Introduction. Centanafadine (CTN) is a potential first-in-class norepinephrine/dopamine/serotonin triple reuptake inhibitor (NDSRI). The efficacy, safety, and tolerability of CTN sustained release (SR) for adults with ADHD was demonstrated in 2 pivotal phase 3 trials (Adler LA, et al. J Clin Psychopharmacol. 2022;42:429-39).
Methods. Adults (18–55 years) meeting DSM-5 criteria for ADHD enrolled in these double-blind, multicenter, placebo-controlled trials and randomized to treatment if ADHD Investigator Symptom Rating Scale (AISRS) score was ≥28 at screening (if not receiving pharmacologic treatment for ADHD) or ≥22 at screening and ≥28 at baseline (BL) (if receiving treatment). Having had no prior benefit from ≥2 ADHD therapies of 2 different classes, taking prohibited medications, and positive alcohol/drug screen were exclusionary. Trials had 4 periods: (1) screening and washout (≤28 days), (2) single-blind placebo run-in (1 week), (3) double-blind treatment (6 weeks), and (4) follow-up (10 days after last dose). Patients with ≥30% improvement in the Adult ADHD Self-report Scale (ASRS) from start to end of screening were screen failures; those with ≥30% ASRS improvement from start to end of placebo run-in were terminated early. Patients were randomized 1:1:1 to twice-daily CTN SR (200 or 400 mg total daily dose [TDD]) or matching placebo. The 200 mg/d group received CTN SR 200 mg TDD from days 1–42; the 400 mg/d group received 200 mg TDD on days 1–7, and increased to 400 mg TDD on day 8. This analysis assessed CTN SR effects based on median BL AISRS severity score (<38 or ≥38) using a mixed model for repeated measures analysis. Least squares mean (LSM) differences (95% CI) from BL at day 42 were compared between individual CTN SR dose groups and placebo, tested at a 2-sided significance level of 0.05.
Results. In total, 859 patients were randomized (200 mg TDD, n=287; 400 mg TDD, n=287; placebo, n=285). Significant LSM differences on the AISRS were observed vs placebo in the overall population (200 mg TDD and 400 mg TDD, $P<0.0001$ for each), in the low BL severity (200 mg TDD [$P=0.016$]; 400 mg TDD [$P=0.019$]), and in the high BL severity (200 mg TDD [$P=0.005$]; 400 mg TDD [$P=0.003$]) populations at day 42. Significant LSM differences vs placebo ($P<0.01$) began at day 7 (200 mg) and day 14 (400 mg) overall, remaining significant to day 42. Significant LSM differences were observed vs placebo ($P<0.05$) from day 14 (400 mg TDD) and day 21 (200 mg) in the low severity populations, and from day 21 (400 mg TDD) and day 7 (200 mg TDD) in the high severity population, remaining significant ($P<0.05$) to day 42.
Conclusions. CTN SR, a potential first-in-class NDSRI, is efficacious for patients with adult ADHD of low or high BL symptom severity, with significant improvements observed vs placebo within the first 3 weeks.
Study Registration: NCT03605680, NCT03605836
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Dosing, Patterns, Effectiveness, and Treatment Satisfaction with Deutetrabenazine When Initiated Using a 4-Week Patient Titration Kit: Interim Results of the START Study

Andrew J. Cutler[1], Gus Alva[2], Ira Glick[3], Martijn Konings[4], Stacy Finkbeiner[5], James Bennett[6], Lital Pinto Buium[7] and Karen E. Anderson[8]

[1]SUNY Upstate Medical University, Department of Psychiatry, Lakewood Ranch, FL, United States; [2]ATP Clinical Research, Costa Mesa, CA, United States; [3]Sunwise Clinical Research, LLC., Lafayette, CA, United States; [4]Teva Branded Pharmaceutical Products R&D, Inc., Global Medical Affairs, West Chester, PA, United States; [5]Teva Branded Pharmaceutical Products R&D, Inc., North America Medical Affairs, Parsippany, NJ, United States; [6]Teva Branded Pharmaceutical Products R&D, Inc., SCD Statistics, West Chester, PA, United States; [7]Teva Branded Pharmaceutical Products R&D, Inc., Innovative Medicine Data Management, Netanya, Israel and [8]Georgetown University, Department of Psychiatry & Department of Neurology, Washington, DC, United States

Introduction. Deutetrabenazine is a vesicular monoamine transporter type 2 inhibitor (VMAT2i) for treatment of adults with tardive dyskinesia (TD) and Huntington disease (HD)-related chorea. A 4-week patient titration kit was launched (July 2021) to assist patients in titrating to optimal deutetrabenazine dosages.
Methods. START is an ongoing, routine-care, 2-cohort (TD and HD) study evaluating deutetrabenazine dosing patterns, effectiveness, and treatment satisfaction when initiated using a 4-week patient titration kit, with further titration allowed based on effectiveness and tolerability. Patient satisfaction with the kit was assessed via questionnaire at week 8. Results from the first 50 patients enrolled in the TD cohort are presented in this interim analysis.
Results. 50 patients in the TD cohort were included (mean age, 58.7 years, 66% female, 74% White, mean baseline Abnormal Involuntary Movement Scale [AIMS] total motor score, 13.8). 39 of 50 (78%) patients successfully completed the titration kit (completed within 5 weeks or reached optimal dose [≥24 mg/day] within 4 weeks; mean [SE] days, 27.5 [0.32]). Mean (SE) time to reach optimal dosage for the 38 (76%) patients who reached it was 46.3 (5.48) days. Mean (SE) deutetrabenazine dosages were 27.7 (0.92) mg/day at week 4, 32.5 (1.00) mg/day at week 8, and 32.8 (1.18) mg/day at week 12. After completion of the kit, mean (SE) dosage was 31.8 (1.24) mg/day, and 95% of patients reaching week 12 had a maintenance dosage ≥24 mg/day. Mean (SE) adherence with the kit was 97.2% (1.39%). 22% of patients had an adverse event (AE); AEs led to dose reduction for 2%, drug interruption for 2%, and study discontinuation for 6% of patients. Serious and treatment-related adverse events were reported for 2% and 6% of patients. 24 of 49 (49%)23 of 49 patients achieved treatment success ("much"/"very much" improved) at week

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12 per Clinical Global Impression of Change (GIC); 23 or 49 (47%) per Patient GIC. Total motor AIMS scores were reduced by 4.8 points at week 12. Among the 39 (78%) patients who responded to the questionnaire, 72% found it easy to understand when/which dosage to take, 77% easy to remember to take their medication, 74% easy to change the dose weekly, 69% easy to follow kit instructions, and 77% easy to use the kit overall.

Conclusions. 78% of patients with TD successfully completed the 4-week titration kit in approximately 4 weeks, with adherence rates of 97.2%. 95% of patients reaching week 12 had a maintenance dosage ≥24 mg/day. 49% of patients achieved treatment success based on Clinical GIC. Patients reported high levels of satisfaction with the titration kit and 77% found it easy to use. The 4-week patient titration kit enabled patients to titrate DTBZ to an optimal dosage and experience effectiveness similar to the pivotal clinical trials.

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Evaluating Viloxazine ER (Qelbree) Administered with Psychostimulants For Pediatric ADHD: Analysis of a Phase 4 Safety Trial

Ann Childress[1], Kimberley Hayman[2], Kobby Asubonteng[2], Ilmiya Yarullina[2], Jami Earnest[2] and Jonathan Rubin[2]

[1]Center for Psychiatry and Behavioral Medicine, Inc., Las Vegas, NV, USA and [2]Supernus Pharmaceuticals, Inc., Rockville, MD, USA

Introduction. Viloxazine extended-release (ER) is an FDA-approved, nonstimulant medication for pediatric (≥6 years) and adult ADHD. Apart from use as monotherapy, nonstimulants may be combined with stimulants when patients experience inadequate response or difficulties with medication tolerability. This phase IV, open-label trial (NCT04786990) evaluated the safety and tolerability of viloxazine ER administration with psychostimulants in children and adolescents with ADHD. Differences between morning and evening use of viloxazine ER were also assessed.

Methods. Children and adolescents (6 – 17 years) experiencing inadequate response (ADHDRS-5 ≥24 and CGI-S ≥3) to psychostimulant treatment (methylphenidate or amphetamine) were enrolled. Subjects maintained stable stimulant use throughout the trial. Following an up to 4-week screening period, subjects continuing to show inadequate response received flexibly dosed viloxazine ER (100-400 mg/day children; 200-600 mg/day adolescents) each morning during Weeks 1-4 and each evening during Weeks 5-8. Safety, tolerability, and efficacy were assessed relative to Baseline, and for change from baseline for morning vs. evening dosing.

Results. 56 subjects received viloxazine ER with 85.7% of these completing the study. Adverse events were reported by 55.4% of subjects, most commonly headache (17.9%), decreased appetite (12.5%), and upper respiratory tract infection (10.7%); onset was more common during AM dosing trial weeks [50% of subjects reported AEs during Weeks 1-4 and 36% during Weeks 5-8]. AEs were largely mild (32.1%) or moderate (21.4%) and led to discontinuation for 2 (3.6%) subjects. Baseline mean (SD) Investigator Rated-ADHD-Rating Scale 5th ed. (IR-ADHD-RS-5) score was 37.2 (8.35), n=56. Significant improvement in IR-ADHD-RS-5 was seen by Week 1[-6.9 (8.16), n=56; P<.0001)] and continued through Weeks 4 and 8 [-13.5 (9.70) p<.0001 and -18.2 (9.99) p<.0001, respectively]. Over 50% of subjects were rated much or very much improved on CGI-I at endpoint. Scores on the sleep disturbance Scale for Children (SDSC) scale also improved at both Weeks 4 and 8 [-8.8 (14.03) P<.0001 and -10.3(17.39) P=.0002, respectively], as did Parent-ratings of morning and evening ADHD symptoms and behavior, suggesting that morning and evening administration of viloxazine ER were both efficacious.

Conclusions. Viloxazine ER showed acceptable safety and tolerability when administered with stimulant medications in this Phase IV open-label trial. Administration of viloxazine ER in the evening instead of the morning did not appear to affect safety, nor the trajectory of drug response or sleep improvement.

Funding. Supernus Pharmaceuticals, Inc.

Qelbree (viloxazine extended-release capsules): Final Results of the Long-Term, Phase 3, Open-Label Extension Trial in Adults with ADHD

Ann Childress[1], Andrew Cutler[2], Len Adler[3], Nicholas Fry[4], Kobby Asubonteng[4], Andrea Formella[4] and Jonathan Rubin[4]

[1]Center for Psychiatry and Behavioral Medicine, Inc., Las Vegas, NV, USA; [2]Department of Psychiatry, SUNY Upstate Medical University, Syracuse, NY, USA; [3]NYU Grossman School of Medicine, New York, NY, USA and [4]Supernus Pharmaceuticals, Inc., Rockville, MD, USA

Introduction. Viloxazine extended-release (ER) is an FDA-approved nonstimulant medication for ADHD in children (≥6 years) and adults. Approval in adults was based on a double-blind (DB) pivotal trial [NCT04016779] showing statistically significant efficacy on the Adult ADHD Investigator Symptom Rating Scale (AISRS; primary outcome). Here we report final results from the long-term, open-label extension (OLE) safety trial [NCT04143217] conducted as a following to the DB trial.

Methods. Upon completing DB treatment, consenting subjects who enrolled in the OLE received viloxazine ER 200 mg/day, with flexible titration to an optimal maintenance dose (200-600 mg/day). Addition of a stimulant was permitted, at investigator's discretion, following Week 12. OLE trial enrollment was

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