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Supplementary Material

Article Title: Viloxazine Extended Release in Adults With Attention-Deficit/Hyperactivity Disorder and Depression and/or Anxiety Symptoms: Results From a Decentralized, Open-Label, Phase 4 Trial

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

Supplementary Methods

Study Design, Participants, and Treatment

Prospective participants were aged ≥18 years, living in the contiguous United States, and recruited using digital tools (eg, social media, advertising). Potential participants were directed to a website where they could access basic information about the study, provide their contact information, and answer prequalifying questions. Those who met the prequalifying criteria were contacted to schedule a screening televisit and received an email invitation to download the study app. After downloading the mobile app, potential participants received study details, an electronic informed consent form, and contact information for the principal investigator and virtual clinical trial support team. Female participants were required to be nonpregnant (confirmed by home pregnancy test mailed to participant), and participants capable of bearing children had to agree to use acceptable contraception. Exclusion criteria included a history of substance use disorder (except nicotine or cannabis) within 6 months of screening; presence of an unstable, clinically significant cardiovascular condition; a history of schizophrenia, schizoaffective disorder, bipolar disorder, or psychiatric condition that in the investigator's judgement would interfere with study participation; a history of moderate or severe head trauma or neurological or systemic medical disease likely to affect central nervous system functioning; or significant risk of suicide (based on investigator opinion, attempted suicide ≤6 months before screening, or answering "yes" to Columbia Suicide Severity Rating Scale [C-SSRS] suicidal ideation questions 4 or 5, or C-SSRS suicidal behavior questions). Potential participants were also excluded if they had taken viloxazine ER (extended-release capsules; Qelbree®) within 3 months of screening, were currently taking another nonstimulant medication (atomoxetine, clonidine, or guanfacine) for attention-deficit/hyperactivity disorder or were using a medication contraindicated with viloxazine ER per the US Food and Drug Administration–approved prescribing information.

Raters were initially screened by a review of their curriculum vitae and their responses to a Rater Qualification Questionnaire. Specific training was provided for the screening assessment (Mini-International Neuropsychiatric Interview for ADHD Studies [MINI-AS]) and efficacy assessments (Adult ADHD Investigator Symptom Rating Scale [AISRS], Montgomery–Åsberg Depression Rating Scale [MADRS], Hamilton Anxiety Rating Scale [HAM-A], and Clinical Global Impression of Severity/Change [CGI-S/C]), and qualified raters were certified upon completion of the training. When possible, participants had the same raters at subsequent visits.

The screening period consisted of up to 2 televisits. The first screening televisit, conducted within 3 weeks after obtaining informed consent, collected the participant's demographic information; medical, psychiatric, and social history; Mini-International Neuropsychiatric Interview for ADHD Studies; prior and concomitant medications; and baseline C-SSRS. The second screening televisit, conducted within 1 week before the first dose of viloxazine ER, collected baseline clinician-reported outcomes and concomitant medications. The 2 screening televisits could be combined into a single televisit. Participants who met the eligibility criteria used the study mobile app to complete baseline patient-reported outcomes. At the discretion of the investigator based on response and tolerability, investigators could adjust the participant's dose in up to 200 mg increments once per week, to a minimum of 200 mg/day or up to the maximum recommended dosage of 600 mg/day. Based on tolerability, investigators could also instruct the participant to take the medication in the evening. Per the study protocol, efficacy assessments were not completed for any visit (including the end of study [EOS] visit) where the participant had not taken ≥1 dose of viloxazine ER within the 7 days before that study visit.

Assessments

At each televisit, participants were asked if they missed any doses of study medication since the prior televisit. Study medication dosage changes were recorded at each study visit. Participants were instructed to return all study medication bottles (empty or not) at the end of their study participation, and the remaining capsules in the returned bottles were counted. Concomitant medication use or changes were recorded at each study visit.

The MADRS measures depression severity in patients with mood disorders using a 10-item investigator-rated diagnostic questionnaire.[1]Each item is rated on a 7-point Likert scale (0 [no abnormality] to 6 [severe]), with a possible score range of 0–60. A higher total score indicates more severe depression (0–6, “normal”; 7–19, “mild”; 20–34, “moderate”; >34, “severe”).[1]

The HAM-A is a clinical measure of anxiety symptoms rated on a 5-point Likert scale (0 [not present] to 4 [very severe]).[2]The ratings/scores of all 14 items are summated to yield a total score (ranging from 0 to 56), where ≤ 17 indicates “mild anxiety severity,” 18 to 24 indicates “moderate anxiety severity,” 25 to 30 indicates “moderate to severe anxiety severity,” and ≥ 31 indicates “severe anxiety.”[2]

Clinically meaningful responses for depression and anxiety symptoms were defined as ≥50% reduction from baseline in MADRS, PHQ-8, HAM-A, or GAD-7 total score, which are considered clinically meaningful improvements in depression/anxiety clinical trials. Remission of depression and anxiety symptoms was defined as MADRS total score ≤10, PHQ-8 total score ≤5, HAM-A total score ≤7, or GAD-7 total score ≤4.[3-5]

For blood pressure and pulse readings, all participants received the same blood pressure device model (certified for remote physiological monitoring) and instructions for use. At

screening (baseline measurement), participants measured their blood pressure and pulse rate and recorded the values in the study mobile app before dosing. At all other televisits (week 4 to week 14/EOS), participants measured their blood pressure and pulse rate during the televisit and reported the results to the study team.

Analysis Populations

Safety data were summarized for the safety analysis population, which included all participants who provided informed consent and received ≥1 dose of viloxazine ER. C-SSRS outcomes were summarized using the number and percent of participants by categories for suicidal ideation, suicidal behavior, suicidal ideation or behavior, and nonsuicidal self-injurious behavior. Efficacy analyses were conducted among the full analysis set, defined as participants in the safety analysis population who had a valid Adult ADHD Investigator Symptom Rating Scale (AISRS) assessment at baseline and ≥1 valid AISRS postbaseline assessment.

Statistical Methods

Statistical analyses were performed using SAS version 9.4 or higher. No formal hypothesis testing was planned, and no statistical power calculation was considered in determining the sample size for this decentralized open-label study. No adjustments for multiplicity were performed. Between-group difference in the number of concomitant medications was evaluated using Wilcoxon rank-sum test. Continuous variables were summarized using means, standard deviations and 95% confidence intervals, while categorical variables were summarized using counts and percentages.

Supplementary References

1. Müller MJ, Himmerich H, Kienzle B, et al. Differentiating moderate and severe depression using the Montgomery-Asberg depression rating scale (MADRS). *J Affect Disord*. 2003;77(3):255-260.

2. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32:50-55.

3. Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. *Arch Gen Psychiatry*. 1991;48(9):851-855.

4. Steele M, Jensen PS, Quinn DM. Remission versus response as the goal of therapy in ADHD: a new standard for the field? *Clin Ther*. 2006;28(11):1892-1908.

5. Spitzer RL, Kroenke K, Williams JB, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166(10):1092-1097.

Supplementary Table 1. Baseline Social Characteristics

Characteristic, n (%)	Viloxazine ER (n = 161)
Highest level of education	
Never attended school or less than high school	0
Completed some high school	2 (1.2)
High school graduate	11 (6.8)
Attended college, but no degree	43 (26.7)
Skilled trade or technical certificate	8 (5.0)
Associate's degree or equivalent 2-year college degree	20 (12.4)
Bachelor's degree (4-year college degree)	38 (23.6)
Some graduate school, but no degree	5 (3.1)
Master's degree	27 (16.8)
Doctoral degree	7 (4.3)
Prefer not to say	0
Income level	
<$15,000/year	14 (8.7)
$15,000 to <$30,000/year	27 (16.8)
$30,000 to <$65,000/year	37 (23.0)
$65,000 to <$100,000/year	40 (24.8)
$100,000 to <$125,000/year	16 (9.9)
$125,000 to <$150,000/year	12 (7.5)
$150,000 to <$175,000/year	4 (2.5)
$175,000 to <$200,000/year	3 (1.9)
≥$200,000/year	3 (1.9)
Prefer not to say	5 (3.1)
Marital status	
Never married, single	42 (26.1)
Never married, living with partner	24 (14.9)
Married or in civil union	62 (38.5)
Married but separated	3 (1.9)
Divorced, single	21 (13.0)
Divorced, living with partner	7 (4.3)
Widowed, single	2 (1.2)
Widowed, living with partner	0

Abbreviations: ER, extended release.

Supplementary Table 2. Summary of Planned and Confirmed Viloxazine ER Dose

Parameter	Planned Dose[a]	Confirmed Dose[b]
Viloxazine ER dose, mg, mean (SD), [range]		
Week 1	200.0 (0) [200–200]	N/A[c]
Weeks 2–4	400.0 (0) [400–400]	356.0 (83.13) [200–400]
Weeks 5–9	362.7 (84.67) [200–600]	357.9 (84.58) [200–600]
Weeks 10–14/EOS	373.5 (89.66) [200–600]	369.7 (81.09) [200–600]
Dosing category, n (%)		
Week 1		
200 mg	161 (100)	N/A
Weeks 2–4		
200 mg	N/A	33 (20.5)
400 mg	150 (93.2)	117 (72.7)
600 mg	N/A	0
Weeks 5–9		
200 mg	26 (16.1)	28 (17.4)
300 mg	2 (1.2)	2 (1.2)
400 mg	104 (64.6)	102 (63.4)
600 mg	2 (1.2)	1 (0.6)
Weeks 10–14		
200 mg	19 (11.8)	18 (11.2)
300 mg	2 (1.2)	1 (0.6)
400 mg	87 (54.0)	88 (54.7)
600 mg	5 (3.1)	2 (1.2)

[a]Dose that was prescribed per the study protocol.

[b]Dose that participants reported they had been taking; queried at the week 4, week, 9, and week 14/EOS televisits.

[c]After week 1, no scheduled visit took place until week 4; therefore, confirmed dose could not be determined during this interval.

Abbreviations: EOS, end of study; ER, extended release, N/A, not applicable.

Supplementary Table 3. Concomitant Medication Use

Medication Category,[a] n (%)	Viloxazine ER (n = 161)
Antidepressants	72 (44.7)
Selective serotonin reuptake inhibitors	36 (22.4)
Bupropion-containing medications[b]	28 (17.4)
Serotonin and norepinephrine reuptake inhibitors	12 (7.5)
Trazodone	7 (4.3)
Tricyclic antidepressants	5 (3.1)
Vilazodone	2 (1.2)
Mirtazapine	2 (1.2)
Hypericum perforatum (St John's wort)	1 (0.6)
Stimulants	46 (28.6)
Amphetamine products	39 (24.2)
Methylphenidate products	8 (5.0)
Phentermine	1 (0.6)
Anxiolytics and/or medications with sedative-hypnotic effects	24 (14.9)
Nonspecific antihistamines[c]	12 (7.5)
Benzodiazepines	6 (3.7)
Buspirone	6 (3.7)
Melatonin	3 (1.9)
Benzodiazepine-related hypnotics	1 (0.6)
Beta-blocking agents	11 (6.8)
Anticonvulsants	8 (5.0)
Second-generation antipsychotics	4 (2.5)
Opiates	2 (1.2)
Acamprosate	1 (0.6)
Antiemetics with dopamine blocking properties	1 (0.6)
Buprenorphine hydrochloride/naloxone hydrochloride	1 (0.6)
Dopamine agonists	1 (0.6)
Withania somnifera (Indian ginseng)	1 (0.6)

[a]Concomitant medications were defined as medications continuing or starting after the first dose of viloxazine ER through the end of study. Medications were coded using the World Health Organization Drug Dictionary version Global September 2023. Concomitant medications were categorized based on commonly referenced categories and were not based on the indication for which they were being used.

[b]Includes patients taking bupropion with dextromethorphan (n = 2).

[c]Dicyclomine, diphenhydramine, hydroxyzine, or dicycloverine.

Abbreviations: ER, extended release.

Supplementary Table 4. Proportion of Participants With CGI-S and CGI-C Scores of 1 or 2

Parameter	Viloxazine ER
CGI-S score of either 1 (asymptomatic) or 2 (borderline), n/n (%)	
Baseline	0/149
Week 4	3/147 (2.0)
Week 9	10/123 (8.1)
Week 14/EOS	19/102 (18.6)
CGI-C score of either 1 (very much improved) or 2 (much improved), n/n (%)	
Week 4	60/148 (40.5)
Week 9	67/124 (54.0)
Week 14/EOS	65/103 (63.1)

Abbreviations: CGI-C, Clinical Global Impression of Change; CGI-S, Clinical Global Impression of Severity; EOS, end of study; ER, extended release.

Supplementary Table 5. Safety Outcomes by Baseline Concomitant Stimulant Use[a]

Parameter, n (%)	With Stimulant (n = 46)	Without Stimulant (n = 115)
Any TEAE	32 (69.6)	82 (71.3)
TEAE considered related to viloxazine ER	31 (67.4)	80 (69.6)
TEAE leading to viloxazine ER withdrawal	5 (10.9)	19 (16.5)
Serious TEAE considered related to viloxazine ER	3 (6.5)	2 (1.7)
Severe TEAE	2 (4.3)	5 (4.3)
Most common TEAEs in the overall study population[b]		
Nausea	12 (26.1)	22 (19.1)
Insomnia	9 (19.6)	22 (19.1)
Fatigue	8 (17.4)	7 (6.1)
Migraine	5 (10.9)	7 (6.1)
Constipation	4 (8.7)	18 (15.7)
Decreased appetite	4 (8.7)	8 (7.0)
Suicidal ideation	4 (8.7)	1 (0.9)
Somnolence	3 (6.5)	11 (9.6)
Abdominal discomfort	3 (6.5)	3 (2.6)
Headache	2 (4.3)	15 (13.0)
Dry mouth	1 (2.2)	10 (8.7)

[a]Evaluated in the safety analysis population (n = 161). Concomitant medications were defined as medications continuing or starting after the first dose of viloxazine ER through the end of study.

[b]Most common TEAEs defined as those occurring in ≥5% of participants in either group.

Abbreviations: ER, extended release; TEAE, treatment-emergent adverse events.

Supplementary Table 6. Baseline Values and Change From Baseline in Blood Pressure, Pulse Rate, and Body Weight

Parameter, Mean (SD)	Viloxazine ER
Systolic blood pressure, mmHg[a]	
Baseline value (n = 158)	117.5 (11.62)
Change from baseline at week 4 (n = 140)	6.0 (12.47)
Change from baseline at week 9 (n = 118)	7.7 (13.75)
Change from baseline at week 14/EOS (n = 90)	3.0 (14.38)
Diastolic blood pressure, mmHg[a]	
Baseline value (n = 158)	76.6 (9.16)
Change from baseline at week 4 (n = 140)	4.6 (10.08)
Change from baseline at week 9 (n = 118)	4.7 (10.29)
Change from baseline at week 14/EOS (n = 90)	2.9 (10.46)
Pulse rate, beats per minute[a]	
Baseline value (n = 158)	79.6 (11.46)
Change from baseline at week 4 (n = 136)	5.2 (12.66)
Change from baseline at week 9 (n = 116)	4.7 (12.41)
Change from baseline at week 14/EOS (n = 88)	5.5 (11.30)
Body weight, kg	
Baseline value (n = 161)	90.0 (26.78)
Change from baseline at week 4 (n = 149)	−0.7 (5.03)
Change from baseline at week 9 (n = 131)	−0.8 (5.50)
Change from baseline at week 14/EOS (n = 108)	−1.6 (5.69)

[a]Measured while sitting.

Abbreviations: EOS, end of study; ER, extended release.

Supplementary Table 7. Suicidality Evaluation by C-SSRS[a]

Parameter, n (%)	Screening, Lifetime (n = 161)	Screening, Past 6 Months (n = 161)	Week 4, Since Last Visit (n = 149)	Week 9, Since Last Visit (n = 123)	Week 14/EOS, Since Last Visit (n = 103)	Overall (n = 150)
Suicidal ideation	82 (50.9)	25 (15.5)	6 (4.0)	3 (2.4)	1 (1.0)	8 (5.3)
Wish to be dead	82 (50.9)	24 (14.9)	6 (4.0)	3 (2.4)	1 (1.0)	8 (5.3)
Nonspecific suicidal thought	39 (24.2)	6 (3.7)	4 (2.7)	0	0	4 (2.7)
Suicidal ideation, no intent	24 (14.9)	2 (1.2)	0	0	0	0
Ideation with intent, no plan	23 (14.3)	0	0	0	0	0
Ideation with plan/intent	23 (14.3)	0	0	0	0	0
Suicidal behavior	20 (12.4)	1 (0.6)	0	0	0	0
Actual attempt	18 (11.2)	0	0	0	0	0
Interrupted attempt	10 (6.2)	0	0	0	0	0
Aborted attempt	5 (3.1)	0	0	0	0	0
Suicidal behavior	0	1 (0.6)	0	0	0	0
Suicidal ideation or behavior	82 (50.9)	26 (16.1)	6 (4.0)	3 (2.4)	1 (1.0)	8 (5.3)
Nonsuicidal self-injurious behavior	0	0	0	0	0	0

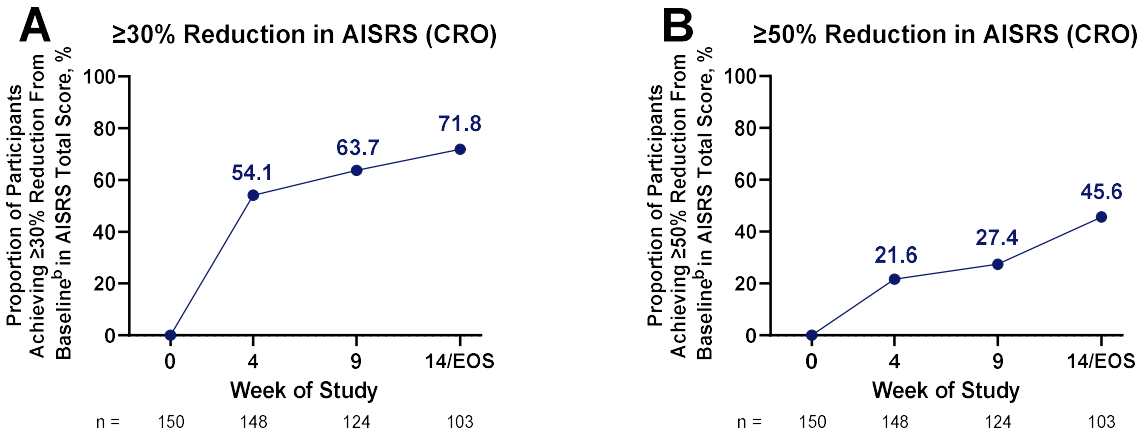
[a]Measured among participants in the safety analysis population (n = 161).
Abbreviations: C-SSRS, Columbia Suicide Severity Rating Scale; EOS, end of study.

Supplementary Figure 1. Achievement of ≥30% or ≥50% reduction from baseline in AISRS total score.[a]

[a]Proportion of participants achieving (A) ≥30% or (B) ≥50% reduction from baseline by visit in AISRS total score. The 30% and 50% reduction from baseline thresholds were assessed post hoc and were selected for consistency with a phase 3 clinical trial of viloxazine ER in adults (Nasser A, et al. *CNS Drugs*. 2022;36(8):897-915). Week 14/EOS analyses were based on assessments assigned to the nominal week 14 visit. Early termination visits were mapped to the next scheduled analysis visit according to the study schedule. Participants who were lost to follow-up or did not complete an early termination visit were excluded.

[b]Measured among participants in the full analysis set (n = 150).

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AISRS, Adult ADHD Investigator Symptom Rating Scale; CRO, clinician-reported outcome; EOS, end of study.

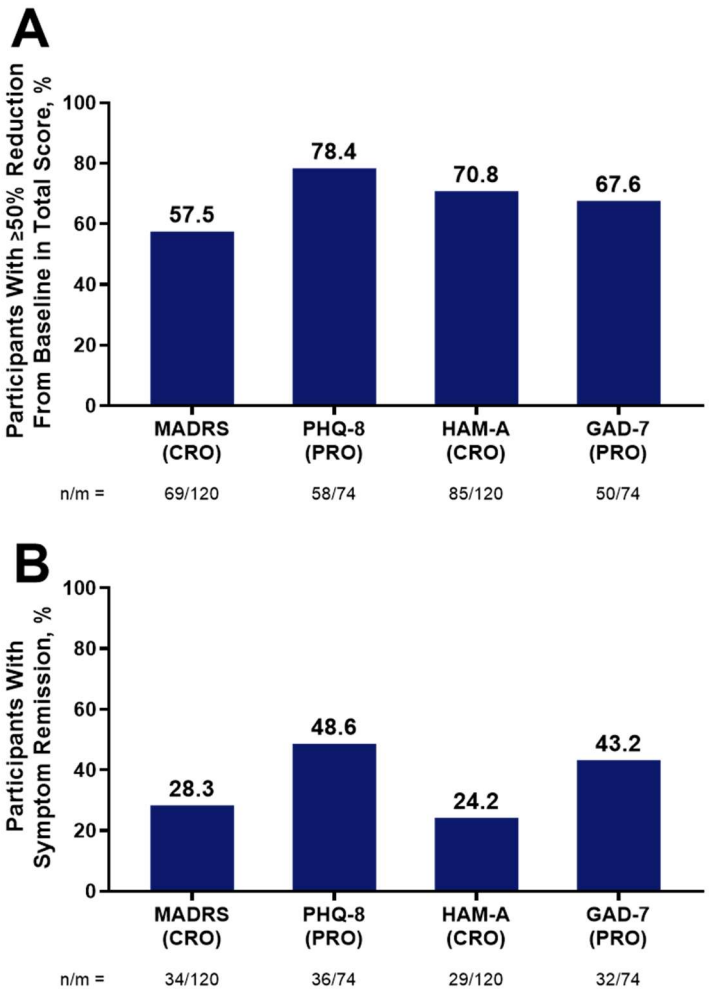


Supplementary Figure 2. Achievement of response or remission for depression and anxiety symptoms at week 14/EOS.[a,b]

[a]Proportion of participants achieving (A) ≥50% reduction from baseline in MADRS, PHQ-8, HAM-A, or GAD-7 total score or (B) symptom remission, defined as MADRS total score ≤10, PHQ-8 total score ≤5, HAM-A total score ≤7, or GAD-7 total score ≤4.[3–5]

[b]Week 14/EOS analyses were based on assessments assigned to the nominal week 14 visit. Early termination visits were mapped to the next scheduled analysis visit according to the study schedule. Participants who were lost to follow-up or did not complete an early termination visit were excluded.

Abbreviations: CRO, clinician-reported outcome; EOS, end of study; GAD-7, General Anxiety Disorder 7-item scale; HAM-A, Hamilton Anxiety Rating Scale; n, number of responders; m, number of participants with nonmissing data at each visit; MADRS, Montgomery-Åsberg Depression Rating Scale; PHQ-8, Patient Health Questionnaire-8 item; PRO, patient-reported outcome.



Supplementary Figure 3. Graphical Abstract