 or de novo enrollment with approval by the sponsor on a case-by-case basis
  - Current diagnosis of SAD as defined in the *DSM-5* and confirmed by the MINI
  - HAMD-17 total score <18 at screening or baseline

Key Exclusion Criteria (All Studies)

- 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, in the opinion of the investigator or based on Columbia Suicide Severity Rating Scale scores at screening and baseline visits
- Other exclusion criteria were related to nasal pathology, current malignant disease, use of psychotropic medication, or a positive drug screen at study entry

Age of Onset Assessments and Post Hoc Analysis

- Medical and psychiatric histories were obtained at the screening visit, and the LSAS, which assesses severity of fear and avoidance in social and performance situations,[9] was administered
- Outcomes of interest included history of psychiatric illness based on the screening interview for medical and psychiatric comorbidities, alcohol and drug use, previous suicide attempts, baseline LSAS score, self-reported age of onset of SAD, and SAD treatment history
  - If no previous psychotropic drug treatment was reported, the year of visit 1 was used as the year of first treatment of SAD
- Subjects were categorized according to early onset (≤10 years of age) or adolescent/adult onset (≥11 years of age) of SAD, and outcomes were summarized for early-onset and adolescent/adult-onset groups
- Efficacy results on the primary endpoint of difference in anxiety compared with placebo from visit 2 to visit 3, measured by average SUDS score change, were summarized for PALISADE-1 and PALISADE-2
- Safety and tolerability of fasedienol were assessed based on adverse event reporting through treatment and follow-up; treatment-emergent adverse events (TEAEs) were summarized by treatment group for the PALISADE-1 and PALISADE-2 studies

RESULTS

Age of Onset

- Overall, 31% of subjects had an onset of SAD at age 10 years or younger (**Table 1**)
- The proportions of subjects with early onset of SAD were similar for PALISADE-1, PALISADE-2, and the LTSS

Table 1. Proportions of Subjects with Early Onset vs Adolescent/Adult Onset of SAD, Fasedienol Phase 3 Studies

Study	Early Onset (≤10 Years) n (%)	Adolescent/ Adult Onset (≥11 Years) n (%)	Total N
PALISADE-1	69 (30.9)	154 (69.1)	223
PALISADE-2	41 (29.1)	100 (70.9)	141
LTSS	78 (32.0)	166 (68.0)	244
Overall	188 (30.9)	420 (69.1)	608

LTSS, long-term safety study; SAD, social anxiety disorder.

- Mean age of onset of SAD was 14 years overall, 7 years in the early-onset group, and 17 years in the adolescent/adult-onset group (**Table 2**)

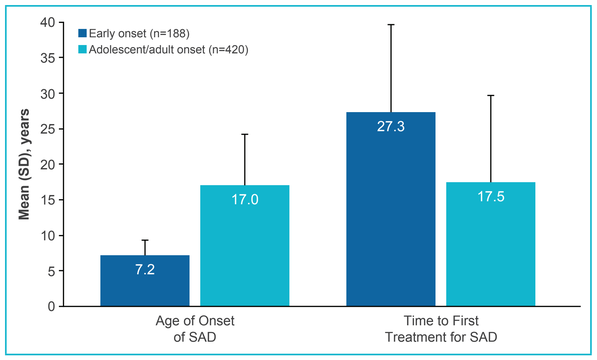
Table 2. Age of Onset and SAD Treatment History Among Subjects with Early Onset vs Adolescent/Adult Onset of SAD, Overall Population

Parameter	Early Onset (≤10 Years)	Adolescent/ Adult Onset (≥11 Years)	Total N
Subjects, N	**188**	**420**	**608**
Current age (years), mean (SD)	36.1 (12.7)	35.4 (11.9)	35.6 (12.1)
Median (range)	32 (19–64)	33 (18–64)	33 (18–64)
Age of onset of SAD (years), mean (SD)	7.2 (2.1)	17.0 (7.3)	14.0 (7.6)
Median (range)	7 (2–10)	15 (14–57)	13 (2–57)
Age of first SAD treatment (years), mean (SD)	34.5 (12.2)	34.5 (12.3)	34.5 (12.3)
Median (range)	31 (18–64)	32 (14–65)	32 (14–65)
Time from onset to first treatment for SAD (years), mean (SD)	27.3 (12.4)	17.5 (12.2)	20.6 (13.0)
Median (range)	24 (9–57)	14 (0–48)	18 (0–57)

SAD, social anxiety disorder; SD, standard deviation.

- Age of first treatment for SAD was similar between groups (35 years for both groups), resulting in a substantially longer gap between onset of SAD and first treatment in the early-onset group compared with the adolescent/adult-onset group (**Figure 2**)
  - Both groups showed long gaps between onset of SAD and onset of first treatment

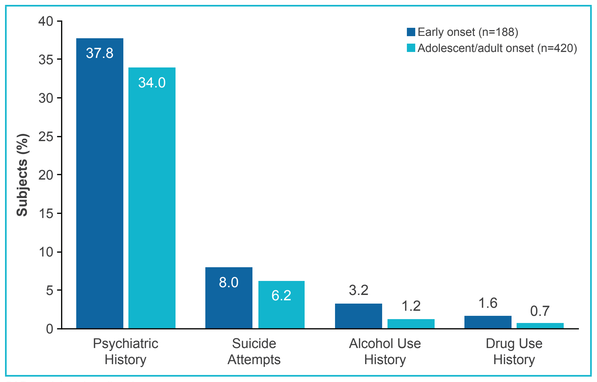
Figure 2. Mean Age of Onset and Time to First Treatment of SAD, Overall Population



SAD, social anxiety disorder; SD, standard deviation.

- Mean LSAS scores at baseline were similar for the early- and adolescent/adult-onset groups (mean [standard deviation], early: 96.9 [17.8]; adolescent/adult: 96.2 [16.1])
- Psychiatric history and suicide attempts were similar between the 2 groups (**Figure 3**)
- Alcohol and drug use rates were low overall and more than double in subjects with early-onset SAD vs those with adolescent/adult-onset SAD

Figure 3. Mental Health History Among Subjects with Early Onset vs Adolescent/Adult Onset of SAD, Overall Population



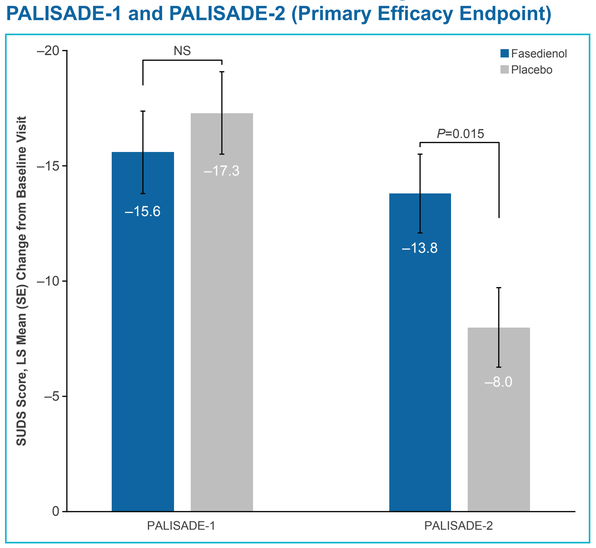
SAD, social anxiety disorder.

- SAD treatment histories were also similar between the early- and adolescent/adult-onset groups
  - Previous psychotropic drug treatment for SAD was reported by 20.7% and 21.2% of subjects with early-onset and adolescent/adult-onset SAD, respectively; previous non-drug mental health treatment for SAD was reported by 19.1% and 16.2% of subjects, respectively

Efficacy and Safety

- In PALISADE-1, least squares (LS) mean (standard error [SE]) change in average SUDS score from visit 2 (baseline) to visit 3 was similar between fasedienol (N=111) and placebo (N=111) (**Figure 4, left**)
- In PALISADE-2, fasedienol (N=70) had a greater LS mean (SE) change in average SUDS score from visit 2 (baseline) to visit 3 compared with placebo (N=70) (**Figure 4, right**)

Figure 4. LS Mean (SE) Change in SUDS Score from Visit 2 to Visit 3 for Fasedienol vs Placebo During a PSC Task in PALISADE-1 and PALISADE-2 (Primary Efficacy Endpoint)



IP, investigational product; LS, least squares; NS, not significant; PSC, public speaking challenge; SE, standard error; SUDS, Subjective Units of Distress Scale.

- In PALISADE-1 and PALISADE-2, fasedienol was well tolerated; few TEAEs occurred in >1 subject in any treatment arm (**Table 3**)
- No serious or severe adverse events were reported

Table 3. TEAEs During or After the Double-Blind Treatment Period, PALISADE-1 and PALISADE-2

	PALISADE-1		PALISADE-2	
	Fasedienol (n=111)	Placebo (n=112)	Fasedienol (n=70)	Placebo (n=70[a])
Subjects with ≥1 TEAE, n (%)	12 (10.8)	11 (9.8)	8 (11.4)	5 (7.1)
TEAEs reported in >1 subject in any treatment group, n (%)				
Headache	3 (2.7)	3 (2.7)	0	1 (1.4)
COVID-19	0	2 (1.8)	1 (1.4)	1 (1.4)

[a]One subject was randomized to placebo but was discontinued before treatment due to a positive urine screen.
COVID-19, coronavirus disease 2019; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Results of this analysis indicate that approximately 30% of study subjects with SAD had a self-reported onset of illness in childhood, at 10 years of age or younger
- Remarkably, the time to first treatment for SAD was, on average, 27 years from time of onset for the early-onset group and, on average, 18 years from onset for the adolescent/adult-onset group, underscoring a high unmet need for diagnosis and treatment of SAD, especially among children and adolescents
- Baseline severity of SAD and psychiatric and treatment histories were similar between subjects with early vs adolescent/adult onset of SAD
- History of alcohol/drug use was higher in the early-onset group than the adolescent/adult-onset group
- Results from two phase 2 and one phase 3 trial suggest that fasedienol is an effective treatment for acute anxiety associated with SAD, acknowledging one phase 3 trial conducted during the pandemic did not separate from placebo; the safety profile was similar to placebo in all studies
- When completed, ongoing phase 3 studies[11,12] will provide larger sample sizes for exploration of age of onset and treatment response

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Acknowledgments

This study was sponsored by Vistagen Therapeutics, Inc., South San Francisco,CA, USA. Medical writing and editorial support for this poster were provided by Noud van Helmond, MD, PhD, of Peloton Advantage, LLC, an OPEN Health company, and funded by Vistagen Therapeutics, Inc.

Disclosures

Louis Monti, Ester Salmán, and **Ross A. Baker:** Employees and owners of stock or stock options in Vistagen Therapeutics, Inc. **Stephen Coffey** and **Rita Hanover:** Statistical consultants to Vistagen Therapeutics, Inc. **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 and has licensed it to Vistagen Therapeutics, Inc., for use in clinical trials.

Presented at the Anxiety and Depression Association of America Conference, April 3–6, 2025, Las Vegas, NV