Centanafadine Sustained Release in the Treatment of Adult Attention-Deficit/Hyperactivity Disorder: Secondary Outcomes From a Phase 2a Study

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Introduction. Centanafadine (CTN) is a potential first-in-class norepinephrine/dopamine/serotonin triple reuptake inhibitor (NDSRI) being investigated for the treatment of attention-deficit/hyperactivity disorder (ADHD). In a phase 2a study in adult males with ADHD, CTN sustained release (CTN SR) treatment significantly improved ADHD Rating Scale-IV (ADHD-RS-IV) total and subscale scores and was well tolerated. Additional efficacy outcomes from this study are reported.
Methods. This flexible-dose (CTN SR 200–500 mg/d), single-blind, exploratory study enrolled males aged 18–55 years who met *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* criteria for ADHD and had a baseline ADHD-RS-IV total score ≥28 and Clinical Global Impression-Severity score of ≥4. The study had a screening period, a 1-week placebo run-in, and a 4-week CTN SR treatment phase. Previously unreported secondary outcomes of ADHD-RS-IV change from end of the single-blind placebo run-in and ADHD-RS-IV response (≥30% and ≥50% score reductions) at weeks 1, 2, 3 (on-treatment), and 6 (follow-up) are presented. Analyses were based on observed results using descriptive statistics.
Results. Of 45 patients enrolled, 41 received ≥1 dose of study medication and 37 completed the 4-week treatment phase (mean [SD] age, 38.24 [11.88] years; 91.9% White). At baseline, mean (SD) ADHD-RS-IV total, Inattentive subscale, and Hyperactive/Impulsive subscale scores were 38.7 (6.19), 22.81 (2.55), and 15.89 (4.8), respectively. Mean (SD) changes in ADHD-RS-IV total scores were −11.14 (8.64), −16.14 (11.08), and −20.86 (11.11) at weeks 1, 2, and 3, and −11.53 (8.78) at week 6. Correspondingly, mean (SD) changes in Inattentive subscale scores were −6.32 (4.99), −9.76 (6.4), and −12.16 (6.61) at weeks 1, 2, and 3, and −6.36 (5.7) at week 6, and in Hyperactive/Impulsive subscale scores were −4.81 (4.74), −6.38 (5.94), and −8.7 (5.81) at weeks 1, 2, and 3, and −5.17 (4.33) at week 6. ADHD-RS-IV ≥30% response was observed in 13 (35.14%), 23 (62.16%), and 28 (75.68%) patients at weeks 1, 2, and 3, and in 12 (33.33%) patients at week 6. ADHD-RS-IV ≥50% response was observed in 6 (16.22%), 16 (43.24%), and 23 (62.16%) patients at weeks 1, 2, and 3, and in 8 (22.22%) patients at week 6. The pattern of ≥30% and ≥50% response in Inattentive and Hyperactive/Impulsive subscale scores was similar to that observed with ADHD-RS-IV total score response.
Conclusions. These secondary outcomes support published primary results showing that CTN SR improved ADHD-RS-IV total and subscale scores. CTN SR treatment improved total ADHD symptoms within the first 2 weeks and was well tolerated. These findings support the usefulness of CTN SR, a potential first-in-class NDSRI, in providing rapid treatment benefit to adults with ADHD.
Study Registration: NCT01939353
Previous presentation: ASCP 2023, May 30–June 2, 2023, Miami Beach, FL
Funding. Otsuka

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

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Introduction. Fasedienol (PH94B; 3β-androsta-4,16-dien-3-ol) is a synthetic neuroactive nasal spray from the androstane family of pherines. Intranasal fasedienol activates receptors in peripheral nasal chemosensory neurons connected to subsets of neurons in the olfactory bulbs that in turn are neurally connected to neurons in the limbic amygdala involved in the pathophysiology of SAD and potentially other anxiety and mood disorders. Fasedienol is locally metabolized in the olfactory mucosa without systemic uptake or binding to CNS receptors. The objective of the present study was to compare fasedienol vs. placebo during a public speaking challenge in subjects with SAD.
Methods. This was a multi-center, double-blind, randomized, placebo-controlled study (NCT05011396). After screening (Visit 1), all subjects completed Visit 2 (V2, Baseline, placebo nasal spray administered to all subjects) and participated in a 5-minute public speaking challenge (PSC) during which Subjective Units of Distress Scores (SUDS) were recorded. Subjects with SUDS >= to 70 were invited back a week later for the Visit 3 (V3) treatment visit and randomly allocated to receive either fasedienol (3.2 µg intranasally) or placebo, then undergo a second 5-minute PSC, with SUDS scores recorded. After the V3 PSC, subjects completed a Patient Global Impression of Change (PGI-C) and trained raters completed a Clinical Global Impression of Improvement (CGI-I). CGI-I responders were defined as those assigned scores of 1 (very much improved) or 2 (much improved); PGI-C responders reported scores of 1 (very much less anxious) or 2 (much less anxious). ANCOVA with baseline SUDS as a covariate was used to compare change in mean SUDS from V2 to V3 for the subjects administered fasedienol at V3 vs those who received placebo at V3.
Results. Fasedienol-treated patients (n=70) demonstrated a statistically significant greater change in mean SUDS score (least-squares (LS) mean = -13.8) compared with placebo (n=71, LS mean = -8.0), for a difference between groups of -5.8 (p=0.015). The proportion of CGI-I responders was higher in the fasedienol group 37.7% vs. placebo 21.4% (p=0.033), as was the proportion

https://doi.org/10.1017/S1092852924002037 Published online by Cambridge University Press