functioning in patients with PDP which utilized a modified version of the FSQ (mFSQ) as the primary outcome measure. In this analysis, we provide additional data on the patient-reported mFSQ within specific domains and correlation to the Schwab & England ADL scale.

Methods. Eligible patients entered a 16-week single-arm, open-label study of once-daily oral pimvanserin (34mg). The 6 domain FSQ was modified to assess 5 domains by removing the work/performance domain since this was not applicable to the patients in this study. The mean change from baseline to week 16 was evaluated in mFSQ domains (Basic ADL, Intermediate ADL, Psychological Function, Quality of Interaction, Social Activity). In addition, correlation between Schwab & England ADL scale and observed mFSQ value across post-Baseline visits were evaluated.

Results. A total of 29 patients were enrolled in the study, mean age (70.2 years), 62% males. The MMRM LSM (SE) for mSFQ from baseline to Week 16 were the following within each domain: Basic ADL (n=22), 8.1 (2.41), p=0.0031; Intermediate ADL (n=21), 7.0 (3.00), p=0.0286; Psychological Function (n=22), 13.3 (1.94), p <.0001; Quality of Interaction (n=22), 12.3(2.07), p <.0001; and Social Activity (n=18), 25.8 (7.52), p=0.0026. All mFSQ domains were showing improvement at 16 weeks from baseline; however, the largest change was seen in Social Activity. The correlation of mFSQ and the Schwab & England ADL scales resulted in a correlation coefficient of r=0.6 (p <.0001) for patient total score and r=0.5 (p<.0001) for caregiver total score. There was a consistent trend among both scales which was demonstrating improvement among patients and caregivers.

Conclusions. This was the first open-label clinical trial to utilize the mFSQ in patients with PDP. In this small, proof-of-concept study, treatment with pimavanserin was associated with improvement across all mFSQ domains; most improvement was seen in social activity. Additionally, the mFSQ was significantly correlated with the Schwab & England ADL, thus this appears to be a promising scale deserving of further evaluation and use in clinical studies as well as in the clinic to complement other assessments.

Funding. Acadia Pharmaceuticals, Inc.

Phase 2A Efficacy, Safety, and Tolerability Study of PH80 Nasal Spray for Acute Management of Menopausal Vasomotor Symptoms (Hot Flashes) in Women

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Introduction. Vasomotor symptoms (hot flashes) are the most common symptom of menopause, affecting about 75% of menopausal women and about 40% of perimenopausal women. PH80, an investigational neuroactive nasal spray, is hypothesized to be a potential treatment for moderate to severe hot flashes due to menopause given that it rapidly activates olfactory to limbic-hypothalamic neural circuits that control autonomic activity, including body temperature and sweating. The primary objective of this Phase 2A clinical study was to explore the efficacy, safety, and tolerability of intranasal administration of PH80 for the acute management of hot flashes due to menopause.

Methods. The study was a randomized, double-blind, placebo-controlled, exploratory Phase 2A clinical study. PH80 nasal spray containing epoxyestrenolone 0.8 µg per 50 µL was self-administered intranasally; two sprays in each nostril (total dose = 3.2 µg) up to four times daily as needed for 4 consecutive weeks. One additional dose was allowed at night if subjects were awakened by hot flashes. During the study period, subjects recorded the number and severity of hot flashes, disruption in function, and sweating related to hot flashes. Patient global impression of change (PGI-C) and clinician global impression of severity (CGI-S) were also assessed.

Results. At baseline, subjects reported a daily mean of 7.7 hot flashes in the PH80 group (n = 18) and 8.0 in the placebo group (n = 18). After 1 week of treatment, the number of hot flashes dropped to 2.8 for PH80 and 6.4 for placebo (P <.001), and after 4 weeks of treatment, the number of hot flashes dropped to 1.5 for PH80 and 5.1 for placebo (P <.001). Treatment with PH80 significantly reduced the severity, disruption in function, and sweating associated with hot flashes during the treatment period as compared with subjects in the placebo group. There was a significant improvement in PGI-C for PH80 vs placebo at endpoint (P = .015) and a strong trend for improvement on CGI-S (P = .053). PH80 was well-tolerated with no serious adverse events (AEs); the AE profiles of PH80 and placebo were comparable. All 36 subjects completed 4 weeks of treatment and with no study discontinuations due to AEs.

Conclusions. The rapid onset, significant reduction in symptoms, and improved function induced by intranasal PH80 in menopausal women with hot flashes compared with placebo, observed as early as the end of week 1 of treatment, provide a strong signal for continued development of PH80 for the acute treatment of hot flashes due to menopause. The safety data further suggest that, if approved, PH80 will provide a substantial safety benefit over all currently available agents.

Funding. Vistagen Therapeutics, Inc. Editorial assistance was provided by Peloton Advantage, an OPEN Health company, funded by Vistagen Therapeutics, Inc.

https://doi.org/10.1017/S1092852924001561 Published online by Cambridge University Press

Evaluation of Dermal Irritation with the Dextroamphetamine Transdermal System (d-ATS) in Healthy Adults and Patients with ADHD

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Background. The d-ATS patch was developed as an alternative to oral amphetamine formulations for attention-deficit hyperactivity disorder (ADHD). The US Food & Drug Administration (FDA) recommends evaluating irritation of transdermal patches under intended (rotating application sites) and exaggerated use (repeated application to one site). These studies assessed irritation after d-ATS application.

Methods. *Intended Use:* In **Study 1**, adults with ADHD, d-ATS was applied daily (9-hour application) for 4 weeks rotated between 5 sites (left/right: hip, flank, chest, upper arm, upper back), with irritation assessed on Days 1, 7, 14, 27, and 28. In **Study 2**, children and adolescents with ADHD, d-ATS was applied daily (9 hours) for 5 weeks to the hip (left or right), with irritation assessed daily.

Exaggerated Use: In **Study 3**, adults with ADHD, d-ATS was applied daily (9 hours) to the hip (repeated application to one site) for 4 weeks, with irritation assessed daily. In **Study 4**, healthy adults, 1 d-ATS and 1 placebo patch were applied daily (24 hours) for 21 days to the back (repeated application to 1 site), with irritation assessed daily.

Irritation was assessed by a trained evaluator 30-60 min after patch removal using Berger and Bowman Dermal Response (0-7, with 7 being the worst reaction) and Other Effects (0-3, with 3 being the worst reaction) scores. Dermal Response and Other Effects scores were added together for the combined score. A combined score of ≥3 was considered clinically meaningful irritation.

Results. *Intended Use:* In Study 1 (N=15), meaningful irritation after patch removal was reported in 9/15 subjects (60%). The mean (SD) combined score was 1.05 (0.21), with no treatment-emergent adverse events at the application site. In Study 2 (N=110), all combined irritation scores were ≤3 for d-ATS, with a combined score of 3 reported by 2% of patients. There were no discontinuations due to dermal reactions in either study.

Exaggerated Use: In Study 3 (N=20), meaningful irritation was reported in 19/20 subjects (95%). The mean (SD) combined score was 1.63 (0.78). In Study 4, mean (SD) combined scores were 2.1 (0.73) for d-ATS and 1.3 (0.69) for placebo (N=206 for both), with no discontinuations due to dermal reactions.

Conclusions. These results support previous findings that d-ATS is safe and well tolerated for ADHD. After intended use, irritation was minimal and did not cause study discontinuations.

Funding. Noven Pharmaceuticals, Inc.

Cariprazine as Adjunctive Treatment for Major Depressive Disorder: Benefit and Risk Assessment Using Number Needed to Treat and Number Needed to Harm

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Purpose. This post hoc analysis investigated efficacy and tolerability of adjunctive cariprazine (CAR) in patients with major depressive disorder (MDD) using evidence-based medicine metrics of number needed to treat (NNT), number needed to harm (NNH), and likelihood to be helped or harmed (LHH).

Methods. Data sources were five completed Phase II/III, 6-8 week, randomized, double-blind, placebo-controlled studies. Efficacy outcomes included acute response (≥50% decrease from baseline on the Montgomery-Åsberg Depression Rating Scale [MADRS] total score). Tolerability outcomes included commonly occurring adverse events (AEs) and rates of discontinuation because of an AE, with data pooled across all studies for the CAR 1-2 mg/day plus 1.5 mg/day dose groups, 2-4.5 mg/day plus 3 mg/day dose groups, and for all groups where CAR dose was ≥1 mg/day. NNT and NNH were calculated for adjunctive CAR vs. adjunctive placebo.

Results. MADRS response rates at Week 8 for CAR 2-4.5 mg/day vs. placebo were 134/271 (49.4%) vs. 101/264 (38.3%), resulting in a NNT of 9 (95% CI 6-36). In study NCT03738215, MADRS response rates at Week 6 for CAR 1.5 mg/day vs. placebo were 110/250 (44.0%) vs. 87/249 (34.9%), resulting in a NNT of 11 (95% CI 6-193). For the pooled CAR ≥1 mg/day group, MADRS response rates at Week 6 were 765/1887 (40.5%) for CAR vs. 354/1101 (32.2%) for placebo, resulting in a NNT of 12 (95% CI 9-21). For the pooled CAR ≥1 mg/day group, rates of akathisia vs. placebo were 209/1893 (11.0%) vs. 25/1108 (2.3%) for placebo, resulting in a NNH of 12 (95% CI 10-14). This appears dose related as the NNH for akathisia vs. placebo was 24 (95% CI 17-43) for the 1-2 mg/day plus 1.5 mg/day dose groups, and 9 (95% CI 7-11) for the 2-4.5 mg/day plus 3 mg/day dose groups. For the pooled CAR ≥1 mg/day group, rates of discontinuation because of an AE vs. placebo were 122/1893 (6.4%) vs. 26/1108 (2.3%) for placebo, resulting in a NNH of 25 (95% CI 19-38). This appears dose related as the NNH for discontinuation because of an AE vs. placebo was 94 (ns) for the 1-2 mg/day plus 1.5 mg/day dose groups, and 17 (95% CI 13-28) for the 2-4.5 mg/day plus 3 mg/day dose groups. For the pooled CAR ≥1 mg/d group, rates of weight gain ≥7% from baseline vs. placebo were 35/1893 (1.8%) vs. 12/1108 (1.1%) for placebo, resulting in a NNH of 131 (ns). LHH comparing MADRS response vs. discontinuation because of an AE is >1, and >>1 for the lower dose range. Indirect comparisons of the above results with that of the effect sizes seen in positive studies of other adjunctive antipsychotic treatments vs. adjunctive placebo in MDD demonstrate similar values for NNT for response, and

https://doi.org/10.1017/S1092852924001561 Published online by Cambridge University Press