# 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.
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# 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

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of PGI-C responders: fasedienol 40.6% vs. placebo 18.6% (p=0.003). Fasedienol was well-tolerated with no treatment-emergent adverse events above 1.5% occurrence.
**Conclusion.** The Phase 3 PALISADE-2 trial results demonstrated that a single dose of fasedienol prior to a stressful PSC produced efficacy on patient-rated SUDS and PGI-C, as well as the clinician-rated CGI-I. The results also confirmed the nasal-amygdala neural circuits as a new portal for administration of pharmaceuticals. The data support continued development of fasedienol as a first-in-class, rapid-onset, well-tolerated treatment option for SAD without addictive properties.
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# Feasibility of a Risperidone Implant for the Maintenance Treatment of Schizophrenia for up to 12 Months After a Single Administration

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**Introduction.** Disruptions of antipsychotic therapy lead to greater symptoms and increased likelihood of relapse. One way to improve medication adherence has been with long-acting formulations, usually administered by injection. Implantable technology has been used to support medication continuity in a few therapeutic areas, e.g., contraception. Despite the potential benefits from implants, this modality is not yet available for maintenance treatment of schizophrenia. Delpor, Inc. is developing an investigational risperidone implant (DLP-114) that releases therapeutic drug levels for up to 12-months. Initial clinical findings are reported below.
**Methods.** The DLP-114 implant is a titanium cylinder approximately 4-5 cm long and 5 mm in diameter. It has membranes mounted on each end and is loaded with a proprietary formulation of risperidone.

The clinical study (NCT04418466) was an open-label study in stable schizophrenia patients to evaluate the safety, tolerability, and pharmacokinetics (PK) of switching from oral risperidone to DLP-114. Schizophrenia patients (N=28), stable on a 2-3 mg dose of oral risperidone for ≥2 weeks were randomized to receive either 6- or 12-month DLP-114 implant devices. Each patient received two DLP-114 devices implanted in the abdomen. Device placements were conducted through a 10-minute procedure using local anesthetic and a custom placement tool. Plasma levels of risperidone and 9-hydroxyrisperidone were tracked over the treatment period, and patients were clinically monitored for signs of relapse. Patient safety (including local tolerance and emergent AEs) and PK were the principal endpoints. Secondary clinical endpoints included PANSS and CGI scores.

**Results.** The placement and removal procedures were well tolerated. Of 28 enrolled patients, two were lost to follow up and one asked to have the implant removed prior to the end of the dosing period. One nonrelated SAE (pulmonary embolism) was reported. Treatment-related AEs were generally mild, and included implant site pain/soreness/tenderness, drowsiness, ecchymosis, increased appetite, insomnia, and headache. The PK profile in both groups followed near zero-order kinetics with both dosing periods until the end of study. The average steady-state plasma concentration ranged between 7-13 ng/mL. One patient was removed from the study with signs of impending relapse. All other patients were clinically stable for the study duration, with average PANSS scores from 50-60 and CGI-I scores from 3-4. PANSS and CGI-I scores were comparable between the oral and the implant phases of the study.
**Conclusions.** DLP-114 was well tolerated for up to 12 months. Average PANSS and CGI-I scores were similar between the oral and implant treatment phases, suggesting that, for most patients, DLP-114 provided a comparable therapeutic benefit to 2-3 mg of daily oral risperidone over time. Plasma concentrations of risperidone and 9-hydroxyrisperidone were substantially constant for 6-12 months, but values for steady-state Cave fell slightly below the target of 10-14 ng/mL.
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# A Veteran with PTSD and Bipolar Disorder Type I with Psychotic Features

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This case discusses a 33-year-old transgender Army Veteran, diagnosed with co-occurring Bipolar Disorder Type 1 (Bipolar I) and Post-Traumatic Stress Disorder (PTSD), both with psychotic features. The patient exhibited recurrent mood swings, delusions, auditory hallucinations, and passive suicidal thoughts. Concurrent symptoms, such as disrupted sleep, irritability, and intrusive thoughts, complicated diagnosis and treatment. The patient's medical history included migraines, chronic pain, medication-induced seizures, traumatic brain injury (TBI), and Borderline Personality Disorder.

During the assessment, the patient displayed mood fluctuations, cognitive issues, and intermittent tearfulness. They were averse to sedative medications and preferred non-pharmacological approaches. The Alpha-Stim (Cranial Electrical Stimulator – CES) was recommended for anxiety, depression, insomnia, and chronic pain.

Medication options (Aripiprazole, Lurasidone, and Risperidone) were discussed, and the patient chose Aripiprazole. The

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