

Fasedienol Nasal Spray for Acute Treatment of Social Anxiety Disorder in Participants with Baseline LSAS Scores ≥ 95 : Subgroup Analyses from Two Multi-center, Randomized, Placebo-controlled Public Speaking Challenge Trials

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INTRODUCTION

Fasedienol is an investigational synthetic neuroactive nasal spray from the androstane family of pherines currently in Phase 3 development for the acute treatment of social anxiety disorder (SAD)¹:

- Designed to trigger neural signals in the olfactory bulb, which travel to the “fear centers” of the limbic amygdala, and other brain regions involved in emotion and behavior
- Rapid onset of effect on both emotional & physical symptoms of peak anxiety, as needed, without sedation or dizziness (associated with benzodiazepines or beta blockers)
- No detectable absorption (no observed drug/drug interactions)
- No observed binding to neurons in the brain, including abuse liability receptors (not a benzodiazepine)
- Favorable safety and tolerability data (reported in all clinical trials completed to date)
- Patient-tailored administration, as needed (up to 6 times per day)

OBJECTIVE

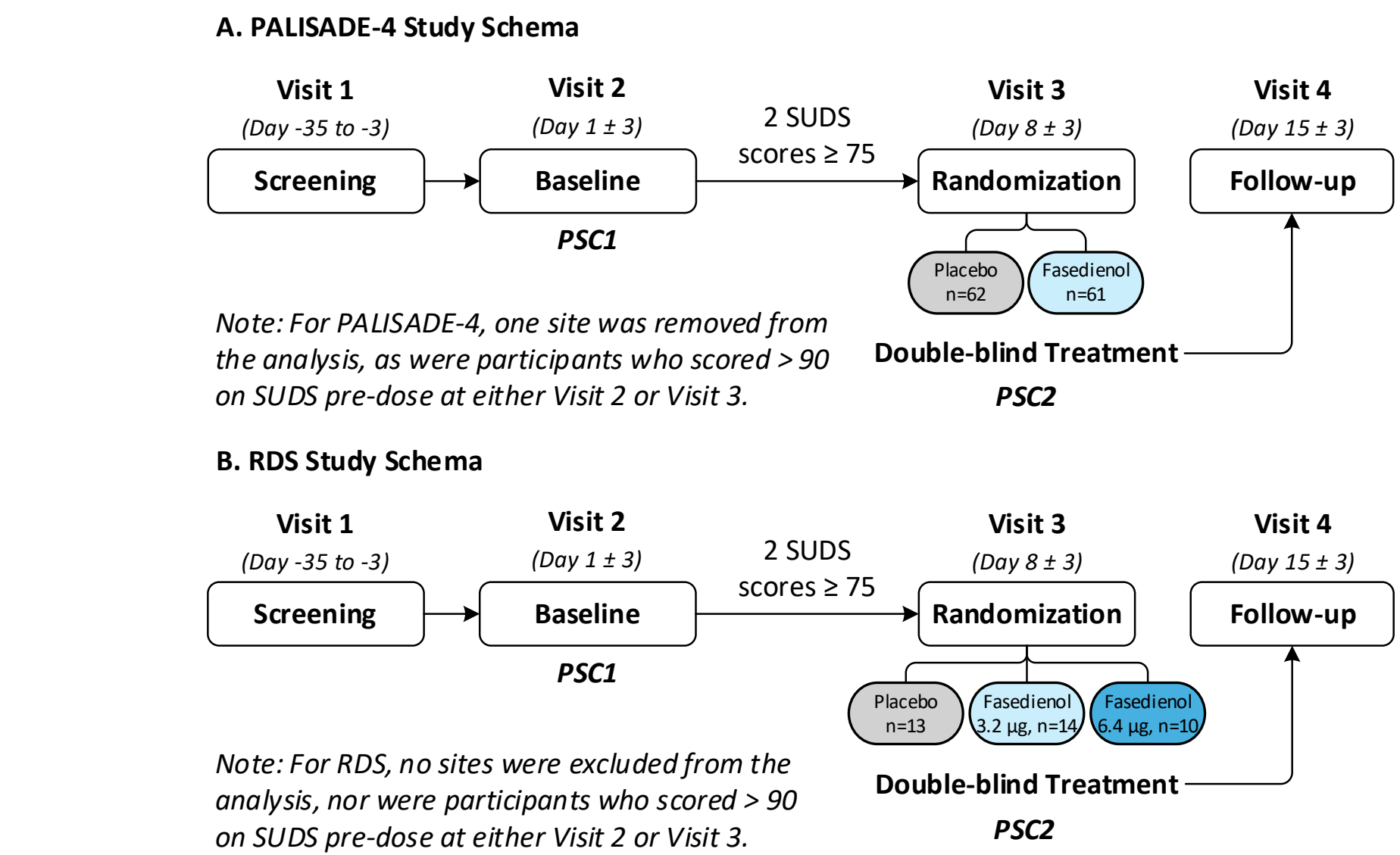
The objective of the present analyses was to evaluate the efficacy of fasedienol in participants with very severe SAD, defined as a baseline (V1) Liebowitz Social Anxiety Scale (LSAS) score ≥ 95 , in PALISADE-4 (NCT06615557) and Repeat Dose Study (RDS, NCT06809179). The subgroup analysis was post-hoc for PALISADE-4 and prespecified for RDS.

METHODS

Data Source

- PALISADE-4 was a Phase 3 multicenter, double-blind, randomized, placebo-controlled trial of fasedienol nasal spray for the acute treatment of anxiety induced by a PSC (**Figure 1A**).
- RDS was an exploratory Phase 2, three-arm, multicenter, randomized, double-blind, placebo-controlled trial to assess the efficacy, safety, and tolerability of a repeat dose of fasedienol 10 min after the first for the acute treatment of anxiety induced by a PSC (**Figure 1B**). The trial was not powered to show efficacy.

Figure 1. Study schema for PALISADE-4 (A) and RDS (B). The analyses included data from participants enrolled in PALISADE-4 and the RDS with very severe social anxiety as defined by baseline LSAS scores of ≥ 95 .



Participants (both trials)

Key Inclusion Criteria

- 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 (LSAS)^{2,3} total score ≥ 70 at screening (Visit 1)
- Clinician-rated 17-item Hamilton Depression Rating Scale¹⁰ (HAM-D-17) total score of < 18 at screening

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, in the opinion of the investigator or based on Columbia-Suicide Severity Rating Scale scores at screening and baseline visits

Post Hoc/Pre-specified Subgroup Data Analyses

- Medical and psychiatric histories were obtained at the screening visit (Visit 1), and the LSAS total score, which assesses severity of anxiety/fear and avoidance in social and performance situations was administered
- Efficacy was analyzed post hoc for participants with a ≥ 95 LSAS score at Visit 1 in PALISADE-4 (see Fig 1A) and pre-specified in RDS according to the statistical analysis plan (see Fig 1B). The difference in the patient reported SUDS for fasedienol compared with placebo from visit 2 to visit 3, was summarized for PALISADE-4 and RDS in the very severe subpopulations.³
- Statistical comparisons between fasedienol and placebo were made using two-tailed t-tests after correcting for pre-investigational product SUDS score and Fisher's exact test for the difference in proportions
- Safety and tolerability of fasedienol were assessed based on adverse event reporting through treatment and follow-up.

RESULTS

- On the primary endpoint, PALISADE-4 did not show statistical separation from placebo, possibly due to high placebo response rates in the overall randomized population
- Overall, 55% (123/223) of participants in the full analysis set were very severe in PALISADE-4, and 61% (37/61) in RDS.
- The baseline and demographic characteristics of the very severe subpopulation were not substantially different than the full analysis set population.
- Both PALISADE-4 and RDS showed similar safety and tolerability profiles across treatment arms to all clinical trials completed to date.
- Figure 2A shows an advantage for participants with very severe baseline (V1) social anxiety and a minimal improvement on placebo across the 25 min PSC. There was no difference between fasedienol and placebo on the primary outcome measure was significant vs. placebo (Figure 2B).
- Figure 2D confirms the minimal response to placebo among participants assessed with very severe social anxiety at baseline (V1); it also shows a suggestion of enhanced drug response in the fasedienol double-dose group, with relatively large effect sizes on difference from placebo in average SUDS scores for all fasedienol-treated participants (Figure 2C).
- Figure 2D also shows a nominally significant improvement in anticipatory anxiety (red ellipse), as measured by average SUDS score improvement at min 16 and 17 in the double-dose fasedienol group of -15.2 vs. placebo (increased anxiety of +5.69, $P=.05$, Cohen's $d=.83$); single dose also improved on anticipatory anxiety with an average SUDS score of -6.43, $P=.10$ vs. placebo, Cohen's $d=.63$.
- Figures 3 shows patient-reported PGI-C improvements consistent with the findings from SUDS in the very severe subpopulation.

Figure 2. Improvement in Average SUDS Scores among Participants with Very Severe Social Anxiety (LSAS ≥ 95). (A) PALISADE-4 minute-by minute pre-IP adjusted SUDS scores: V3(15-25)-V3(0) – V2(15-25)-V2(0). **Rectangle indicates SUDS anxiety level during the PSC (min 20 to minute 25).** (B) PALISADE -4 improvement in average pre-IP-adjusted SUDS score: V3(20-25)-V3(0) – V2(20-25)-V2(0). (C) RDS improvement in average pre-IP-adjusted SUDS score: V3(20-25)-V3(0) – V2(20-25)-V2(0). (D) RDS minute-by minute pre-IP adjusted SUDS: V3(15-25)-V3(0) – V2(15-25)-V2(0). **Ellipse indicates anticipatory anxiety (minutes 16 and 17) and rectangle indicates SUDS anxiety level during the PSC (minute 20 to minute 25).**

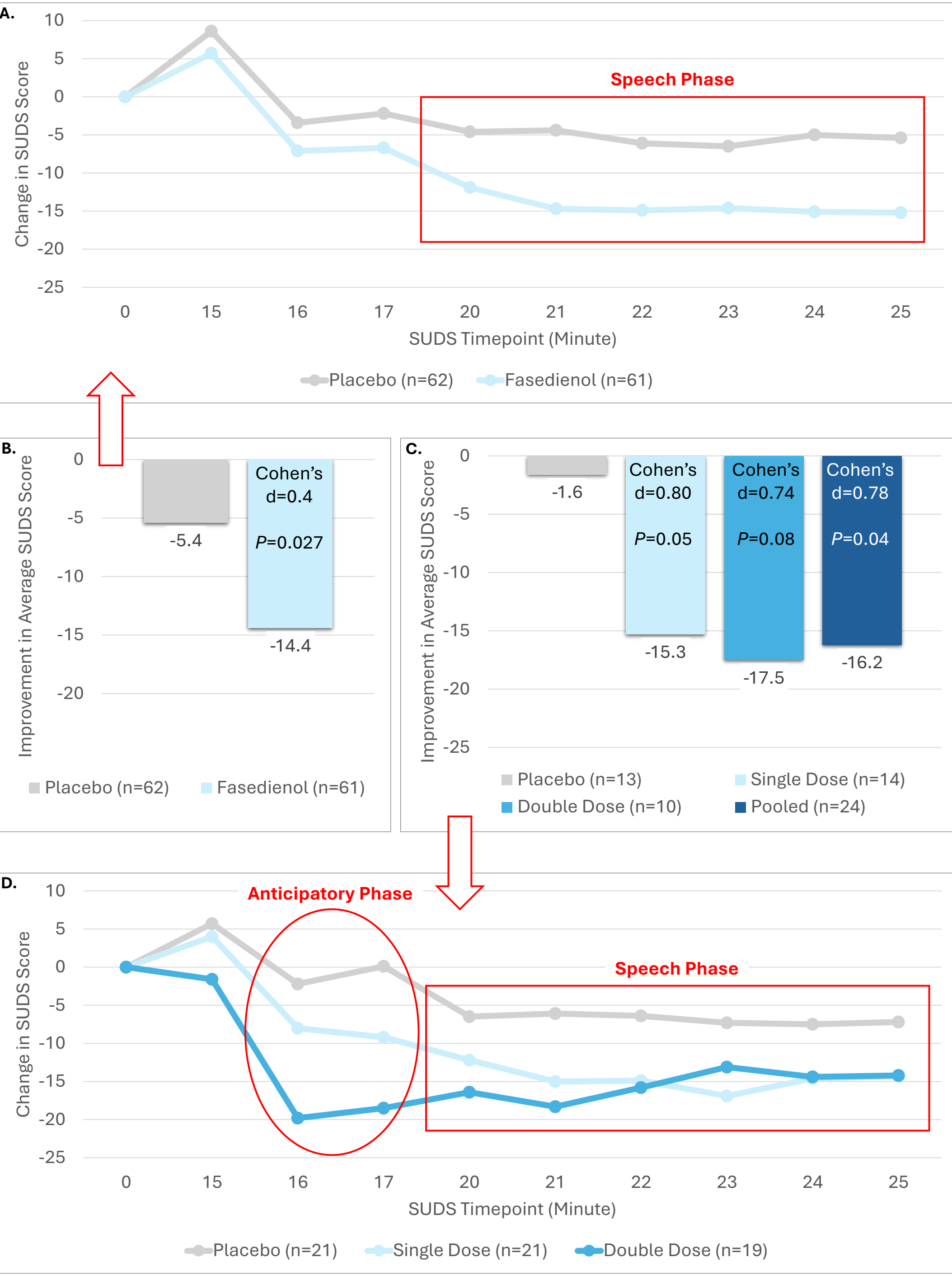
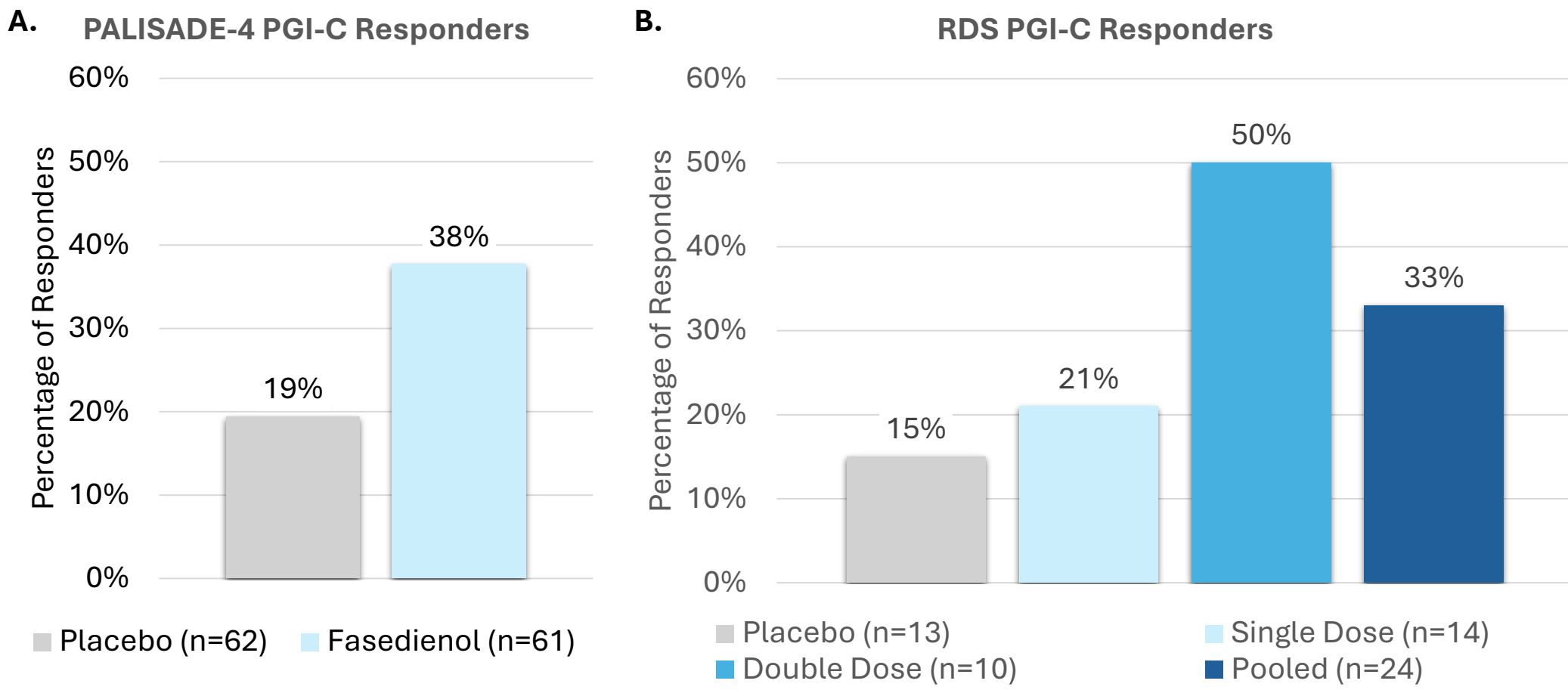


Figure 3. Proportion of PGI-C responders in very severe subpopulation. (A) PALISADE-4. (B) RDS.



CONCLUSIONS

- The subpopulation analyses from 2 trials shows a clear positive efficacy signal with strong effect sizes for fasedienol in participants with very severe baseline social anxiety as defined by baseline LSAS scores of ≥ 95 .
- The majority of participants in both studies met criteria for very severe social anxiety, indicating that the subpopulation was reasonably representative of the overall trial population.
- The patient-reported PGI-C in very severe participants also supports the SUDS findings in both trials
- Results from RDS showed participants with very severe social anxiety may benefit from a second dose of intranasal fasedienol 10 minutes after the first on improvements in average SUDS score during the PSC, on anticipatory anxiety pre-PSC, and on the PGI-C.
- Overall, the subpopulation analysis of very severe social anxiety from 2 trials supports fasedienol as an active drug and that further clinical development is warranted to confirm effectiveness of fasedienol in the acute treatment of SAD.

Note: Results are preliminary, pending final CSR.

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DISCLOSURES

Michael R. Liebowitz serves as a consultant to Vistagen, is a member of the Vistagen Scientific Advisory Board, owns stock and stock options in Vistagen, and receives licensing fees for use of the Liebowitz Social Anxiety Scale. Azmi Nasser, Aubrey Reid, Imogene Dunn, Eric Davis, Ross A. Baker, Angel Angelov, and Louis Monti are employees of Vistagen, and own stock and/or stock options in Vistagen.

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