A Randomized, Placebo-Controlled Trial of Guanfacine Extended Release in Adolescents With Attention-Deficit/Hyperactivity Disorder

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Objective: Despite the continuity of attention-deficit/hyperactivity disorder (ADHD) into adolescence, little is known regarding use of nonstimulants to treat ADHD in adolescents. This phase 3 trial evaluated the safety and efficacy of guanfacine extended release (GXR) in adolescents with ADHD.

Method: This 13-week, multicenter, randomized, double-blind, placebo-controlled trial evaluated once-daily GXR (1–7 mg per day) in adolescents with ADHD aged 13 to 17 years. The primary endpoint was the change from baseline in the ADHD Rating Scale–IV (ADHD-RS-IV) total score; key secondary endpoints included scores from the Clinical Global Impressions–Severity of Illness (CGI-S), and Learning and School domain and Family domain scores from the Weiss Functional Impairment Rating Scale–Parent Report (WFIRS-P) at week 13.

Results: A total of 314 participants were randomized (GXR, n = 157; placebo, n = 157). The majority of participants received optimal doses of 3, 4, 5, or 6 mg (30 [22.9%], 26 [19.8%], 27 [20.6%], or 24 [18.3%] participants, respectively), with 46.5% of participants receiving an optimal dose above the currently approved maximum dose limit of 4 mg. Participants receiving GXR showed improvement in ADHD-RS-IV total score compared with placebo (least-squares mean score change, –24.55 [GXR] versus –18.53 [placebo]; effect size, 0.52; $p < .001$). More participants on GXR also showed significant improvement in CGI-S scores compared with placebo (50.6% versus 36.1%; $p = .010$). There was no statistically significant difference between treatments at week 13 in the 2 WFIRS-P domains. Most treatment-emergent adverse events were mild to moderate, with sedation-related events reported most commonly.

Conclusion: GXR was associated with statistically significant improvements in ADHD symptoms in adolescents. GXR was well tolerated, with no new safety signals reported.

Clinical Trial Registration Information—Dose-Optimization in Adolescents Aged 13-17 Diagnosed With Attention-Deficit/Hyperactivity Disorder (ADHD) Using Extended-Release Guanfacine HCl; http://ClinicalTrials.gov/; NCT01081132.

Key Words: attention-deficit/hyperactivity disorder, nonstimulants, guanfacine, GXR

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Attention-deficit/hyperactivity disorder (ADHD) is among the most common neurobehavioral disorders presenting for treatment in children and adolescents.[1,2] A US Centers for Disease Control and Prevention and Health Resources and Services Administration report estimated the 2011 prevalence of US youth, aged 4 to 17 years with an ADHD diagnosis, to be 11%.[3] ADHD is often persistent, with more than 80% of children maintaining the disorder into adolescence.[4] Children and adolescents with ADHD share many characteristics of the disorder,[5] although inattention tends to be more common than overt hyperactivity in adolescents.[6,7]

Compared to unaffected peers, adolescents with ADHD manifest more dysfunction in psychiatric, social, academic, legal, and family functioning.[4,5,8] For example, adolescents with ADHD often experience difficulties interacting with peers, which may result in becoming associated with other disenfranchised adolescents.[9] Given the increasing demands, autonomy, and multitasking required of adolescents, academic failure is often accentuated.[8] Adolescents with ADHD have an increased risk of substance abuse, especially if they have psychiatric comorbidities (e.g., conduct or bipolar disorders).[10,11] In addition, adolescents with ADHD are more likely to be involved in driving-related offenses and accidents[12,13] as well as irresponsible sexual encounters leading to pregnancies and sexually transmitted diseases.[14] Children and adolescents with ADHD are also more likely to be exposed to a dysfunctional family environment, as evidenced by higher levels of family stress and marital discord.[15,16] Hence, ADHD in adolescence is a disorder of high clinical and public health significance.

Although stimulants have long been recognized among first-line therapies for ADHD,[17,18] approximately 30% of adolescents may not adequately respond to or tolerate stimulant

Supplemental material cited in this article is available online.

medications. Stimulant use has been associated with reduced appetite, nausea, insomnia, and potential cardiovascular adverse events (AEs),[19-21] and may exacerbate comorbid conditions such as tics and anxiety, suggesting a need for nonstimulant medications.[18] Currently, US Food and Drug Administration (FDA)–approved nonstimulants for children and adolescents with ADHD include atomoxetine, guanfacine extended release (GXR), and clonidine extended release.[22-24]

The use of guanfacine in adolescents has not been extensively studied. GXR monotherapy (1–4 mg) for the treatment of ADHD was evaluated in 2 short-term, placebo-controlled, pivotal, fixed-dose efficacy studies.[25,26] Although both studies enrolled children (6–12 years) and adolescents (13–17 years), adolescents represented only ~25% of the participant pool. Subgroup analyses comparing treatment response stratified by age revealed numerical improvement, but no significant treatment effect, in adolescents. Compared with children, the adolescents in both studies totaled fewer participants and demonstrated higher placebo response rates. Furthermore, due to fixed-dose study designs and higher body weights, analyses of doses on a milligram-per-kilogram basis revealed that the majority of adolescent participants received doses <0.05 mg/kg, the lowest dose to show consistent, clinically relevant improvement on the ADHD Rating Scale–IV (ADHD-RS-IV) total score in these studies.[25,26]

After evaluation of both GXR safety/pharmacokinetic data in adolescents (doses up to 9 mg per day[27]) and prescribing data from immediate-release guanfacine,[28] the dose range of GXR 1 to 7 mg was chosen for this study, allowing adolescent participants with ADHD to receive mg/kg doses within the efficacious range of 0.05 mg/kg per day to 0.12 mg/kg per day previously identified in the short-term pivotal studies. The primary objective of this study was to assess the efficacy of dose-optimized GXR versus placebo in the treatment of adolescents with ADHD, as measured by the ADHD-RS-IV. Key secondary objectives were to evaluate the effects of GXR on the Clinicians' Global Impressions–Severity of Illness (CGI-S) scale scores, and on changes in function associated with ADHD as measured by the Learning and School domain and Family domain scores from the Weiss Functional Impairment Rating Scale–Parent Report (WFIRS-P). Safety and tolerability of GXR in adolescents were also evaluated, adding to safety findings from the small adolescent cohorts in prior GXR studies.[25,26]

METHOD

Participants

Inclusion criteria included adolescent outpatients aged 13 to 17 years with a diagnosis of ADHD (any subtype). Consistent with *DSM-IV-TR* criteria, a primary ADHD diagnosis was confirmed by clinical evaluation using the behavior module of the Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime version (K-SADS-PL)[29] at screening (visit 1). Participants were also required to have a minimum ADHD-RS-IV total score of 32 and a minimum CGI-S score of 4 at baseline (visit 2). Supine and standing blood pressure measurements within the 95th percentile for age, sex, and height were also required.

Participants were excluded if they had any current controlled or uncontrolled comorbid psychiatric diagnosis (except oppositional defiant disorder), including severe comorbid Axis II disorders or severe Axis I disorders, such as anxiety disorder, posttraumatic stress disorder, depression, bipolar illness, psychosis, pervasive developmental disorder, obsessive-compulsive disorder, substance abuse disorder within 6 months, or other symptomatic manifestations or lifetime history of bipolar or unipolar illness (e.g., active suicidality), psychosis, or conduct disorder that, in the opinion of the investigator, contraindicated treatment with GXR or could confound efficacy or safety assessments. Other exclusion criteria included history/presence of structural cardiac abnormalities, serious heart rhythm abnormalities, syncope, cardiac conduction problems, exercise-related cardiac events, orthostatic hypotension, history of controlled or uncontrolled hypertension, or clinically significant bradycardia. Participants who used any medications that affect blood pressure or heart rate, have central nervous system effects, or affect cognitive performance (such as sedating antihistamines) were also excluded. Psychosocial treatment was permitted during the study if it had been ongoing for >1 month at the time of the baseline visit, and any changes/modifications to psychosocial treatment during the study had to be cleared by medical staff.

Participants and their parent/legally authorized representative (LAR)/caregiver had to understand and be willing to fully comply with study procedures. Each parent/LAR/caregiver was required to give signed informed consent, and each participant was required to give written assent; forms were approved by the institutional review boards of participating centers. This study was conducted in accordance with the International Conference on Harmonisation of Good Clinical Practice under the principles of the Declaration of Helsinki.

Study Design

This phase 3, multicenter, double-blind, placebo-controlled, randomized study was designed to assess safety, efficacy, and tolerability of once-daily dosing of GXR in adolescents with a diagnosis of ADHD who were given doses ≤7 mg using a flexible dose-optimization design (ClinicalTrials.gov Identifier: NCT01081132). Participants were enrolled at 48 sites across the United States. This study consisted of 5 periods: screening, 7-week dose optimization (visits 3–9), 6-week dose maintenance (visits 10–13), 2-week dose taper (visits 14 and 15), and follow up (visit 16).

Eligible participants were randomized to GXR or placebo (1:1 ratio) on a studywide basis by automatic interactive response technology. At least 25% of randomized participants were to be female, and treatment assignments were balanced within weight groups (34.0–41.4, 41.5–49.4, 49.5–58.4, and 58.5–91.0 kg). After randomization, all participants underwent dose optimization (visits 3–9), with 1 dose reduction permitted if necessary. Starting the morning after baseline, all participants received 1 mg per day of GXR or placebo, and the dose was titrated up to the maximal permitted dose for a participant's respective weight group in the absence of any significant safety or tolerability issues. The dose was allowed to increase in 1-mg increments (after a minimum of 1 week on the current dose) on a weekly basis to a maximal dose based on the participant's baseline weight and tolerability (4 mg per day for those 34.0–41.4 kg to 7 mg per day for those 58.5–91.0 kg). Participants were considered at optimal dose if they achieved ≥30% reduction in ADHD-RS-IV total score from baseline and a CGI–Global Improvement (CGI-I) score of 1 or 2 at a given tolerated dose (defined as a "responder"; response to treatment was also analyzed throughout the dose maintenance phase). Investigators were encouraged to increase the dose if these criteria were not met, and the dose was tolerated. Furthermore, if a participant achieved a ≥30% reduction in ADHD-RS-IV total score, tolerated the optimal dose, and (in the opinion of the investigator) could potentially achieve additional symptom reduction, the dose could be increased.

All participants were instructed to take their assigned number of tablets once daily in the morning, to dose consistently with respect to the time of eating, and to avoid administration with a high-fat meal. To assess compliance, participants were asked to bring unused and empty used drug containers to each visit for a tablet count; participants who took 80% to 120% of the dispensed medication were regarded as being compliant.

Assessments

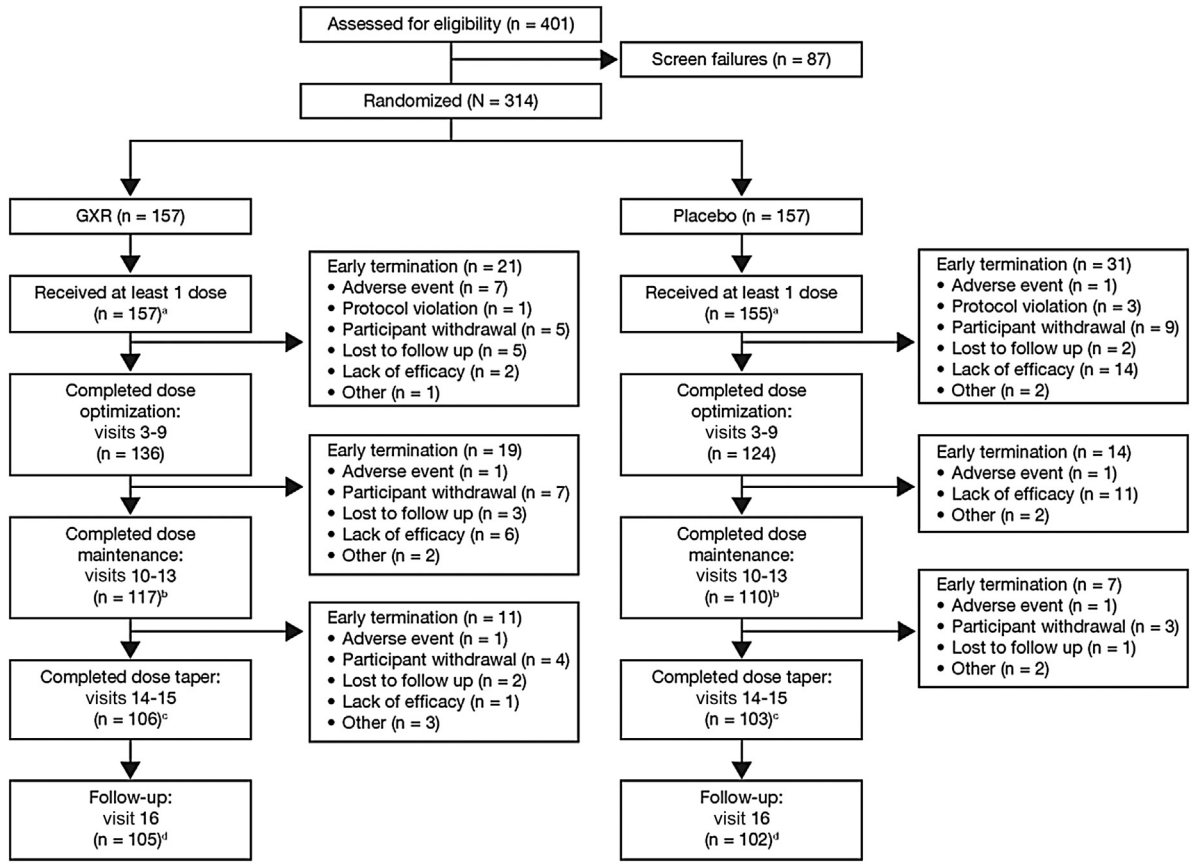
The primary efficacy endpoint was change from baseline in the ADHD-RS-IV total score at week 13. The investigator-rated ADHD-RS-IV is a validated instrument,[30] medication-sensitive in clinical studies of children and adolescents with ADHD.[31-34] It consists of 18 items corresponding to the core ADHD symptoms of the *DSM-IV-TR* criteria, scored on a 4-point Likert scale from 0 (no symptoms) to 3 (severe symptoms).[35]

A dichotomized CGI-S score[36] at the last on-treatment assessment (LOTA) was a key secondary endpoint. The CGI-S scale, which has demonstrated sensitivity to medication effects in trials with children and adolescents,[31,37] was used to assess severity of illness over time on a scale ranging from 1 (normal, not ill at all) to 7 (among the most extremely ill participants). CGI-S scores were dichotomized: ≤ 2 (normal/borderline mentally ill) and >2 (mildly ill or greater).

Changes from baseline for the WFIRS-P Learning and School domain and Family domain[38,39] at week 13 were also key secondary endpoints. The WFIRS-P is a parent-reported scale assessing 6 domains of daily functioning likely to be impaired in ADHD (Family, Learning and School, Life Skills, Child's Self-Concept, Social Activities, and Risky Activities). The Learning and School domain and Family domain were specifically evaluated for treatment-related changes based on previous findings suggesting that scores on these domains were as follows: closely linked to ADHD symptom scores; affected (indirectly) in past adolescent medication trials; and likely to respond to successful treatment.[40-42] The WFIRS-P consists of 50 questions scored on a Likert scale ranging from 0 (never or not at all) to 3 (very often or very much). This scale has been used previously in clinical studies of ADHD, and has demonstrated sensitivity in children and adolescents aged 6 to 17 years with ADHD treated with nonstimulants or stimulants.[41,43-45] Of note, the Risky Activities domain includes questions on behaviors that may initially appear in adolescence, such as smoking, illicit drug use, involvement with the police, and dangerous or sexually inappropriate behavior.

CGI-I scores, which have also demonstrated sensitivity to medication effects in children and adolescents,[25,26] were an additional secondary endpoint. CGI-I scores were dichotomized as follows: improved ("very much improved" and "much improved") and not improved (all remaining responses). Other secondary endpoints included changes from baseline in ADHD-RS-IV hyperactivity/impulsivity and inattentiveness subscale scores, changes from baseline in the WFIRS-P Global and remaining domain (Life Skills, Self-Concept, Social Activities, and Risky Activities) scores.

FIGURE 1 Participant disposition. Note: FAS = full analysis set; GXR = guanfacine extended release. [a]Comprises safety population and FAS. [b]Last visit before taper, and considered as the endpoint for statistical purposes (provided that participants were still taking study drug). [c]Includes the taper period. [d] Includes the follow-up visit.



Safety outcomes included the following: treatment-emergent adverse events (TEAEs; monitored from the time that informed consent was signed until 7 days after the last dose of the investigational product); results of laboratory tests (screening, baseline, and final/early termination visits); vital signs (temperature, supine and standing systolic and diastolic blood pressure [all blood pressure measurements determined manually by cuff using the same method, arm, and position throughout the study], and pulse rate; all study visits); electrocardiography (ECG) measurements (screening, baseline, and final/early termination visits); and physical examinations (screening and final/early termination visits). AEs of special interest included sedative AEs, syncope, orthostatic hypotension, hypertension, and bradycardia.

Statistical Analysis

The observed change in ADHD-RS-IV total score from baseline to week 13 for the full analysis set (FAS; all randomized participants administered ≥1 dose of study drug) was analyzed using a mixed-effect model for repeated measures (MMRM),[46,47] which was fit to the observed changes from baseline score to all postrandomization, pretaper, on-treatment visits (visits 3–13/weeks 1–13). Baseline score was considered a continuous covariate, whereas treatment group (2 levels), weight group (4 levels), and visit (11 levels) were considered categorical. Terms for treatment group–by-visit and baseline-by-visit interactions were also included, and the comparison between treatment groups was based on week 13.

The dichotomized CGI-S and CGI-I responses were analyzed using a Cochran–Mantel–Haenszel test stratified by weight group to assess treatment group effects. Changes from baseline to week 13 for the WFIRS-P Global score and domain scores and for the Hyperactivity/Impulsivity and Inattention subscales of the ADHD-RS-IV were analyzed using MMRM, with methodology similar to that of the primary efficacy analysis.

An initial sample size calculation required 280 participants (140 per treatment arm) to be enrolled. However, as agreed with the US FDA, a blinded sample size review of the observed SD of ADHD-RS-IV scores was conducted after enrollment of 80% of the participants; from this, it was determined that 310 participants (155 per treatment arm) should be randomized, to detect a 4-point difference for the primary efficacy measure (ADHD-RS-IV total score) assuming an SD of 11.6 points at ≥85% power and a 2-sided $\alpha = 0.05$ using a 2-sample t test with a 1:1 allocation ratio for GXR and placebo.

RESULTS

Study Participants

Between September 2011 and May 2013, a total of 314 participants were randomized (GXR, n = 157; placebo, n = 157; Figure 1) from 48 study centers, with each center enrolling between 1 and 20 participants. The FAS and safety populations included 312 participants (2 participants randomized to placebo discontinued before taking any double-blind treatment). The demographic characteristics were generally similar across treatment groups (Table 1); the relative proportions of participants with oppositional defiant disorder were comparable between treatment groups. The mean age was 14.5 years, and the majority of participants were of white ethnicity (72.8%) and male (64.7%). At least 1 prior stimulant medication was used by 77.4% of participants in the placebo group and 70.1% in the GXR group. The most frequently used prior stimulant medications were methylphenidate hydrochloride (48.4%), mixed amphetamine salts (34.6%), lisdexamfetamine mesylate (27.9%), dexmethylphenidate hydrochloride (14.4%), and methylphenidate (10.3%). Among participants who previously received stimulants, the most frequent reasons for stopping stimulant treatment were side effects (35.8%) and lack of efficacy (34.5%). Prior antipsychotics were received by 3.9% in the placebo group and 4.5% in the GXR group, and prior nonstimulant use was reported in 31.0% in the placebo group

TABLE 1 Baseline and Disease Characteristics

Characteristic	GXR n = 157		Placebo n = 155		Total N = 312	
Age, y, mean (SD)	14.5	(1.35)	14.6	(1.44)	14.5	(1.39)
Sex, n (%)						
Male	103	(65.6)	99	(63.9)	202	(64.7)
Female	54	(34.4)	56	(36.1)	110	(35.3)
Race, n (%)						
White	113	(72.0)	114	(73.5)	227	(72.8)
African American or black	24	(15.3)	29	(18.7)	53	(17.0)
Asian	2	(1.3)	3	(1.9)	5	(1.6)
American Indian or Alaska Native	1	(0.6)	1	(0.6)	2	(0.6)
Other[a]	17	(10.8)	8	(5.2)	25	(8.0)
BMI, kg/m^2, mean (SD)	22.00	(3.343)	21.69	(3.239)	21.85	(3.290)
ADHD subtype, n (%)						
Predominately inattentive	46	(29.3)	45	(29.0)	91	(29.2)
Predominately hyperactive-impulsive	5	(3.2)	4	(2.6)	9	(2.9)
Combined subtype	106	(67.5)	106	(68.4)	212	(67.9)
Diagnosis of oppositional defiant disorder, n (%)	20	(12.7)	16	(10.3)	36	(11.5)
Time since ADHD diagnosis, y, mean (SD)	4.8	(3.92)	5.4	(3.83)	5.1	(3.88)

Note: ADHD = attention-deficit/hyperactivity disorder; BMI = body mass index; GXR = guanfacine extended release; SD = standard deviation.
[a]*Includes biracial, more than 1 race, Ethiopian, and unknown.*

and 31.2% in the GXR group. The most frequently used prior nonstimulant was atomoxetine (0.6%)/atomoxetine hydrochloride (14.4%); participants who stopped using atomoxetine hydrochloride reported lack of efficacy (57.8%) and side effects (28.9%) as the most frequent reasons for stopping treatment. Treatment groups were balanced with respect to all prior medications. Mean treatment compliance was 99%. Reasons for study withdrawal are summarized in Figure 1. The most frequently reported reason for early termination was lack of efficacy (5.7% of participants on GXR, 15.9% on placebo), followed by withdrawal by participant (10.2% GXR, 8.3% placebo) and loss to follow-up (GXR 7.0%, placebo 2.5%).

Dose Titration and Responder Analysis

For participants who were randomized to GXR and completed dose optimization, the mean optimal GXR dose was 4.3 mg. The majority of participants received optimal doses of 3, 4, 5, or 6 mg (30 [22.9%], 26 [19.8%], 27 [20.6%], or 24 [18.3%] participants, respectively), with <20% of participants receiving an optimal dose of 1 mg (2 participants [1.5%]), 2 mg (12 participants [9.2%]), or 7 mg (10 participants [7.6%]). A total of 85.5% of participants reached their weight-adjusted optimal dose between 0.05 to 0.12 mg/kg per day. By the beginning of dose maintenance (visit 10), 58.5% (72 of 123) and 74.8% (101 of 135) of participants on placebo and GXR, respectively, had achieved responder status during the optimization period ($p = .003$). Those who did not achieve response were allowed to continue into the maintenance phase at the dose level that was determined by the investigator to be appropriate at the end of the dose optimization period. By the end of maintenance (visit 13), 56.6% (60 of 106) and 78.9% (86 of 109) of those on placebo and GXR, respectively, were responders ($p < .001$), and at week 13 LOTA, 45.8% (71 of 155) and 66.9% (103 of 154) of those on placebo and GXR, respectively, were responders ($p < .001$; see Figure S1, available online).

Efficacy

The FAS was used to assess comparative efficacy information. At week 13, using MMRM analysis, participants receiving GXR compared with placebo achieved a statistically significant improvement (reduction) from baseline in ADHD-RS-IV total score (primary efficacy endpoint; $p < .001$; Figure 2). The least-squares (LS) mean change from baseline was –24.6 and –18.5 for GXR and placebo, respectively (effect size [ES] = 0.52). The week 13 change from baseline in ADHD-RS-IV was also significantly greater ($p < .001$) for GXR versus placebo as measured in a supportive analysis of covariance model using last observation carried forward (LOCF) methodology. Using the MMRM model, GXR treatment group also demonstrated statistically significant improvements compared with placebo throughout dose maintenance (weeks 8–13; $p < .001$ for each visit).

At LOTA, a significantly larger proportion of participants on GXR versus placebo achieved a CGI-S score ≤2 (50.6% versus 36.1%; $p = .010$; see Figure S2, available online). The difference in the percentage of participants treated with GXR in the "normal/borderline mentally ill" category relative to those treated with placebo was 14.5 (95% CI = 3.6 to 25.5). Participants on GXR versus placebo also showed a statistically significant improvement on the CGI-S throughout dose maintenance ($p < .05$ for each visit). A significantly greater proportion of participants who received GXR compared with placebo were also improved on the CGI-I at LOTA (67.5% versus 45.8%; $p < .001$), as well as throughout dose maintenance ($p < .01$ for each of these visits).

No significant between-group differences were observed at week 13 for any WFIRS-P domain score. At week 13, participants on GXR versus placebo achieved numerically greater, although not statistically significant, reductions from baseline in both the WFIRS-P Learning and School (LS mean difference between GXR and placebo, –0.115 [95% CI = –0.254 to 0.024]; ES = 0.22; $p = .104$) and Family domain scores (LS mean difference, –0.057 [95% CI = –0.192 to 0.078]; ES = 0.11; $p = .408$) (Figure 3).

Statistically significant reductions from baseline in ADHD-RS-IV hyperactivity/impulsivity subscale scores were observed for participants receiving GXR compared with placebo from week 7 through week 13 ($p < .001$ for each week). At week 13, the LS mean change from baseline was –12.1 for GXR versus –8.9 for placebo (ES = 0.56; $p < .001$). Similarly, statistically significant reductions from baseline in ADHD-RS-IV Inattentive subscale scores were observed in

FIGURE 2 Least-squares (LS) mean change from baseline in Attention-Deficit/Hyperactivity Disorder Rating Scale–IV (ADHD-RS-IV) total score by visit (full analysis set). Note: GXR = guanfacine extended release; SEM = standard error of the mean.

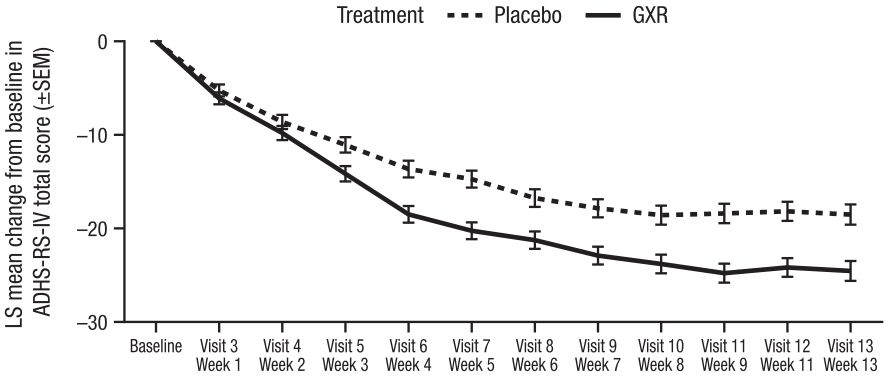
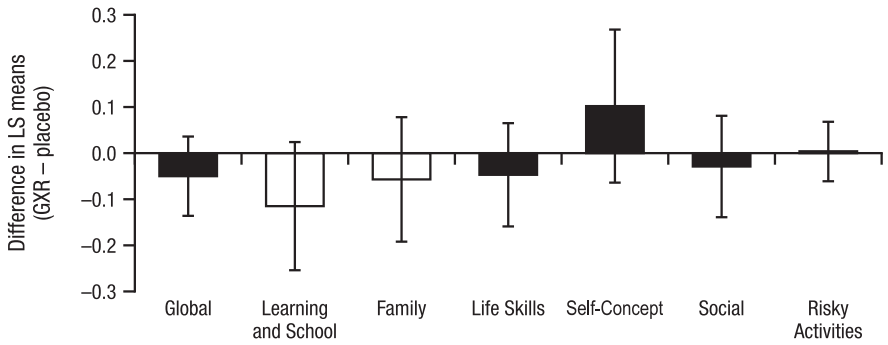


FIGURE 3 Least-squares (LS) mean change (95% CI) from baseline in Weiss Functional Impairment Rating Scale–Parent Report (WFIRS-P) global domain scores at week 13 (full analysis set). Note: White bars denote the key secondary endpoints: change in scores for WFIRS-P Learning and School domain and Family domain. GXR = guanfacine extended release.



the GXR group compared with placebo from week 9 through week 13 ($p \leq .015$ for each week). At week 13, the LS mean change from baseline was –12.4 for GXR compared with –9.7 for placebo, with an ES of 0.39 ($p = .002$).

Safety

The most frequently reported TEAEs were somnolence (43.9%), headache (26.8), and fatigue (22.3%) for participants on GXR, and somnolence (21.3%), headache (18.1%), and fatigue (12.3%) for participants on placebo (Table 2). The majority of sedative TEAEs were mild/moderate, and their incidence decreased over time. No clinically meaningful differences were observed in the mean (SD) duration of sedative events between participants receiving GXR (27.4 [26.94] days) or placebo (43.3 [37.52] days), and the majority of sedative TEAEs resolved before dose taper for participants on GXR (78.9%) or placebo (57.1%). One participant receiving GXR reported a syncopal event (loss of consciousness and concussion resulting from a football collision, considered unrelated to treatment).

At week 13/LOCF, GXR was associated with a decrease from baseline in supine pulse rate compared with placebo (–3.7 beats/min versus +1.0 beats/min); similar results were observed for standing pulse rate (–2.0 beats/min versus +1.0 beats/min). At week 13/LOCF, there were small differences between placebo and GXR participants in terms of mean changes from baseline in postural orthostatic blood pressure for systolic (placebo, –0.1 mm Hg; GXR, –2.8 mm Hg) and diastolic (placebo, –0.0 mm Hg; GXR, –1.6 mm Hg) values. At week 13/LOCF, both supine and standing blood pressure decreased more from baseline in the GXR cohort compared with placebo for systolic (supine: GXR –1.6 mm Hg versus placebo +0.5 mm Hg; standing: GXR –4.4 mm Hg versus placebo +0.5 mm Hg) and diastolic (supine: GXR –1.3 mm Hg versus placebo –0.1 mm Hg; standing: GXR –2.9 mm Hg versus placebo –0.1 mm Hg) values. These pulse and blood pressure decreases are consistent with the known effects of GXR. ECG results were also consistent with previous GXR studies, including change from baseline in heart rate at LOTA (GXR, –7.8 beats/min; placebo, –1.6 beats/min). Mean changes from baseline for PR (GXR, –2.8 milliseconds; placebo, –1.3 milliseconds), QRS (GXR, +0.1 milliseconds; placebo, +0.5 milliseconds), and QTcF (QT interval corrected by the Fridericia formula; GXR, +2.7 milliseconds; placebo, –1.3 milliseconds); intervals were generally unremarkable. One participant on GXR and one on placebo presented with abnormal ECG results deemed clinically significant at LOTA.

No deaths occurred during the study. Among participants receiving GXR, serious TEAEs (n = 4) included the following: homicidal ideation; syncope (described above); vomiting and withdrawal hypertension; and cholecystitis (chronic) and abdominal pain. Other than vomiting and withdrawal hypertension, which were considered related to GXR treatment, all other serious TEAEs were considered unrelated. Serious TEAEs experienced by participants receiving placebo (n = 2) included a ruptured ovarian cyst in 1 participant and a clavicular fracture and pelvic fracture in another.

Among the 9 participants on GXR who had TEAEs leading to discontinuation, 3 participants experienced >1 TEAE, and fatigue was the only TEAE reported by more than 1 participant (n = 2); the remaining events were homicidal ideation, irritability, orthostatic hypotension, somnolence, Wolff–Parkinson–White (WPW) syndrome, diarrhea, headache, nausea, unrelated bradycardia, hypotension, dizziness, constipation, and dizziness postural (Table S1, available online). For the participant on GXR with WPW, although this participant's baseline ECG results were initially read as normal, an independent reviewer determined that the ECG results were consistent with WPW, and the participant was discontinued. TEAEs reported by participants on placebo that led to discontinuation included cognitive disorder, depression, and pelvic fracture. Overall, there were no clinically meaningful differences between GXR and placebo on hematology, clinical chemistry, or urine analyses.

DISCUSSION

This multicenter, phase 3, randomized controlled study evaluated the safety and efficacy of GXR in a large sample of adolescents with ADHD. The study was designed to inform

TABLE 2 Summary of Treatment-Emergent Adverse Events (TEAEs) (≥5% of Participants; Safety Population)

Preferred Term	GXR n = 157 n (%)	Placebo n = 155 n (%)
Any TEAE	147 (93.6)	120 (77.4)
Somnolence	69 (43.9)	33 (21.3)
Headache	42 (26.8)	28 (18.1)
Fatigue	35 (22.3)	19 (12.3)
Dizziness	25 (15.9)	16 (10.3)
Decreased appetite	23 (14.6)	21 (13.5)
Nausea	19 (12.1)	21 (13.5)
Nasopharyngitis	18 (11.5)	9 (5.8)
Sedation	18 (11.5)	3 (1.9)
Increased appetite	14 (8.9)	13 (8.4)
Insomnia	14 (8.9)	6 (3.9)
Upper respiratory tract infection	14 (8.9)	12 (7.7)
Diarrhea	12 (7.6)	13 (8.4)
Dry mouth	12 (7.6)	0
Irritability	11 (7.0)	6 (3.9)
Upper abdominal pain	10 (6.4)	7 (4.5)
Abdominal pain	9 (5.7)	6 (3.9)
Vomiting	9 (5.7)	10 (6.5)
Dizziness postural	8 (5.1)	3 (1.9)
Cough	3 (1.9)	8 (5.2)

Note: GXR = guanfacine extended release.

on several issues that have not been addressed in previous adolescent ADHD treatment studies, including the following: assessment of efficacy using each participant's empirically established optimal dose, rather than using fixed doses; assessment of efficacy and tolerability using a GXR dose range of 1 to 7 mg, which reflects clinically meaningful milligram-per-kilogram dosing regimens not used in prior studies; and the assessment of functional outcomes, which are important clinical domains that have not been assessed in prior studies of nonstimulant medications in adolescents with ADHD. The results provide support of the efficacy of GXR relative to placebo, as indicated by a significant treatment effect obtained on the primary outcome measure, total score on the ADHD-RS-IV (ES = 0.52). Significant treatment effects were also obtained for secondary outcomes, including reductions in the ADHD-RS-IV Inattentive and Hyperactivity/Impulsivity subscale scores, and ratings on the CGI-S and CGI-I scales. No significant treatment differences were observed for parent ratings on the Learning and School domain and Family domain of the WFIRS-P, or for any other domain on this measure. Safety outcomes revealed that GXR was relatively well tolerated, with TEAEs being mostly mild to moderate and their incidences decreasing over time.

These aggregate data add to the literature indicating that GXR is an effective, generally well-tolerated agent in the treatment of ADHD in adolescents at doses of ≤7 mg per day. The current findings are important in extending the empirical basis for nonstimulants generally, and α-agonists/GXR in particular, in treating ADHD in adolescents. Indeed, 46.5% of all participants received treatment exceeding the current FDA-approved maximal dose of 4 mg per day. The range of optimal weight-corrected doses of GXR for most participants (0.05–0.12 mg/kg per day) was similar to that obtained using similar dose titration schedules in children.[25,26] Because dosing guidelines for GXR were originally established largely in children aged 6 to 12 years,[25,26] it is not surprising that adolescents may require higher absolute doses of GXR for optimal ADHD control.

A recent trend in ADHD treatment research[48] is to study functional outcomes related to ADHD, as there is evidence that functional outcomes are also adversely affected in ADHD, in addition to core ADHD symptomatology.[41,49] This is the first GXR study that has investigated parent-reported functionality solely in adolescents, based on the WFIRS-P with a nonstimulant medication. There were no statistically significant differences between placebo and GXR in the 2 key secondary outcomes of functioning (Learning and School domain and Family domain) using the MMRM approach for WFIRS-P at week 13. However, it should be noted that at baseline, the mean score was 1.3 for both the placebo and GXR groups on the Learning and School domain, and the mean scores were 0.9 for placebo and 1.0 for GXR on the Family domain. Per WFIRS interpretation guidelines,[38] a mean score >1.5 is considered to indicate clinical impairment, suggesting that there was limited room for improvement in these functional domains. These results contrast with findings of a recent publication that demonstrated significant improvement in both the WFIRS-P Learning and School domain and Family domain after GXR treatment compared with placebo in both children and adolescents with ADHD; baseline scores were not reported.[50] In the prior study, only 28% of participants were adolescents, and it is unclear how adolescents performed on the WFIRS-P independent of how the children performed.

GXR ≤7 mg administered daily to adolescents was well tolerated, with adverse effects similar to those previously reported in trials with children and adolescents.[25,26,51] The most common TEAEs were sedative events, which resolved in the majority of participants before dose tapering. For cardiovascular outcomes, the effect of GXR was also similar to that in earlier studies, namely, reduction in heart rate and minor reductions in systolic and diastolic blood pressure.[25,26] Although the vast majority of participants were asymptomatic for these changes or required no dose adjustments because of cardiovascular indices, 2 participants on GXR experienced decreased blood pressure resulting in dose adjustment or discontinuation. These data, similar to those in younger children, suggest the need to monitor for signs of hypotension, bradycardia, and syncope, and to measure vital signs before initiation of therapy, during dose titration, after dose increases, and periodically while on therapy. Clinicians should also urge patients to avoid becoming dehydrated or overheated.

Our findings of the clinical utility of an extended-release, nonstimulant α-agonist preparation are relevant, given the advantages to the patient and family over short-acting medication in adolescents, especially increased convenience over that with a scheduled medication, less stigma associated

with medication administration in schools, and the potential to reduce diversion of medication for non-ADHD adolescents.[52] Since adolescents have extended academic and extracurricular burdens and may engage in risky behaviors without their parents' knowledge, longer-acting treatment that extends beyond the school day is beneficial for treating ADHD.[53]

It should be noted that a substantial proportion of participants receiving placebo also demonstrated improvement in their CGI-I scores (45.8% achieved scores of "much improved" or "very much improved"); the relatively high CGI-I placebo response rate observed in this study was comparable to that observed in an adolescent ADHD study comparing the efficacy of lisdexamfetamine dimesylate to that of placebo (39.5% of participants on placebo showed improvement on CGI-I).[54] Similarly, 44.1% of participants receiving placebo showed improvements in CGI-I scores in a study of children and adolescents treated with GXR, atomoxetine, or placebo.[50] In contrast, lower CGI-I placebo response rates (26.9%) were reported for adolescents in a study of mixed amphetamine salts extended release,[55] as well as in a European study of lisdexamfetamine dimesylate (14%) in children and adolescents with ADHD.[56] It is unclear why there is a wide range of placebo responses across studies, with relatively high rates observed in this study and others.

Current study findings should be tempered against study limitations. Adolescents with comorbid psychiatric (except oppositional defiant disorder) and medical disorders (including cardiovascular morbidity) were excluded, and, as such, the findings may not generalize to clinical practice. Study results, however, may be generalized to participants with comorbid symptoms (e.g., those with intermittent passive suicidal ideation) rather than comorbid disorders, as these populations were included. Also, GXR dosing and titration were limited by the study protocol; in clinical practice, dosing can be more varied and individualized. However, as GXR is not FDA approved at doses of >4 mg per day, it is unlikely that GXR will be prescribed in clinical practice to optimize dose based on milligram-per-kilogram-per-day strategy, until doses of >4 mg per day become approved.

In addition, this study did not include teacher ratings, partially as a result of logistical challenges that were involved (e.g., contacting multiple teachers over the summer).[57] The study instead relied on investigator-rated and parent/LAR/caregiver–rated reports for assessment of ADHD symptoms; the availability of reliable ADHD symptom checklists and recent findings of the sensitivity of parent reporting in evaluating other medication classes (e.g., extended-release stimulants)[34,58] also suggests that adequate symptom assessment could be achieved without relying on teacher ratings. However, one limitation of parent-reported scales is the possibility of normalization bias, where at baseline, parents may rate their child's symptoms/problems artificially low; then, as the study progresses, parents may consider their child's problems to be more severe than their initial ratings. Finally, the current study did not use evaluators independent of the clinicians involved in study treatment, which may have resulted in incidental unblinding by the evaluators due to their knowledge of possible side effects and/or efficacy.

In conclusion, the results of this short-term multicenter study completed in a large group of adolescents, which are consistent with the results of previous studies in a mostly younger cohort,[25,26] show that GXR is associated with statistically significant improvements in overall core ADHD symptoms compared with placebo. GXR was relatively well tolerated within the dose range of 0.05 to 0.12 mg/kg per day (absolute doses of ≤7 mg per day). The results of this study add to the substantial body of clinical research now demonstrating the efficacy and safety of nonstimulants in general, and GXR in particular, at comparatively higher doses in adolescents with ADHD. &

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FIGURE S1 Percentage of responders[a] by visit (full analysis set). Note: GXR = guanfacine extended release. [a]Response was defined as a percentage reduction from the baseline visit in the Attention-Deficit/Hyperactivity Disorder Rating Scale–IV (ADHD-RS-IV) total score of ≥30% and a Clinical Global Impressions–Improvement (CGI-I) of 1 or 2.

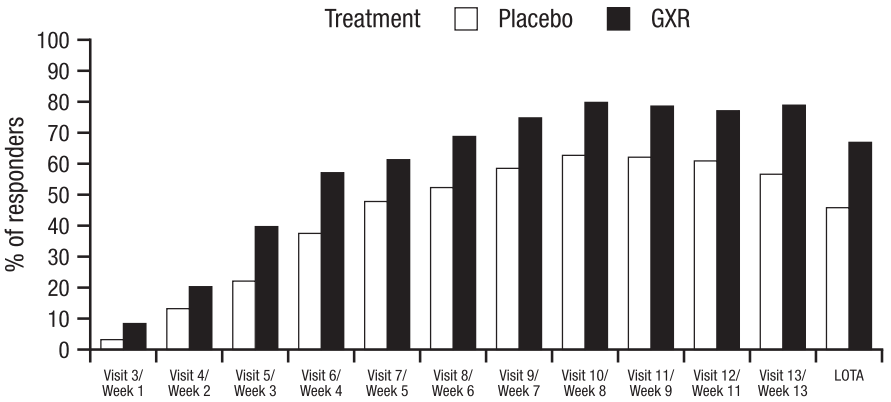

FIGURE S2 Clinical Global Impressions–Severity of Illness Scale (CGI-S) scores at baseline and last on-treatment assessment (LOTA) (full analysis set). Note: GXR = guanfacine extended release.

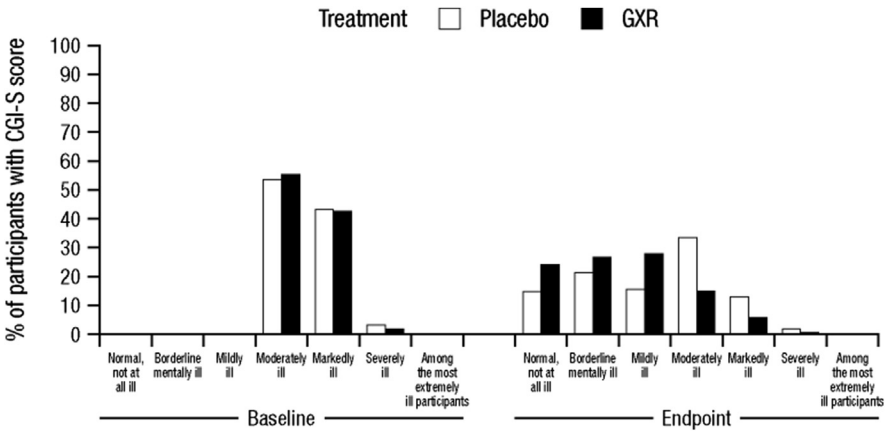

TABLE S1 Treatment-Emergent Adverse Events (TEAEs) Leading to Discontinuation (Full Analysis Set)[a]

Preferred Term[b]	GXR n = 157 n (%)[b]	Placebo n = 155 n (%)[b]
Fatigue	2 (1.3)[c]	0
Bradycardia	1 (0.6)	0
Constipation	1 (0.6)[c]	0
Diarrhea	1 (0.6)[c]	0
Dizziness	1 (0.6)	0
Dizziness postural	1 (0.6)[c]	0
Headache	1 (0.6)[c]	0
Homicidal ideation	1 (0.6)[d]	0
Hypotension	1 (0.6)	0
Irritability	1 (0.6)[c]	0
Nausea	1 (0.6)[c]	0
Orthostatic hypotension	1 (0.6)[c]	0
Somnolence	1 (0.6)[c]	0
Wolff-Parkinson-White syndrome	1 (0.6)	0
Cognitive disorder	0	1 (0.6)[c]
Depression	0	1 (0.6)[c]
Pelvic fracture	0	1 (0.6)[d]

Note: GXR = guanfacine extended release.

[a] *Some participants had multiple TEAEs that led to discontinuation; total discontinuations due to TEAEs = 9 for GXR, 3 for placebo.*

[b] *Percentages are based on the number of enrolled (randomized) participants in each treatment group and total.*

[c] *Considered by the investigator to be related to the investigational product.*

[d] *Events were serious adverse events.*