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A Phase 3, Placebo-Controlled Trial of Once-Daily Viloxazine Extended-Release Capsules in Adolescents With Attention-Deficit/Hyperactivity Disorder

Azmi Nasser, PhD,* Tesfaye Liranso, PhD,† Toyin Adewole, MD,* Nicholas Fry, MS,* Joseph T. Hull, PhD,* Gregory D. Busse, PhD,‡ Fatima Chowdhry, MD,* Andrew J. Cutler, MD,§ Nandita Joshi Jones, MD,|| Robert L. Findling, MD,¶ and Stefan Schwabe, MD, PhD#

Abstract:

Purpose: This phase 3 clinical trial evaluated the efficacy and safety of viloxazine extended-release capsules (VLX-ER) as a monotherapy for attention-deficit/hyperactivity disorder (ADHD) in adolescents (12–17 years).

Methods: Eligible subjects (n = 310) were randomized to receive once-daily 200 and 400 mg VLX-ER, or placebo for 6 weeks. The primary efficacy end point was change from baseline (CFB) at the end of study (EOS) in ADHD Rating Scale-5 Total score. Key secondary end points were Clinical Global Impression—Improvement score at EOS, CFB at EOS in Conners 3—Parent Short Form Composite T-score, and CFB at EOS in Weiss Functional Impairment Rating Scale—Parent Total average score.

Results: In the 200-mg/d and 400-mg/d VLX-ER treatment groups, a significant improvement was found in the CFB at EOS in ADHD Rating Scale-5 Total ($P = 0.0232$, $P = 0.0091$) and Inattention ($P = 0.0424$, $P = 0.0390$) and Hyperactivity/Impulsivity ($P = 0.0069$, $P = 0.0005$) subscale scores versus placebo. The Clinical Global Impression—Improvement score was significantly improved at EOS in the 200-mg/d and 400-mg/d VLX-ER groups versus placebo ($P = 0.0042$, $P = 0.0003$). The Conners 3—Parent Short Form composite T-score and Weiss Functional Impairment Rating Scale—Parent Total average score exhibited improvement in both VLX-ER groups; however, the difference versus placebo was not statistically significant. The most common treatment-related adverse events were somnolence, headache, decreased appetite, nausea, and fatigue. The adverse event–related discontinuation rates were <5% in all groups.

Conclusions: Viloxazine extended-release demonstrated statistically significant and clinically meaningful improvement in ADHD symptoms in adolescents and was generally well tolerated.

Key Words: viloxazine, attention-deficit/hyperactivity disorder, adolescents

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In the United States, approximately 13.5% of adolescents have been diagnosed with attention-deficit/hyperactivity disorder (ADHD) during their lifetime.[1] Attention-deficit/hyperactivity disorder impacts functioning at home, school, and other social settings in complex ways, creating challenges in diagnosis and treatment.[2] Although hyperactivity/impulsivity symptoms of ADHD observed in young children tend to decrease with age, inattention symptoms persist through adolescence.[2,3] Cognitive functions become more developed and consequently may be more affected by the disorder[4]; increased cognitive demands requiring more independence and growing importance of peer interactions further place higher demands on adolescents, leading to difficulties in academic performance, self-perception, and family and peer relations.[2,5–7] Untreated individuals have higher rates of risky driving behavior, obesity, suicidal thoughts, and drug use/addictive behavior.[2,8,9] Attention-deficit/hyperactivity disorder in adolescents and young adults is also frequently accompanied by comorbidities including major depression, bipolar disorder, anxiety, antisocial disorders, tics/Tourette syndrome, and substance use disorders.[10] As such, challenges faced by children with ADHD do not decline as they enter adolescence; rather, they can become more complex and difficult to manage.[2,5]

Current guidelines for the treatment of ADHD in adolescents recommend a Food and Drug Administration (FDA)–approved stimulant or nonstimulant medication with the option of implementing evidence-based training and/or behavioral interventions.[11] Stimulants such as methylphenidate and amphetamine have been the primary pharmacotherapy for ADHD for decades, but they do have some limitations.[12,13] For instance, approximately 20% to 40% of individuals with ADHD may not achieve treatment response or symptomatic remission with stimulants.[14–17] Although a majority of adolescents use their medication appropriately, stimulants have a risk of misuse and diversion, particularly the immediate-release formulations.[18–20] In an administrative claims database review study, there were also certain cases where stimulants were associated with episodes of psychosis.[21]

Nonstimulant medications (atomoxetine, guanfacine, and clonidine) can provide an alternative therapy for adolescents with ADHD.[13] However, current FDA-approved nonstimulants have been shown to be less effective than stimulants[11,13] and are also associated with risks and tolerability issues.[22,23] For instance, atomoxetine is contraindicated in patients with severe cardiovascular disorders.[24–26] Other risks of atomoxetine include the following: severe hepatic injury, increases in blood pressure (BP) and heart rate (HR), and psychotic and manic symptoms.[25,26] Guanfacine and clonidine, on the other hand, are associated with risks of hypotension, bradycardia, syncope, sedation, somnolence, and cardiac conduction abnormalities; their abrupt discontinuation can cause rebound hypertension.[11,23] Among the most common adverse reactions leading to discontinuation are somnolence, fatigue, and irritability.[22,23] Finally, current FDA-approved nonstimulant medications for ADHD (such as atomoxetine) have been described

as having a slower onset of action compared with stimulants (sometimes up to 12 weeks for the effect to be fully established).[27–29]

Concerns about the long-term effects, lack or partial efficacy, and poor tolerance, among other factors, frequently lead to poor medication adherence.[30] A recent study of 2000 electronic medical records of children and youth demonstrated that, despite ADHD being a chronic condition, only 46% of the index prescriptions are refilled within the time frame necessary for the individual to be considered consistently medicated.[31]

Considering these limitations and the unique challenges in effectively managing ADHD symptoms in this age group, novel effective and well-tolerated nonstimulant treatment options, which can quickly achieve symptom control, are needed for adolescents with ADHD for whom current ADHD pharmacotherapies are not optimal.

Viloxazine extended-release capsules (VLX-ER; Qelbree™) is a novel nonstimulant medication which has been approved by the FDA for the treatment of ADHD in children and adolescents (ages 6–17 years). VLX-ER is an extended-release formulation of viloxazine (an immediate-release formulation was approved as an antidepressant therapy in Europe but was discontinued several years ago for reasons not related to safety or efficacy of the medication[32]) has demonstrated activity at norepinephrine transporter. In the in vivo preclinical studies, viloxazine has been shown to increase serotonin (5-HT), norepinephrine, and dopamine levels in the prefrontal cortex,[33,34] a region strongly implicated in ADHD pathophysiology. Only a small transient increase in dopamine levels was observed in the nucleus accumbens, a brain area playing a key role in substance use disorders, suggesting low abuse potential for viloxazine. In vitro, viloxazine exhibits antagonistic activity at 5-HT$_{2B}$ receptors and agonistic activity at 5-HT$_{2C}$ receptors,[34] although the translation of these observations into humans remains to be fully elucidated.

In a previous phase 3, randomized, placebo-controlled trial, we investigated the efficacy and safety of 100-mg/d and 200-mg/d VLX-ER in children (6–11 years of age) with ADHD (NCT03247530). Viloxazine extended-release capsules significantly reduced ADHD symptoms providing clinically meaningful improvement, as measured by the ADHD Rating Scale Edition 5 (ADHD-RS-5) and Clinical Global Impression—Improvement (CGI-I) scales. Viloxazine extended-release was well tolerated at the tested dose levels.[35] These results were consistent with those reported in a phase 2 clinical trial in children.[36] Here, we report the results of a phase 3 trial investigating the efficacy and safety of once-daily 200 and 400 mg VLX-ER in adolescents (12–17 years of age) with ADHD.

MATERIALS AND METHODS

Study Design

A randomized, double-blind, placebo-controlled, 3-arm, parallel-group trial was conducted at 33 sites in the United States (NCT03247517). After the screening phase (up to 28 days), 310 subjects were randomized in a 1:1:1 ratio to placebo, 200-mg/d VLX-ER, or 400-mg/d VLX-ER. All subjects, regardless of the treatment group assignment, were administered 2 oral capsules daily in the morning with or without food throughout the 6-week treatment phase, with an option to sprinkle over soft food (eg, apple sauce) to facilitate swallowing if necessary. All capsules were identical in appearance. Subjects assigned to the placebo group took 2 placebo capsules daily for 6 weeks; subjects in the 200-mg/d VLX-ER treatment group took one 200-mg capsule of VLX-ER and one placebo capsule daily for 6 weeks; subjects in the 400-mg/d VLX-ER treatment group took one 200-mg VLX-ER capsule and one placebo capsule daily during week 1, followed by two 200-mg capsules daily for the remaining 5 weeks (Fig. 1). The
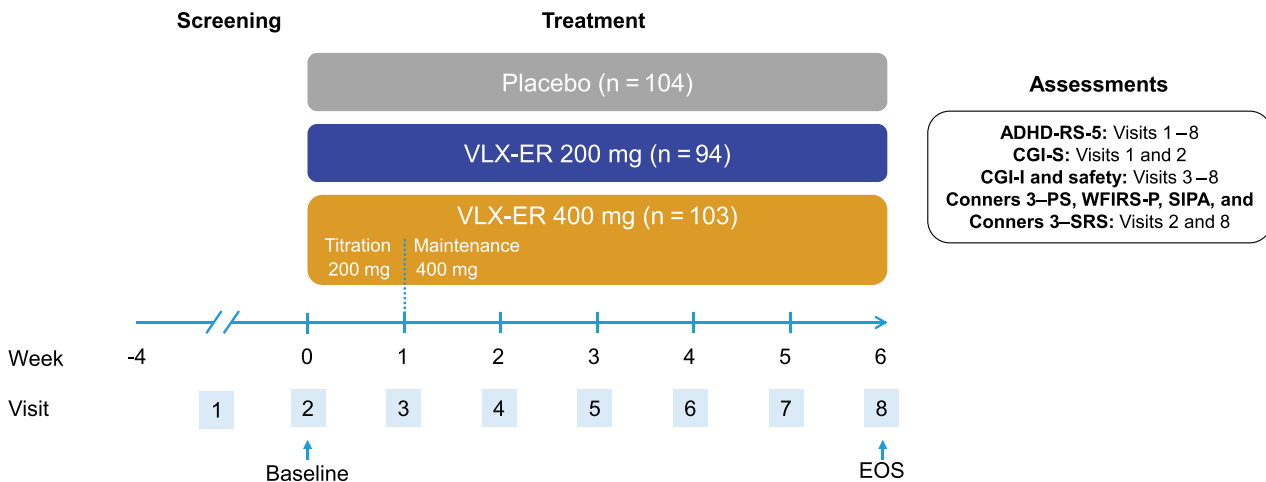
parent(s)/guardian(s) was asked to accommodate dosing into the family's morning routine as consistently as possible, although some flexibility in the timing of the daily dose was permitted if an adverse event (AE) precluded or delayed study medication (SM) administration.

The study protocol was approved by Advarra Institutional Review Board and conducted in accordance with the Helsinki Declaration and the International Council for Harmonization Note for Guidance on Good Clinical Practice. Each subject and parent(s)/legally authorized guardian(s) provided written informed consent/assent before screening or the administration of any study-related procedures. The subject and the parent/guardian were informed about the nature and purpose of the study, as well as of its risks and benefits. It was explained that the subject could withdraw from the study at any time for any reason and that this would not have any effect on his/her potential future medical care. Subjects who completed the 6-week treatment phase and continued to meet the eligibility criteria were offered to participate in a long-term, open-label extension trial (NCT02736656).

Subjects

Male and female subjects (12–17 years of age, weight of ≥35 kg) were eligible to participate if they had a primary diagnosis of ADHD per the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition; American Psychiatric Association, 2013), confirmed via the Mini International Neuropsychiatric Interview for Children and Adolescents (a semistructured interview designed to determine early diagnosis of affective childhood mental disorders and/or current and past episodes of psychopathology, usually administered with the ADHD-RS-5 to improve differential diagnosis and rule out other disorders).[37] To participate in the study, the subjects had to have an ADHD-RS-5 Total score ≥28 and a Clinical Global Impression—Severity of Illness (CGI-S) score ≥4 (ie, overall illness severity of moderate or greater) at screening. Subjects were required to refrain from taking other ADHD medications for a minimum of 1 week before randomization and for the study duration. Subjects were eligible to participate if they were considered medically healthy by the study investigator via assessment of physical examination, medical history, clinical laboratory tests, vital signs, and electrocardiogram (ECG). Females of childbearing potential had to either be sexually inactive (abstinent) or agree to use one of the acceptable birth control methods beginning 30 days before the first dose and throughout the study.

Subjects were not eligible to participate in the trial if they had a current diagnosis of a major psychiatric disorder, a major neurological disorder (including seizures or a history of seizure disorder within the immediate family, or a history of seizure-like events), a significant systemic disease, evidence of suicidality (defined as active suicidal plan or thoughts, or more than one lifetime suicide attempt) within 6 months of or at screening, and/or a body mass index >95th percentile for the appropriate age and sex. Subjects with major depressive disorder who were free of episodes, currently and for 6 months before screening, were eligible to participate. Subjects were further ineligible if they had a history of intolerance or allergic reaction to viloxazine or its excipients, received any investigational drug within 30 days or 5 half-lives before first dosing of SM, or had any reason that in the opinion of the site investigator contraindicated participation. Other exclusion criteria were positive drug screen at the screening visit (a positive test result for amphetamines at screening was allowed for subjects receiving a prescription-stimulant ADHD medication and not responding to treatment—the subject was required to discontinue the stimulant for the study, beginning at least one week before the baseline visit), pregnancy, breastfeeding, or refusal to practice abstinence or acceptable birth control during the study (for females of childbearing potential).

FIGURE 1. Study design.

The safety population included all randomized subjects who received at least 1 dose of SM; the intent-to-treat (ITT) population for efficacy included all subjects who were randomized, took at least 1 dose of SM, and had a baseline and at least 1 postrandomization ADHD-RS-5 assessment.

Assessments

The primary efficacy assessment, the investigator-rated ADHD-RS-5, was conducted at each study visit from visit 1 (screening) to visit 8 (end of study [EOS]). The investigator-rated CGI-S scale was conducted at visits 1 and 2, and the investigator-rated CGI-I scale was conducted at weekly, postbaseline outpatient study visits (visits 3–8). Safety assessments, such as vital signs (Columbia Suicide Severity Rating Scale), review of AEs, and concomitant medications, were performed at all study visits, and ECGs, laboratory tests, and physical examinations were performed at visits 1 and 8. Parent/guardian- or self-administered ratings were performed at visit 2 (baseline) and visit 8 (EOS). Parent/guardian- or self-administered assessments included the Conners 3—Parent Short Form (Conners 3-PS), Weiss Functional Impairment Rating Scale—Parent (WFIRS-P), Stress Index for Parents of Adolescents (SIPA), and Conners 3—Self-Report Short Form (Conners 3-SRS).

Compliance was monitored at each postbaseline visit by counting the number of capsules dispensed and number of capsules returned. If a subject missed a dose of SM, the site investigator counseled the subject/caregiver on the importance of compliance.

Statistical Analysis

Sample size calculations indicated that 72 subjects per treatment group in the ITT population would yield 90% power across treatment groups at a significance level of 0.05 (2-sided) using a 2-sample *t* test, based on an effect size of 0.547 obtained in a previous phase 2b trial for the ADHD-RS-5 Total score at VLX-ER dose of 200 mg.[36] Based on this and accounting for an anticipated

dropout rate of 27.9%, a total of 300 subjects (100 per treatment arm) were projected for the randomized population.

The primary efficacy end point was CFB at EOS (visit 8/week 6) in the ADHD-RS-5 Total score compared with placebo (Fig. 1). The ADHD-RS-5 is a validated scale of 18 items reflecting ADHD symptoms per the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) that are further subdivided into subscales: Inattention (9 items) and Hyperactivity/Impulsivity (9 items). The ADHD-RS-5 Home Adolescent version was administered and rated by a qualified and trained investigator. The investigator rated the frequency and severity of each item on a 4-point Likert scale (0 [no problem] to 3 [severe problem]) based on an interview with the subject's parent/caregiver.[38]

The key secondary efficacy end points included the following: CGI-I score at EOS, CFB in the Conners 3-PS composite T-score at EOS, and CFB in the WFIRS-P Total average score at EOS.

The CGI-I is a single-item rating of clinician's assessment of how much the illness has improved or worsened relative to baseline on a 7-point Likert scale.[39] The clinician's CGI-I rating was based on an interview with parent/caregiver and subject. The Conners 3-PS assesses ADHD-related behavior across 6 content scales scored on a 4-point Likert scale: inattention, hyperactivity, learning problems, executive functioning, defiance/aggression, and peer relations.[40] The WFIRS-P assessed functionality, specifically to what degree a subject's behavior and emotional problems affect their ability to accomplish daily tasks and interactions. It has 50 items grouped into 6 domains scored using a 4-point Likert scale, including the following: family, school, life skills, self-concept, social activities, and risky activities.[41,42]

Additional secondary end points included the following: the ADHD-RS-5 50% responder rate (proportion of responders, defined as subjects who achieved a ≥50% reduction in ADHD-RS-5 Total score, at EOS), the CFB in the SIPA total score at EOS (this scale identifies areas of stress in parent-adolescent interactions across 3 domains [adolescent, parent, and adolescent-

parent] and external life factors [Life Stressors Scale]), the CFB at EOS in each ADHD-RS-5 subscale (Inattention and Hyperactivity/Impulsivity), the CFB in the Conners 3–SRS composite T-score at EOS, and the categorical CGI-I (proportion of responders, defined as subjects who had a CGI-I score of 1 ["very much improved"] or 2 ["much improved"], at each study visit). Exploratory end points included Conners 3-PS/SPS content scales, and individual domain scores in WFIRS-P and SIPA.

The primary efficacy end point was analyzed using a mixed model for repeated measures, which assumes missing data are missing at random. The model included fixed-effect terms for baseline ADHD-RS-5 Total score, age group, treatment, visit, and treatment-by-visit interaction as the independent variables. All secondary measures were analyzed using analysis of covariance (ANCOVA) with treatment as the fixed effect and baseline as a covariate, except for CGI-I, where the baseline CGI-S score was used as a covariate. The least squares (LS) of treatment means, differences between the LS treatment means and placebo, and P values were determined for all measures, with LS mean CFB reported henceforth unless otherwise noted. Statistical analyses were performed using SAS system software, version 9.2 and higher.

Safety and tolerability were assessed by monitoring the incidence of AEs and evaluating clinical laboratory tests, vital signs, physical examinations, ECGs, and suicidal ideation and suicidal behavior (Columbia-Suicide Severity Rating Scale[43]). An AE was defined as any occurrence of unfavorable/unintended sign(s) or symptom(s) observed after the first administration of SM,

including the following: new disease or injury, or exacerbation of an existing disease; deterioration in a laboratory value or other clinical test that resulted in symptoms, a change in treatment, or discontinuation of SM; or recurrence of an intermittent medical condition not present at baseline. A treatment-emergent AE is defined as an AE that started or worsened after first administration of SM. All AEs in this study were recorded after administration of SM, and therefore, all were considered treatment-emergent AE. The relation to study treatment, seriousness, and severity of all AEs were evaluated by the site investigator and were determined as mild if the subject easily tolerated the symptom(s), moderate if discomfort was enough to interfere with daily activity and may have warranted intervention, and severe if the symptom/event significantly affected the subject's daily activity or clinical status and warranted intervention.

The incidence rate, severity, and relationship to SM for all AEs were analyzed based on safety population and summarized by treatment group.

RESULTS

Demographics and Baseline Characteristics

A total of 379 subjects were screened (Supplemental Fig. 1, http://links.lww.com/JCP/A750); 18.2% failed screening before randomization. A total of 310 subjects (12–17 years of age) were randomized (placebo, n = 104; 200-mg/d VLX-ER, n = 100; 400-mg/d VLX-ER, n = 106), with the safety population consisting

TABLE 1. Demographics and Baseline Characteristics: ITT Population

Demographics and Baseline Characteristics	Placebo	VLX-ER 200 mg/d	VLX-ER 400 mg/d	Total
n	104	94	103	301
Age, y				
Mean (SD)	13.8 (1.60)	13.9 (1.48)	14.0 (1.59)	13.9 (1.56)
Median (min, max)	14.0 (12, 17)	14.0 (12, 17)	14.0 (12, 17)	14.0 (12, 17)
Age group, n (%)				
12–14 y	70 (67.3)	63 (67.0)	64 (62.1)	197 (65.4)
15–17 y	34 (32.7)	31 (33.0)	39 (37.9)	104 (34.6)
Sex, n (%)				
Male	58 (55.8)	66 (70.2)	67 (65.0)	191 (63.5)
Female	46 (44.2)	28 (29.8)	36 (35.0)	110 (36.5)
Ethnicity, n (%)				
Not Hispanic and not Latino	74 (71.2)	67 (71.3)	71 (68.9)	212 (70.4)
Hispanic or Latino	30 (28.8)	27 (28.7)	32 (31.1)	89 (29.6)
Race, n (%)				
White	63 (60.6)	53 (56.4)	55 (53.4)	171 (56.8)
Black or African American	39 (37.5)	37 (39.4)	42 (40.8)	118 (39.2)
Multiple	2 (1.9)	2 (2.1)	3 (2.9)	7 (2.3)
American Indian or Alaska Native	0	1 (1.1)	2 (1.9)	3 (1.0)
Asian	0	1 (1.1)	1 (1.0)	2 (0.7)
Weight, mean (SD), kg	55.47 (12.542)	58.77 (12.360)	60.13 (14.610)	58.09 (13.337)
Body mass index, mean (SD), kg/m^2	21.02 (3.310)	21.61 (3.163)	21.95 (3.556)	21.52 (3.364)
ADHD-RS-5, mean (SD)				
Total score	40.5 (6.79)	39.9 (7.22)	39.4 (7.59)	39.9 (7.20)
Inattention	22.4 (3.67)	22.2 (3.66)	21.5 (3.60)	22.0 (3.65)
Hyperactivity/Impulsivity	18.1 (5.35)	17.7 (5.71)	17.9 (5.64)	17.9 (5.55)
CGI-S, mean (SD)	4.6 (0.65)	4.6 (0.70)	4.6 (0.64)	ND

ND, not determined.

TABLE 2. ADHD-RS-5 Results at EOS by Treatment Group

ADHD-RS-5 Measure	Placebo (n = 104)	VLX-ER	
		200 mg/d (n = 94)	400 mg/d (n = 103)
CFB, LS mean (SE)*			
Total score	−11.4 (1.37)	−16.0 (1.45)[§]	−16.5 (1.38)[§]
Inattention subscale	−6.6 (0.74)	−8.7 (0.78)[§]	−8.7 (0.74)[§]
Hyperactivity/Impulsivity subscale	−5.1 (0.69)	−7.7 (0.73)[§]	−8.4 (0.69)[§]
50% Responder rate, n (%)[†,‡]	28 (27)	43 (45.8)[§]	46 (44.6)[§]

*ADHD-RS-5 Total score analyzed using mixed model for repeated-measures ANCOVA model with fixed-effect terms for baseline ADHD-RS-5 Total score, age group, treatment, visit, and treatment-by-visit interaction as fixed independent variables, and subscales are analyzed using ANCOVA model with baseline, age group, and treatment as fixed independent variables from which the LS means and P values are obtained.

[†]P value for 50% responder is derived from Pearson χ^2 test or Fisher exact test; the Fisher exact test is used when there are expected cell counts less than 5; otherwise, the Pearson χ^2 test is used.

[‡]Proportion of responders, defined as subjects who achieved a ≥50% reduction in ADHD-RS-5 Total score at EOS.
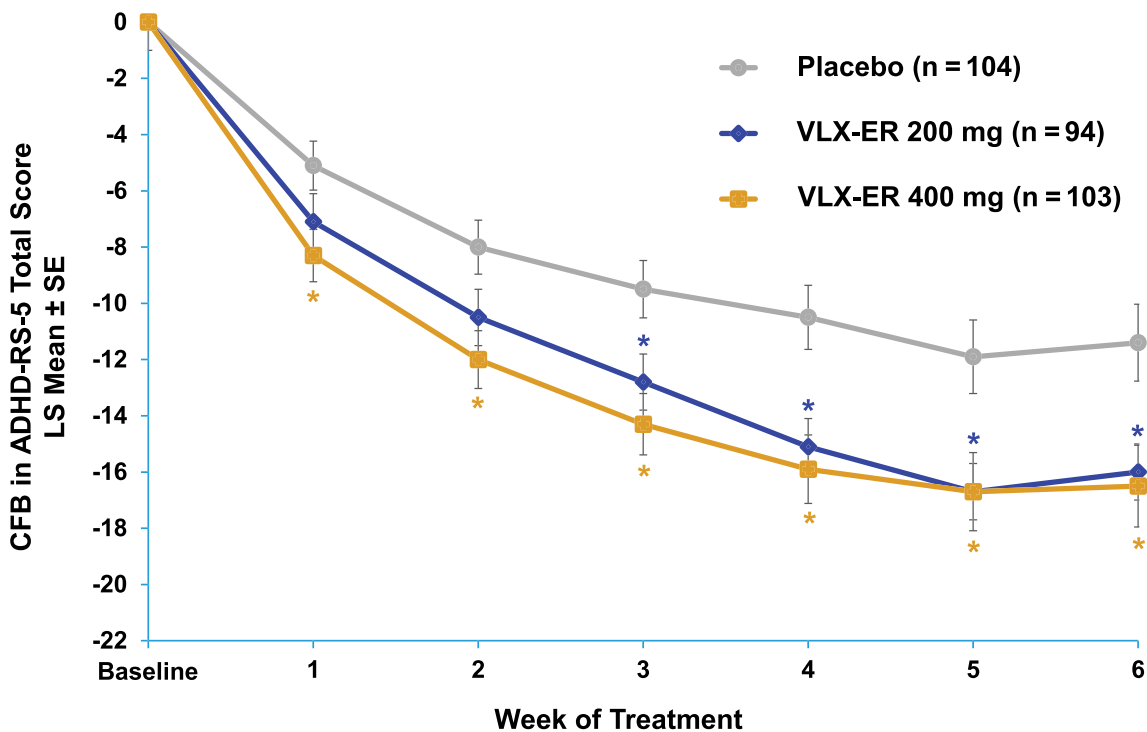
[§]$P < 0.05$ versus placebo.

of 308 subjects (placebo, n = 104; 200-mg/d, n = 99; 400-mg/d, n = 105) and ITT population consisting of 301 subjects (placebo, n = 104; 200-mg/d, n = 94; 400-mg/d, n = 103). Most subjects were male (63.5%), and either White (56.8%) or African American (39.2%; Table 1). Demographics and baseline characteristics in the placebo and either VLX-ER treatment group were similar (Table 1).

ADHD Rating Scale Edition 5

The ADHD-RS-5 Total score at EOS was reduced (improved) from baseline in all 3 arms; however, the reduction was significantly greater in both VLX-ER treatment groups compared with placebo. The CFBs in the ADHD-RS-5 Total score at EOS were −11.4 ± 1.37 (LS mean ± SE) in the placebo group, −16.0 ± 1.45 in the 200-mg/d VLX-ER group, and −16.5 ± 1.38 in the 400-mg/d VLX-ER group (Table 2). The placebo-adjusted CFBs at EOS in the ADHD-RS-5 Total score were −4.5 ± 1.98 (200-mg/d, $P = 0.0232$) and −5.1 ± 1.93 (400-mg/d, $P = 0.0091$). The significant improvement in the ADHD-RS-5 Total score compared with placebo was first observed at week 1 in the 400-mg/d group ($P = 0.0085$) and at week 3 in the 200-mg/d group ($P = 0.0297$); this was sustained through

*$p < 0.05$.

Abbreviations: ADHD-RS-5, ADHD Rating Scale-5; CFB, change from baseline; LS, least squares; VLX-ER, viloxazine extended-release capsules.

FIGURE 2. Change from baseline in the ADHD-RS-5 Total score.

EOS (Fig. 2). The CFBs at EOS in the ADHD-RS-5 Inattention and Hyperactivity/Impulsivity subscale scores were also significantly reduced in the 200-mg/d ($P = 0.0424$ and $P = 0.0069$, respectively) and 400-mg/d ($P = 0.0390$ and $P = 0.0005$, respectively) VLX-ER groups versus placebo (Table 2). A significantly higher percentage of VLX-ER–treated subjects achieved a ≥50% reduction in the CFB in the ADHD-RS-5 Total score at EOS (responders) compared with placebo-treated subjects (placebo: 27%; 200-mg/d VLX-ER: 45.8%, $P = 0.0063$; 400-mg/d VLX-ER: 44.6%, $P = 0.0089$).

Clinical Global Impression—Improvement

The mean CGI-S score at baseline was similar among treatment groups (Table 1). The CGI-I score at EOS was significantly lower in each VLX-ER treatment group compared with placebo. The CGI-I scores at EOS were 3.0 ± 0.11 (LS mean ± SE; placebo), 2.5 ± 0.12 (200-mg/d, $P = 0.0042$), and 2.4 ± 0.12 (400-mg/d, $P = 0.0003$). A significantly higher categorical CGI-I responder rate was observed at week 1 in both the 200-mg/d (14.1%, $P = 0.0254$) and 400-mg/d (16.5%, $P = 0.0063$) VLX-ER treatment groups compared with placebo (4.8%). The percentage of subjects with clinical improvement remained significant at each subsequent week through EOS, with the exception of 200-mg/d group at week 2 ($P = 0.0899$; Fig. 3).

Conners 3

The CFB in the Conners 3-PS composite T-score at EOS was numerically reduced in both VLX-ER arms versus placebo, but the difference was not statistically significant (200-mg/d, $P = 0.6854$; 400 mg/d, $P = 0.0518$). However, there was a significant reduction in the CFB at EOS Conners 3-PS hyperactivity content scale score compared with placebo with the 400-mg/d ($P = 0.0089$), but not the 200-mg/d ($P = 0.1695$), VLX-ER group (Table 3).

The Conners 3-SRS composite T-score and individual content scale T-score analysis did not detect a statistically significant improvement in the VLX-ER groups versus placebo.

Weiss Functional Impairment Rating Scale—Parent

Although numerical improvements were observed in the CFB at EOS in the WFIRS-P Total average score between the 200-mg/d and 400-mg/d VLX-ER treatment arms and placebo, the difference was not statistically significant ($P = 0.2062$ and $P = 0.0519$, respectively). A significant reduction was observed in the CFB at EOS versus placebo for the WFIRS-P risky activities domain score in the 400-mg/d ($P = 0.0077$), but not the 200-mg/d ($P = 0.0996$), VLX-ER group (Table 3).
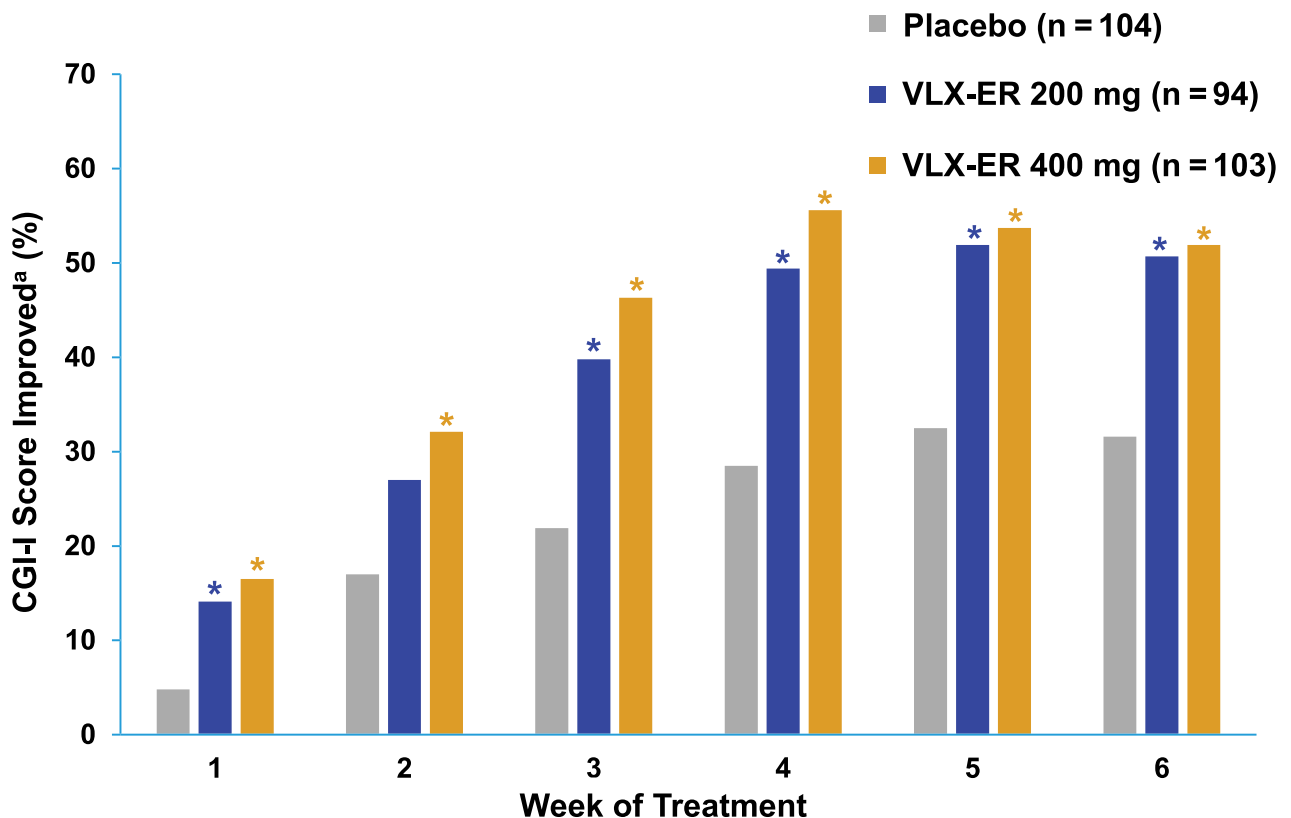
[a]Improvement is defined as a score of 1 ("very much improved") or 2 ("much improved").

*$p < 0.05$.

Abbreviations: CGI-I, Clinical Global Impression-Improvement scale; VLX-ER, viloxazine extended-release capsules.

FIGURE 3. Proportion of subjects with clinical improvement per categorical CGI-I.

Stress Index for Parents of Adolescents

There was no significant difference in CFB at EOS in the SIPA total score for the 200-mg/d or 400-mg/d VLX-ER treatment groups versus placebo ($P = 0.7629$ and $P = 0.7648$, respectively).

Safety and Tolerability

Overall, VLX-ER was well tolerated with low AE-related discontinuation rate 2.9% (6 subjects). The most common AEs that were considered related to treatment, occurred in ≥5% of subjects in any VLX-ER treatment group, and were greater in percentage than placebo were somnolence (13.7%), decreased appetite (6.9%), nausea (4.9%), and fatigue (4.9%; Table 4). Most AEs reported in subjects receiving VLX-ER were mild (30.4%) or moderate (16.7%); severe AEs occurred in 3 subjects (1.5%). One subject (200-mg/d VLX-ER) experienced severe headache considered unrelated to treatment, and 1 subject (400-mg/d VLX-ER) had severe insomnia, considered possibly related to treatment; both resolved without SM interruption. In 1 subject (400-mg/d VLX-ER), severe somnolence, considered related to treatment, led to study discontinuation. A subject in the placebo group experienced severe middle insomnia, which did not require SM interruption. Adverse events leading to study discontinuation (VLX-ER, n = 6; placebo, n = 0) included abdominal pain (0.5%), diarrhea (0.5%), somnolence (1.5%), syncope (0.5%), anxiety (0.5%), and insomnia (0.5%), each occurring in 1 subject, except for somnolence; one of them (syncope) was considered serious (Table 4).

No discontinuations due to abnormal values in laboratory tests occurred during the VLX-ER treatment. The most common treatment-emergent abnormalities included decreases in neutrophil counts in 10 (9.9%), 10 (11.5%), and 7 (7.2%) subjects, and decreases in monocyte counts in 9 (8.9%), 8 (9.2%), and 11 (11.3%) subjects in the placebo, 200-mg/d VLX-ER, and 400-mg/d VLX-ER groups, respectively. Mild to moderate decreases in leukocytes, monocytes, neutrophils, and platelets reported as AEs in 1 subject (200-mg/d VLX-ER) were considered unrelated to SM. Only 2 VLX-ER–treated subjects (400-mg/d) experienced mild liver enzyme elevations

TABLE 3. Conners 3-PS and WFIRS-P Results by Treatment Group and Content Scale/Domain

	Placebo (n = 104)	200-mg/d VLX-ER (n = 94)	400-mg/d VLX-ER (n = 103)
Conners 3-PS			
Composite T-score			
Baseline, mean ± SD (absolute value)	74.6 ± 8.17	72.0 ± 9.11	73.4 ± 8.97
CFB at EOS			
LS mean ± SE	−5.7 ± 1.04	−6.4 ± 1.12	−8.6 ± 1.07
Difference of LS mean ± SE (vs placebo)	—	−0.6 ± 1.54	−2.9 ± 1.49
95% CI of difference	—	−3.6 to 2.4	−5.8 to 0.0
P value (vs placebo)	—	0.6854	0.0518
Content scale T-score			
CFB at EOS, LS mean ± SE			
Inattention	−7.4 ± 1.28	−8.4 ± 1.37	−10.0 ± 1.32
Hyperactivity	−6.2 ± 1.39	−9.0 ± 1.50	−11.4 ± 1.42*
Learning problems	−5.1 ± 1.08	−5.0 ± 1.16	−6.8 ± 1.11
Executive functioning	−7.0 ± 1.17	−8.3 ± 1.25	−9.4 ± 1.20
Defiance/Aggression	−5.2 ± 1.35	−3.7 ± 1.45	−7.9 ± 1.37
Peer relations	−3.8 ± 1.40	−3.8 ± 1.51	−6.0 ± 1.42
WFIRS-P			
Total average score			
Baseline, mean ± SD (absolute value)	1.06 ± 0.487	1.03 ± 0.513	1.03 ± 0.490
CFB at EOS			
LS mean ± SE	−0.19 ± 0.041	−0.27 ± 0.045	−0.31 ± 0.042
Difference of LS mean ± SE (vs placebo)	—	−0.08 ± 0.061	−0.11 ± 0.059
95% CI of difference	—	−0.20 to 0.04	−0.23 to 0.00
P value (vs placebo)	—	0.2062	0.0519
Domain average score			
CFB at EOS, LS mean ± SE			
Family	−0.19 ± 0.059	−0.31 ± 0.063	−0.30 ± 0.060
Self-concept	−0.32 ± 0.062	−0.24 ± 0.067	−0.21 ± 0.063
School	−0.34 ± 0.067	−0.47 ± 0.072	−0.51 ± 0.067
Life skills	−0.17 ± 0.047	−0.25 ± 0.050	−0.30 ± 0.048
Social activities	−0.21 ± 0.054	−0.17 ± 0.059	−0.25 ± 0.055
Risky activities	−0.05 ± 0.036	−0.14 ± 0.039	−0.19 ± 0.036*

LS means, 95% CIs, and *P* values are from ANCOVA model with baseline and treatment as fixed independent variables.

*$P < 0.05$.

CI, confidence interval.

TABLE 4. Summary of AEs

Safety Measure, n (%)	Placebo (n = 104)	VLX-ER		
		200 mg/d (n = 99)	400 mg/d (n = 105)	Overall (n = 204)
At least 1 AE	38 (36.5)	43 (43.4)	56 (53.3)	99 (48.5)
Treatment-related AEs ≥5%				
Somnolence	7 (6.7)	13 (13.1)	15 (14.3)	28 (13.7)
Headache	7 (6.7)	3 (3.0)	7 (6.7)	10 (4.9)
Decreased appetite	0	5 (5.1)	9 (8.6)	14 (6.9)
Nausea	3 (2.9)	5 (5.1)	5 (4.8)	10 (4.9)
Fatigue	1 (1.0)	4 (4.0)	6 (5.7)	10 (4.9)
AE leading to discontinuation, n (%)				
Total*	0	4 (4.0)	2 (1.9)	6 (2.9)
Abdominal pain	0	1 (1.0)	0	1 (0.5)
Diarrhea	0	1 (1.0)	0	1 (0.5)
Somnolence	0	1 (1.0)	2 (1.9)	3 (1.5)
Syncope	0	1 (1.0)	0	1 (0.5)
Anxiety	0	1 (1.0)	0	1 (0.5)
Terminal insomnia	0	0	1 (1.0)	1 (0.5)

*Subjects who discontinued because of 1 or more incidents of AEs.

as AEs: one subject had elevated alanine aminotransferase and aspartate aminotransferase considered possibly related to SM, and another subject had elevated alanine aminotransferase considered unrelated to SM.

Changes in vital signs were generally small and infrequent, with the exception of diastolic BP below normal observed in >10% of subjects in all 3 arms across multiple study days throughout the study. The mean (SD) CFBs at EOS in diastolic and systolic BP (in millimeters of mercury) were −0.5 (8.48) and −0.3 (10.25) in the placebo group, 1.2 (8.44) and −0.3 (9.86) in the 200-mg/d group, and 3.0 (9.34) and 1.1 (9.18) in the 400-mg/d group, respectively. The mean (SD) CFBs at EOS in HR (in beats per minute) were 0.0 (10.94) (placebo), 2.7 (13.35) (200-mg/d), and 4.5 (12.95) (400-mg/d). Mild vital sign abnormalities were reported as AEs in 4 subjects receiving VLX-ER, including increased BP (200 mg/d), increased orthostatic HR (200 mg/d), increased HR (400 mg/d), and hypertension (400 mg/d).

No cardiovascular events leading to discontinuation were observed in any of the VLX-ER groups, and no ECG-related AEs were reported during the study. A subject had a QT interval corrected for HR using Fridericia's method (QTcF) of >450 milliseconds (461 milliseconds) at week 6 (400 mg/d), which was not considered clinically significant. No CFB in QTcF of >60 milliseconds was observed. Small ECG changes included a CFB in QTcF of 30 to 60 milliseconds occurring in 1 subject (1.1%) in the 200-mg/d group, 1 subject (1.0%) in the 400-mg/d group, and no subjects in the placebo group.

Mild weight increase was observed in 1 subject in the placebo group and 1 subject in the VLX-ER 200-mg/d group, and moderate weight increase was reported in 1 subject in the placebo group, all considered unrelated to SM. No body mass index or height changes were reported as AEs. One postbaseline suicidal ideation occurred in 1 subject (1.1%) at week 3 in the 200-mg/d treatment group, which was adjudicated as not related to SM. No deaths occurred during this trial.

DISCUSSION

In this 6-week, phase 3 clinical trial evaluating efficacy and safety of VLX-ER in the treatment of ADHD in adolescents, both 200-mg and 400-mg once-daily doses of VLX-ER were significantly more effective compared with placebo in reducing ADHD symptoms. This was evidenced by significant improvements (−16.0 and −16.5 point reduction) in the ADHD RS-5 at EOS in the 200-mg/d and 400-mg/d treatment groups, respectively, compared with −11.4 in the placebo group. Improvement versus placebo was observed starting at week 1 for both doses and was statistically significant in the 400-mg/d group for the entire treatment period and in the 200-mg/d group from week 3 through EOS (despite both groups receiving 200 mg for the first week). This suggests a relatively quick onset of action of VLX-ER, which is particularly relevant considering the slow onset of action observed with some current FDA-approved nonstimulant medications for ADHD (eg, atomoxetine).[27] These results are consistent with a previous phase 2 trial investigating VLX-ER,[36] as well as a phase 3 trial investigating 100-mg/d and 200-mg/d VLX-ER doses in children.[35]

The choice of the categorical CGI-I responder criteria as a secondary outcome recognizes that some clinicians may not routinely use ADHD symptomatic rating scales and/or they may perceive global ratings of disease severity and improvement more useful than mean changes in symptoms versus placebo.[44] Historically, clinical trials have defined the efficacy threshold for ADHD-RS symptomatic improvement as 25% to 30%; evidence exists, however, that such improvement often leaves individuals with significant symptomatic and functional impairment.[45,46] Hence, a clinical response that integrates both a ≥50% reduction in symptoms and a second measure of clinical improvement (eg, CGI-I of 1 [very much improved] or 2 [much improved]) was suggested as a more meaningful clinical measure of treatment effectiveness.[16] Specifically, previous analyses of the relationship between ADHD-RS-5 and CGI-I scores demonstrated that a considerable symptomatic improvement of 50% to 60% on the ADHD-RS scale is needed to achieve a "much improved" rating on the CGI-I.[44] In the current study, the significant improvements observed in CGI-I score at EOS (key secondary end point) along with significantly greater proportions of subjects "much improved" and "very much improved" in both VLX-ER groups versus placebo were consistent with ADHD-RS-5 results, indicating clinically meaningful improvement.

These data—taken together with the significant improvements found in the CFB for both Inattention and Hyperactivity/Impulsivity subscale scores of the ADHD-RS-5 and significantly higher proportions of subjects with ≥50% improvement in ADHD-RS-5 Total score in the treatment groups versus placebo—suggest that significant numbers of adolescents in this trial experienced a clinically meaningful improvement across the spectrum of core ADHD symptoms. These observations are also in agreement with the results reported for VLX-ER in children.[35]

Although there was no apparent difference on ADHD-RS-5 Total score between the 2 doses of VLX-ER, a somewhat more pronounced effect of 400-mg/d dose compared with 200-mg/d dose was seen in Figure 3. Overall, lack of an apparent dose-response relationship of a psychopharmacotherapy in placebo-controlled clinical trials is common for a number of reasons (eg, nonlinear effects at the site of action). However, not all the individuals in the clinical trial achieve improvement in ADHD symptoms, indicating that there may be a proportion of individuals who would benefit from a higher dose. Furthermore, the discontinuation rate due to AE related to VLX-ER observed in this trial was low and consistent across the doses demonstrating that both doses were well tolerated.

Although significant statistical differences were not observed in the Conners 3-PS composite T-score and WFIRS-P Total average score in this study, it is possible that this reflects limitations in assessing the impact of any ADHD therapeutic agent on quality of life and parent's perspective of adolescent's ADHD symptoms, functionality, and behavior within a 6-week study. Although 6 weeks is a typical study duration for pivotal studies in ADHD,[47] these specific measures in adolescents may require a longer trial duration or longitudinal clinical follow-up. The trend toward significant improvement observed in the current study is supported by the phase 3 study in children, which included a larger sample size (n = 477); 100-mg/d and 200-mg/d VLX-ER doses in this study led to significant improvements in the Conners 3-PS and WFIRS-P scores.[35] Future studies of a longer duration and/or including a larger sample size may help further understand the outcomes of VLX-ER treatment measured by parent-rated Conners 3-PS and WFIRS-P scales.

The phase 3 data reported here suggest a well-tolerated clinical profile with low incidence and mild severity of AEs including a small number of cardiovascular abnormalities and liver enzyme elevations, and only one case of suicidal ideation reported.

Limitations of current FDA-approved stimulant and nonstimulant medications for ADHD include risk of misuse potential for stimulants,[18,48,49] a gradual onset of action for nonstimulants, which in the case of atomoxetine can take up to 12 weeks to achieve maximum response,[27–29] and tolerability issues (such as irritability, insomnia, nausea, and weight decrease) for both.[22,23,26,50,51] Many of these medications either are contraindicated or should be used with caution in certain populations of patients, for instance, patients with cardiac abnormalities or cardiovascular problems,[23,24] agitation, Tourette syndrome, tics, sleep disturbances, bipolar disorder,[52–54] suicidal ideation,[55] sedation, or somnolence.[23,26,54] In addition, the duration of action of stimulants often does not meet the all-day demands of individuals with ADHD.[13,56] Tolerability issues with nonstimulants include somnolence, sedation, fatigue,[23,26] hypotension, and decreased HR.[23] Furthermore, currently approved nonstimulant ADHD medications cannot be sprinkled over the food, which poses a potential challenge for adolescents with ADHD who may have comorbid autism or other developmental disabilities that create difficulties swallowing intact tablet/capsule formulations.[57] In the absence of head-to-head comparison trials, conclusions about the relative efficacy or safety of specific therapies cannot be drawn; however, high rates of comorbidities and complexity of ADHD management overall, and in adolescent individuals in particular, indicate the need for additional effective therapies with favorable safety profile.

In the context of selecting an appropriate treatment of ADHD, it is important to consider the benefit-to-risk ratio of the available therapies. To evaluate the risk-to-benefit ratio for VLX-ER, in a post hoc analysis of 4 VLX-ER pediatric trials, the number needed to treat (a measure of effect size, calculated based on responder rates) and number needed to harm (a measure of tolerability, calculated based on discontinuation rates due to AEs) were estimated. For adolescents with ADHD (12–17 years of age), the number needed to treat was 6 to 7, whereas the number needed to harm was 31, indicating that the risk-to-benefit ratio for VLX-ER was around 5. These data suggest that VLX-ER can be an important addition to the clinician's armamentarium of evidence-based treatment options for adolescents with ADHD.

The results of the current clinical trial should be considered in light of several limitations. The data collected here were based on investigator-rated and parent-rated scales, no teacher ratings were included in this trial. The investigators were required to be qualified and completed training sessions to participate in the study; however, interrater reliability data in this trial were not collected. Finally, no ratings of patient satisfaction with treatment were obtained in this study.

To summarize, this phase 3 trial of 200-mg/d and 400-mg/d doses of VLX-ER in the treatment of ADHD met the primary ADHD-RS-5 efficacy end point. Significant improvements in ADHD-RS-5 Total score versus placebo were detected for 400-mg/d dose by week 1 and for 200-mg/d dose by week 3, which was maintained for 6 weeks, indicating sustained and relatively early effect. Subjects treated with VLX-ER also demonstrated significant improvement in CGI-I scores at EOS versus placebo, with significantly higher responder rates compared with placebo observed in both active treatments groups for both assessment scales (ADHD-RS-5 and CGI-I). Furthermore, VLX-ER exhibited clinically significant efficacy across the Inattention and Hyperactivity/Impulsivity subscales of the ADHD-RS-5. Both doses of VLX-ER were well tolerated and had low discontinuation rates. Taken together, the results of this phase 3 clinical trial demonstrated that VLX-ER can be an effective and tolerable nonstimulant treatment option for adolescents with ADHD.

AUTHOR DISCLOSURE INFORMATION

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