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ARTICLE

A Randomized, Double-Blind, Placebo-Controlled Study of Guanfacine Extended Release in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

OBJECTIVE. With this study we assessed the efficacy and safety of an extended-release formulation of guanfacine compared with placebo for the treatment of children and adolescents with attention-deficit/hyperactivity disorder.

METHODS. In this multicenter, double-blind, placebo-controlled, fixed-dosage escalation study, patients aged 6 to 17 years were randomly assigned to 1 of 3 treatment groups of guanfacine extended release (2, 3, or 4 mg/day) or placebo for 8 weeks. The primary outcome measurement was the Attention-Deficit/Hyperactivity Disorder Rating Scale IV total score. Secondary measurements included Clinical Global Impression of Improvement, Parent's Global Assessment, Conners' Parent Rating Scale–Revised: Short Form, and Conners' Teacher Rating Scale–Revised: Short Form.

RESULTS. A total of 345 patients were randomly assigned to placebo (n = 86) or guanfacine extended release 2 mg (n = 87), 3 mg (n = 86), or 4 mg (n = 86) treatment groups. Least-squares mean changes from baseline to the end point in Attention-Deficit/Hyperactivity Disorder Rating Scale IV total scores were significant in all groups of children taking guanfacine extended release: −16.18 in the 2-mg group, −16.43 in the 3-mg group, and −18.87 in the 4-mg group, compared with −8.48 in the placebo group. All groups of children taking guanfacine extended release showed significant improvement on hyperactivity/impulsivity and inattentiveness subscales of the Attention-Deficit/Hyperactivity Disorder Rating Scale IV, Clinical Global Impression of Improvement, Parent's Global Assessment, Conners' Parent Rating Scale–Revised: Short Form, and Conners' Teacher Rating Scale–Revised: Short Form assessments compared with placebo. The most commonly reported treatment-emergent adverse events were headache, somnolence, fatigue, upper abdominal pain, and sedation. Small to modest changes in blood pressure, pulse rate, and electrocardiogram parameters were observed but were not clinically meaningful.

CONCLUSIONS. Guanfacine extended release met the primary and secondary efficacy end points. It was well tolerated and effective compared with placebo.

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This trial has been registered at www.clinicaltrials.gov (identifier NCT00152009).

Key Words
attention-deficit/hyperactivity disorder, ADHD, α_2-adrenoceptor agonist, guanfacine, SPD503, nonstimulant, stimulant

Abbreviations
ADHD—attention-deficit/hyperactivity disorder
GXR—guanfacine extended release
ECG—electrocardiogram
BP—blood pressure
ADHD-RS-IV—Attention-Deficit/Hyperactivity Disorder Rating Scale IV
CGI-S—Clinical Global Impression of Severity
CGI-I—Clinical Global Impression of Improvement
PGA—Parent Global Assessment
CPRS-R—Conners' Parent Rating Scale–Revised: Short Form
CTRS-R—Conners' Teacher Rating Scale–Revised: Short Form
AE—adverse event
ITT—intention-to-treat
ANCOVA—analysis of covariance
CI—confidence interval
LS—least squares
TEAE—treatment-emergent adverse event
SBP—systolic BP
DBP—diastolic BP
bpm—beats per minute

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ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) affects ~3% to 7% of school-aged children and adolescents.[1–4] Although stimulants are the mainstay of ADHD treatment,[1] any 1 stimulant fails in at least 25% to 30% of cases because of lack of efficacy.[1,5–8] Stimulants have also been associated with safety concerns, including emergence or exacerbation of tics, decreased appetite, insomnia, and

delayed growth.[1,9–12] These limitations support the need for safe and effective nonstimulants for the treatment of ADHD.

α-adrenoceptor agonists have been used for the past 15 to 20 years as an alternative to stimulant therapies.[13–16] Although clonidine, used alone or in combination with methylphenidate, has been shown to be effective in reducing symptoms of ADHD in children,[15,17,18] its clinical usefulness is limited by its relatively short behavioral half-life and adverse effects,[1,19] including sedation, bradycardia, and hypotension, particularly at the start of treatment.[19]

Guanfacine is a more selective α_2-adrenoceptor agonist than clonidine.[20–22] Whereas clonidine binds equally to α_{2A}-, α_{2B}-, and α_{2C}-adrenoceptors (as well as to α_1-adrenoceptors, β-adrenoceptors, histamine receptors, and possibly dopamine receptors), guanfacine binds preferentially to postsynaptic α_{2A}-adrenoceptors in the prefrontal cortex, which have been implicated in attentional and organizational functions.[20–24] This receptor selectivity may more efficiently target centrally mediated noradrenergic effect while minimizing the risk for adverse effects. Compared with clonidine, guanfacine seems to be less sedating and less hypotensive,[23,25,26] and it may have a more favorable pharmacokinetic profile, with a longer plasma half-life and a greater volume of distribution.[22–24]

The efficacy and tolerability of guanfacine immediate release (0.5 to 4.0 mg/day tablets in divided doses) for the treatment of children, adolescents, and adults with ADHD have been reported in open-label and small placebo-controlled trials.[16,24,27–29] Because of its short-half-life, an extended-release formulation (guanfacine extended release [GXR]; SPD503; Shire Development, Inc, Wayne, PA) has been developed for the treatment of ADHD. The potential benefits of this formulation are the allowance of once-daily dosing for improved convenience, increased adherence, and reduced peak-to-trough fluctuations, thereby potentially improving tolerability and optimizing clinical effects. The objective of this study was to assess the efficacy and safety of GXR compared with placebo for the treatment of children and adolescents with ADHD.

METHODS

Patients

Patients who were aged 6 to 17 years inclusive and met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*, criteria for a primary diagnosis of ADHD combined subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype were eligible to participate in the study. Patients were also required to function intellectually at age-appropriate levels; have electrocardiogram (ECG) results within the reference range; and have blood pressure (BP) measurements within the 95th percentile for their age, gender, and height.

Patients were excluded from the study when they had a current, uncontrolled, comorbid psychiatric diagnosis (except oppositional defiant disorder) with significant symptoms, such as any severe comorbid Axis II disorder or severe Axis I disorder, or when other symptomatic manifestations would, in the opinion of the examining physician, contraindicate GXR treatment or confound efficacy or safety assessments. Patients who weighed <55 lb or were morbidly overweight or obese, pregnant, lactating, or hypertensive were also excluded. In addition, patients were not enrolled when they had any of the following: a QTc interval of >440 milliseconds; a history of seizure during the past 2 years (exclusive of febrile seizures); a tic disorder; family history of Tourette's disorder; a positive urine drug screen; any abnormal thyroid function that was not adequately treated; or any cardiac condition or family history of cardiac condition that, in the opinion of the physician investigator, would require exclusion. Patients who had taken an investigational drug within 28 days, were taking medications that affect BP or heart rate, or were taking other medications that have central nervous system effects or affect performance were also not eligible to participate.

The study protocol was approved by the institutional review board at each study center, and the study was performed in accordance with the Declaration of Helsinki (2000) and the International Conference on Harmonization *E6 Good Clinical Practice: Consolidated Guidance (1996)*. Written informed consent was obtained from each patient's parent or legal guardian before enrollment in the study, and written assent was obtained from each patient.

Study Design

This randomized, multicenter, double-blind, parallel-group, placebo-controlled, fixed-dosage escalation study was conducted at 48 centers in the United States from January to August 2003. The study consisted of 3 periods: screening, washout, and double-blind treatment. After a screening period of up to 14 days to determine eligibility, patients entered a washout period during which each patient's current ADHD medication was discontinued for ~1 week or, at minimum, 5 times the established half-life of the medication. The double-blind treatment period consisted of 8 weeks of clinic visits (scheduled 7 ± 2 days apart), 5 weeks of dosage escalation and/or maintenance, and 3 weeks of downward tapering.

Patients were randomly assigned to 1 of 3 groups of GXR treatment (2, 3, or 4 mg/day) or placebo, in a 1:1:1:1 ratio. Matching GXR and placebo tablets were provided to patients in the form of weekly prepackaged individual study drug kits, identical in appearance, according to the randomization schedule. Every morning during the double-blind treatment period, patients took a total of 4 tablets, without regard to meals. Patients who completed the screening and washout periods were assigned to the treatment group of the next available drug kit in ascending order of the drug kit number (or randomization number), which was recorded on the case report form.

All patients who received GXR began dosing at 1 mg/day. GXR dosages were escalated weekly in 1-mg

increments beginning at 1 mg/day at week 1 of the double-blind treatment period, with the highest dosage given during weeks 4 and 5. Beginning at visit 6 (week 6), dosages were reduced weekly in 1-mg decrements until patients reached 2 mg/day (at either visit 6 or visit 7). At visit 7 (week 7), patients, without breaking the study blind, had the option to enroll in an open-label extension study at the 2 mg/day dosage. Patients who participated in the extension study underwent end-of-study assessments at visit 9, and the clinical data from this study would become the baseline data for the extension study. Patients who chose not to participate in the extension study were titrated down to 1 mg/day GXR or placebo at visit 8 (week 8) for 1 week. Dosing was then discontinued, and patients returned to the clinic 2 to 4 days later for assessments (visit 9). Thirty days after the last dose of study drug, patients returned to the clinic for a final visit (visit 10).

Assessments

Efficacy

The primary outcome measure was ADHD Rating Scale IV (ADHD-RS-IV) total score. The ADHD-RS-IV consists of 18 items designed to reflect current symptoms of ADHD on the basis of *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*, criteria. Each item is scored on a scale of 0 (no symptoms) to 3 (severe symptoms). Clinicians administered the ADHD-RS-IV at baseline and at visits 1 through 5, and parents or caregivers were the respondents. The primary efficacy end point was defined as the ADHD-RS-IV total score observed during the last treatment week of the dosage escalation period (weeks 1–5) for which a valid score was obtained.

Secondary efficacy outcome measures included the following rating scales: Clinical Global Impression of Severity (CGI-S), Clinical Global Impression of Improvement (CGI-I), Parent's Global Assessment (PGA), Conners' Parent Rating Scale–Revised: Short Form (CPRS-R), and Conners' Teacher Rating Scale–Revised: Short Form (CTRS-R). The end point of these measures was also defined as the last treatment week of the dosage escalation period for which a valid score was obtained.

Clinicians rated the severity of a patient's condition at screening and baseline on the CGI-S, a 7-point scale ranging from 1 (not ill at all) to 7 (among the most extremely ill patients). At visits 1 through 5, clinicians assessed a patient's change in clinical status relative to baseline on the CGI-I. The PGA is a variation of the CGI-S and CGI-I. Parents noted their child's behavior at screening for the previous week and assessed changes in relation to baseline ratings on the PGA at visits 4 and 5.

The CPRS-R and CTRS-R were used to assess the duration of effect for GXR. They were administered on the last day of a patient's washout period and at visits 4 and 5. Parents completed the CPRS-R at ~6:00 AM, 6:00 PM, and 8:00 PM. Teachers completed the CTRS-R at ~10:00 AM and 2:00 PM.

Safety

Safety assessments included adverse event (AE) monitoring, vital sign measurements, physical examination, clinical laboratory tests (hematology; chemistry, including cortisol levels and human growth hormone; and urinalysis), 12-lead ECG, and reasons for early terminations. AEs were assessed and vital sign measurements, including BP and pulse rate, were performed at all study visits. Laboratory tests and physical examination, including weight and height, were performed at screening and at visit 9. A 12-lead ECG was performed at screening and at visits 3, 7, and 9. A minimum of 3 ECGs were performed at baseline, and the baseline ECG intervals for each patient were defined as the mean of the intervals from the ECGs.

Statistical Analyses

Approximately 70 patients were needed in each of the 4 treatment groups (280 patients in total) to use a 2-sample *t* test to detect an effect size of 0.50 between a single active group and the placebo group for changes from baseline in ADHD-RS-IV total score at >80% power and an α level of .05 (2-tailed). The intention-to-treat (ITT) population was defined as all patients who were randomly assigned and had a baseline and at least 1 primary efficacy measurement recorded during dosage escalation. The safety population was defined as all patients enrolled into the study.

The primary efficacy analysis was performed on the ADHD-RS-IV total score change from baseline to end point for the ITT population, using an analysis of covariance (ANCOVA) model, and included terms for baseline ADHD-RS-IV total score, treatment, and site. On the basis of the results from the ANCOVA model, Dunnett's adjustment for multiple pairwise mean comparisons was used to compare the ADHD-RS-IV change in scores for each of the 3 active drug groups with placebo. For the Dunnett's test, the family-wise type I error was set at 0.05 (2-sided).

The same ANCOVA model and Dunnett's adjustment were used to analyze changes in scores from baseline to end point for the secondary efficacy measures, CPRS-R and CTRS-R, for the ITT population. For the CGI-I and PGA, the nonparametric Cochran-Mantel-Haenszel test, with adjustment for center, was used to evaluate treatment effects at end point. The test was performed separately for each pair of active dose versus placebo. Before the analysis, this variable was dichotomized into 2 categories, with "very much improved" and "much improved" characterized as "improved" and the remaining levels characterized as "not improved."

Length of exposure to study drug was calculated on the basis of the date of first dispensing and last dose of study drug. Descriptive statistics were used to summarize AEs, vital signs, physical examination, clinical laboratory tests, and ECG. Where applicable, changes from baseline at each study visit were analyzed for differences among treatment groups by using ANCOVA.

All statistical tests were 2-tailed and performed at the 5% significance level, and all confidence intervals (CIs) were 2-sided with 95% coverage. All group com-

TABLE 1 **Patient Demographics (All Randomly Assigned Patients)**

Parameter	Placebo ($n = 86$)	GXR			Total ($n = 345$)
		2 mg ($n = 87$)	3 mg ($n = 86$)	4 mg ($n = 86$)	
Age, mean (range), y	10.6 (6.0–17.0)	10.6 (6.0–16.0)	10.8 (6.0–17.0)	10.1 (6.0–17.0)	10.5 (6.0–17.0)
Age category, *n* (%)					
6–8 y	23 (26.7)	18 (20.7)	21 (24.4)	29 (33.7)	91 (26.4)
9–12 y	43 (50.0)	51 (58.6)	39 (45.3)	41 (47.7)	174 (50.4)
13–17 y	20 (23.3)	18 (20.7)	26 (30.2)	16 (18.6)	80 (23.2)
Gender, *n* (%)					
Male	64 (74.4)	67 (77.0)	69 (80.2)	57 (66.3)	257 (74.5)
Female	22 (25.6)	20 (23.0)	17 (19.8)	29 (33.7)	88 (25.5)
Ethnic origin, *n* (%)					
White	63 (73.3)	59 (67.8)	58 (67.4)	62 (72.1)	242 (70.1)
Black	8 (9.3)	17 (19.5)	10 (11.6)	11 (12.8)	46 (13.3)
Hispanic	7 (8.1)	6 (6.9)	13 (15.1)	8 (9.3)	34 (9.9)
Asian or Pacific Islander	1 (1.2)	0 (0.0)	0 (0.0)	1 (1.2)	2 (0.6)
Native American	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	1 (0.3)
Other	7 (8.1)	5 (5.7)	4 (4.7)	4 (4.7)	20 (5.8)
Weight, mean (range), lb	93.8 (55.0–175.0)	98.9 (55.0–271.0)	97.9 (55.0–197.0)	93.2 (54.0–207.0)	96.0 (54.0–271.0)
Height, mean (range), in	57.1 (46.0–73.0)	58.0 (47.0–73.0)	57.8 (44.0–71.0)	56.2 (46.0–71.0)	57.3 (44.0–73.0)
ADHD subtype, *n* (%)					
Inattentive	19 (22.1)	28 (32.2)	20 (23.3)	23 (26.7)	90 (26.1)
Hyperactive-impulsive	0 (0.0)	4 (4.6)	1 (1.2)	2 (2.3)	7 (2.0)
Combined	67 (77.9)	55 (63.2)	65 (75.6)	61 (70.9)	248 (71.9)
Time since ADHD diagnosis, mean (range), y	2.71 (0.0–12.0)	2.31 (0.0–13.0)	3.03 (0.0–10.0)	2.39 (0.0–13.0)	2.61 (0.0–13.0)

parisons from analysis of variance and ANCOVA models were based on type III sums of squares. For all continuous efficacy parameters, the following statistics were calculated from the ANCOVA or analysis of variance model: least-squares (LS) mean, difference in LS mean between active and placebo, and 95% CIs for the difference.

Additional posthoc analyses included analysis of the primary efficacy variable by actual dose, analysis of the primary efficacy variable by (baseline) weight-adjusted actual dose, analysis of responder rates, analysis of treatment-emergent AEs (TEAEs) by actual dose and weight-adjusted actual dose, and analysis of vital sign results by actual dose.

RESULTS

Patient Demographics and Disposition

A total of 345 patients were enrolled and randomly assigned to treatment: 86 received placebo, and 259 received GXR (2 mg: $n = 87$; 3 mg: $n = 86$; 4 mg: $n = 86$). Mean age was 10.5 years. The majority of patients were male (74.5%) and white (70.1%) and had a diagnosis of the combined ADHD subtype (71.9%). Patient demographics and disease diagnoses were similar across treatment groups (Table 1).

Sixty-two percent of patients completed the study (Fig 1). The most common reasons for discontinuation among all randomly assigned groups were AEs (12.5%

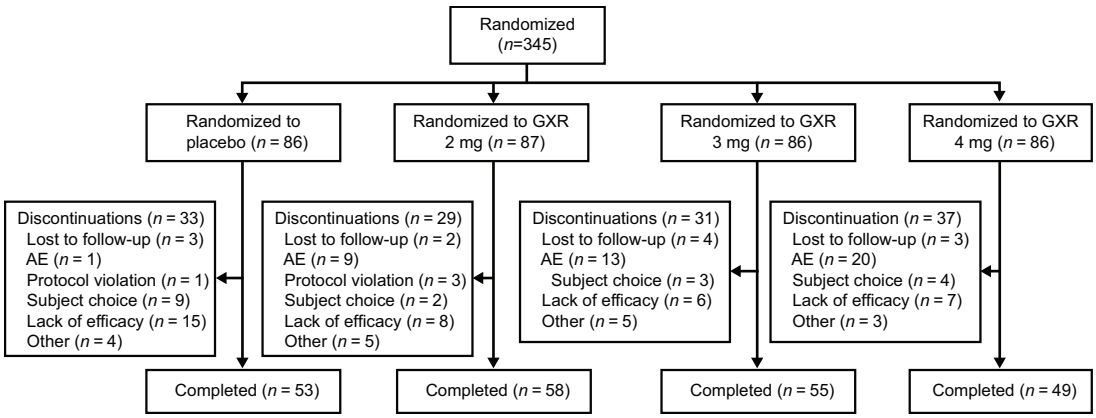

FIGURE 1
Patient recruitment and disposition.

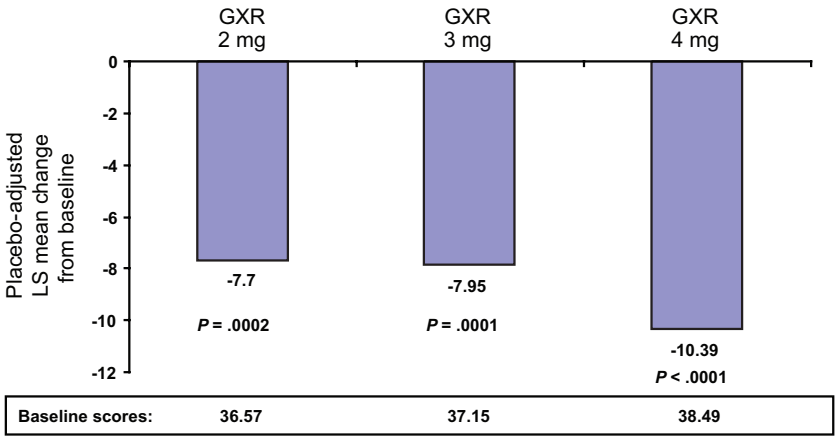

FIGURE 2
Placebo-adjusted LS mean end-point changes from baseline in ADHD-RS-IV total score according to randomized dose (ITT population). Shown are *P* values versus placebo.

of patients) and lack of efficacy (10.4% of patients). The incidence of discontinuation as a result of AEs was higher in the groups of children taking GXR (16.2% combined) than in the placebo group (1.2%). The incidence of discontinuation as a result of lack of efficacy was highest in the placebo group (17.4%), compared with the combined rate of 8.1% in the groups of children taking GXR. Adherence, as assessed by tablet counts, was high and similar between all randomly assigned patients (97.4%) and the ITT population (97.6%).

Efficacy

Overall, there were statistically significant differences among the treatment groups ($P < .0001$). The mean reduction in ADHD-RS-IV score at end point across all groups of children taking GXR was −16.7 compared with −8.9 for placebo. Reductions in ADHD-RS-IV total scores from baseline to end point were significant in all groups of children taking GXR compared with placebo, and placebo-adjusted LS mean end point changes from baseline increased with increasing randomized dosages of GXR (Fig 2). Placebo-adjusted LS mean end point changes from baseline in the GXR 2-mg, 3-mg, and 4-mg groups were −7.70 (95% CI: −12.25 to −3.15; $P = .0002$), −7.95 (95% CI: −12.50 to −3.40; $P = .0001$), and −10.39 (95% CI: −14.97 to −5.82; $P < .0001$), respectively. Posthoc analysis of the ADHD-RS-IV treatment effect size by randomized dosage was 0.64 for the 2-mg group, 0.66 for the 3-mg group, and 0.86 for the 4-mg group. Placebo-adjusted LS mean end point changes from baseline were significant in the 2-mg group ($P = .0394$) but not in the 3-mg or 4-mg groups by week 2, when all patients who were receiving GXR were on 2-mg doses. Placebo-adjusted LS mean end point changes from baseline were significant in all GXR dosage groups by week 3 and continued through week 5 ($P < .05$; Fig 3).

When examined by weight-adjusted actual dosage, placebo-adjusted LS mean end point changes from baseline were significant in the GXR 0.05 to 0.08 mg/kg group (−6.81; 95% CI: −11.17 to −2.45; $P = .0005$), in the GXR 0.09 to 0.12 mg/kg group (−13.80; 95% CI: −19.20 to −8.41; $P < .0001$), and in the GXR 0.13 to 0.17 mg/kg group (−15.58; 95% CI: −23.01 to −8.16; $P < .0001$) but did not reach significance in the GXR 0.01 to 0.04 mg/kg group (−5.06; 95% CI: −10.25 to 0.13; $P = .0587$; Table 2). Effect sizes in the GXR treatment groups calculated posthoc were 0.58, 1.19, and 1.34 for the 0.05 to 0.08 mg/kg, 0.09 to 0.12 mg/kg, and 0.13 to 0.17 mg/kg groups, respectively.

Posthoc analysis of ADHD-RS-IV total scores by actual dosage supported primary efficacy results, and placebo-adjusted LS mean end point changes from baseline increased as patients received increasing actual dosages of GXR. Placebo-adjusted LS mean end point changes from baseline were significant in patients who were receiving GXR 2-mg (−6.68; 95% CI: −11.28 to −2.09; $P =$

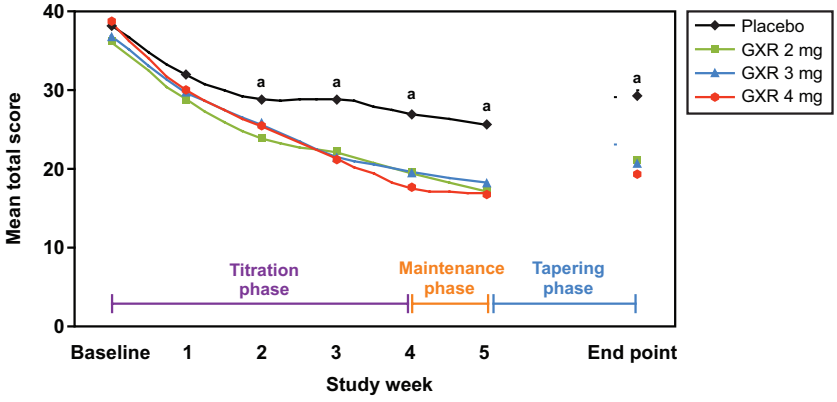

FIGURE 3
ADHD-RS-IV: mean total score according to randomized dose (ITT population). [a] Placebo-adjusted LS mean changes from baseline were significant at week 2 for the GXR 2-mg group ($P < .05$), at all GXR dose groups at visits 3 through 5 ($P < .05$ for all), and at the end point ($P < .001$ for all).

TABLE 2 **ADHD-RS-IV Total Scores by Weight-Adjusted Dosage at End Point (ITT Population)**

Parameter	Placebo	Weight-Adjusted Actual Dosage of GXR, mg/kg			
		0.01–0.04	0.05–0.08	0.09–0.12	0.13–0.17
End point	29.28	22.15	22.65	15.47	15.14
Absolute change from baseline	−8.86	−11.48	−15.12	−21.71	−27.86
% reduction from baseline	23	34	40	58	63
Placebo-adjusted LS mean change from baseline	—	−5.06	−6.81	−13.80	−15.58
P	—	.0587	.0005	<.0001	<.0001
95% CI	—	−10.25 to 0.13	−11.17 to −2.45	−19.20 to −8.41	−23.01 to −8.16

.0015), 3-mg (−8.53; 95% CI: −13.31 to −3.76; $P <$ .0001), and 4-mg actual doses (−12.72; 95% CI: −17.92 to −7.52; $P <$ .0001).

All groups of children taking GXR showed significant improvement on both the hyperactivity/impulsivity and inattentiveness subscales of the ADHD-RS-IV compared with placebo. Mean changes from baseline in hyperactivity/impulsivity in the placebo and GXR 2-mg, 3-mg, and 4-mg groups were −4.06, −6.94, −7.09, and −9.46, respectively. Mean changes from baseline in inattentiveness were −4.78, −8.46, −8.71, and −9.51, respectively. Placebo-adjusted LS mean end point changes from baseline in hyperactivity/impulsivity and inattentiveness are shown in Table 3.

Patients were categorized as the combined ADHD subtype (72.3% of the ITT population) or inattentive ADHD subtype (25.8% of the ITT population) at baseline. The magnitude of improvement in ADHD-RS-IV total scores from baseline to end point was greater in each group of children taking GXR than in the placebo group, in patients of both the combined and inattentive ADHD subtypes. Mean changes from baseline in the combined subtype in the placebo and GXR 2-mg, 3-mg, and 4-mg groups were −8.45, −17.57, −15.38, and −21.41, respectively. Mean changes from baseline in the inattentive subtype were −10.44, −11.64, −17.59, and −13.30, respectively. Placebo-adjusted LS mean end point changes from baseline in the combined subtype were significant in all GXR groups: −9.06 in the 2-mg group (95% CI: −14.78 to −3.34; $P = .0007$), −8.43 in the 3-mg group (95% CI: −13.75 to −3.12; $P = .0007$), and −12.55 in the 4-mg group (95% CI: −18.10 to −7.00; $P < .0001$). In the inattentive subtype, placebo-adjusted LS mean end point changes from baseline were not significant in any of the GXR groups, most likely as a result of inadequate statistical power.

In subgroups of patients aged 6 to 8 years, all groups of children taking GXR showed significant improvement from baseline in ADHD-RS-IV total scores compared with placebo. Mean changes from baseline in patients aged 6 to 8 years in the placebo and GXR 2-mg, 3-mg, and 4-mg groups were −3.82, −16.88, −17.85, and −25.85, respectively. Mean changes from baseline in patients aged 9 to 12 years were −9.49, −16.57, −16.92, and −15.36, respectively. Placebo-adjusted LS mean end point changes from baseline in patients aged 6 to 8 years were −16.07 in the 2-mg group (95% CI: −28.97 to −3.18; $P = .0112$), −13.26 in the 3-mg group (95% CI: −24.41 to −2.12; $P = 0.0161$), and −22.71 in the 4-mg group (95% CI: −33.72 to −11.70; $P < .0001$). In patients aged 9 to 12 years, placebo-adjusted LS mean end point changes from baseline were −6.37 (95% CI: −13.29 to 0.55; $P = .0780$), −6.57 (95% CI: −13.97 to −0.82; $P = .0927$), and −5.61 (95% CI: −13.27 to −2.04; $P > .1$), respectively. The LS mean placebo-adjusted changes from baseline to end point were not statistically significant in any GXR group in the 13- to 17-year-old subgroup compared with placebo. In this subgroup, mean changes from baseline in the placebo and GXR 2-mg, 3-mg, and 4-mg groups were −13.47, −10.53, −12.48, and −15.93, respectively. These were secondary analyses that were not powered to make any conclusions from reported *P* values.

Significant improvement in CGI-I scores at end point

TABLE 3 **ADHD-RS-IV Scores: LS Mean and Placebo-Adjusted LS Mean End-Point Changes From Baseline in Hyperactivity/Impulsivity and Inattentiveness Subscales (ITT Population)**

Parameter	Placebo	GXR		
		2 mg	3 mg	4 mg
Hyperactivity/impulsivity subscale				
LS mean	−3.51	−7.33	−7.32	−9.31
Placebo-adjusted LS mean	—	−3.82	−3.81	−5.80
P	—	.0002	.0002	<.0001
95% CI		−6.05 to −1.59	−6.03 to −1.58	−8.03 to −3.56
Inattentiveness subscale				
LS mean	−4.92	−8.7	−9.11	−9.44
Placebo-adjusted LS mean	—	−3.95	−4.19	−4.52
P	—	.0011	.0006	.0002
95% CI	—	−6.54 to −1.36	−6.78 to −1.60	−7.13 to −1.90

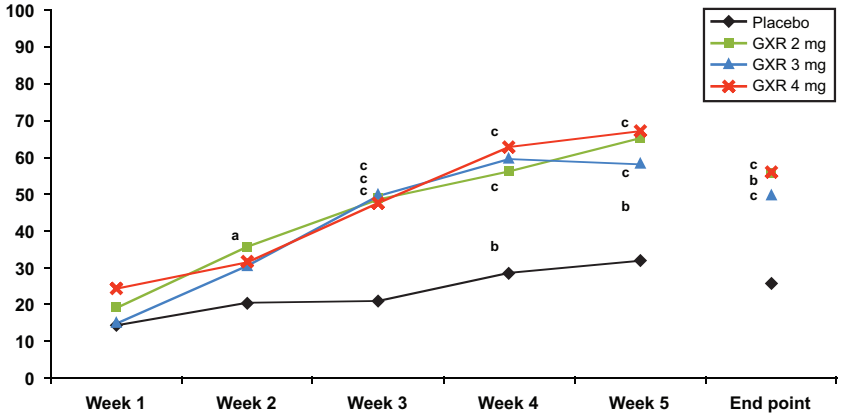

FIGURE 4
Percentage of subjects with improvement in CGI-I scores (ITT population). Shown are *P* values versus placebo. CGI-I and PGA improved response was defined as ratings of "very much improved" or "much improved." [a] $P < .05$; [b] $P < .01$; [c] $P < .001$.

was shown in 25.64%, 55.95%, 50.00%, and 55.56% of patients in the placebo and GXR 2-mg, 3-mg, and 4-mg groups, respectively (Fig 4). Improvement in CGI-I scores was significant in the GXR 2-mg group compared with the placebo group by week 2 ($P = .0194$) and in all GXR groups by week 3 continuing through week 5 ($P < .05$). Significant improvement in PGA scores at end point was shown in 23.08%, 62.12%, 50.82%, and 66.10% of patients in the placebo and GXR 2-mg, 3-mg, and 4-mg groups, respectively.

In addition, a posthoc responder analysis showed that, compared with placebo-treated patients, patients who were treated with GXR (2 mg, 3 mg, and 4 mg) were more likely to meet the responder criteria of a 30% decrease in ADHD-RS-IV total score and a CGI-I score of 1 or 2 ("very much improved" or "much improved") over time (Fig 5). The differences between placebo and GXR doses were statistically significant ($P < .05$) for all active doses beginning week 3 through study end.

Duration of Effect

All groups of children taking GXR showed significant improvement from baseline in CPRS-R and CTRS-R mean day total scores, compared with placebo (Fig 6). On the CPRS-R, placebo-adjusted LS mean day total end point changes from baseline were −6.55 in the 2-mg group (95% CI: −12.99 to −0.12; $P = .0448$), −7.36 in the 3-mg group (95% CI: −13.95 to −0.77; $P = .0242$), and −12.70 in the 4-mg group (95% CI: −19.31 to −6.11; $P < .0001$). On the CTRS-R, placebo-adjusted LS mean day total end point changes from baseline were −11.57 (95% CI: −17.19 to −5.95; $P < .0001$), −13.48 (95% CI: −19.26 to −7.69; $P < .0001$), and −12.53 (95% CI: −18.30 to −7.76; $P < .0001$), for the 2-mg, 3-mg, and 4-mg doses, respectively.

At 12 hours after dosing, placebo-adjusted LS mean end point changes from baseline on the CPRS-R were significant in all GXR groups: −7.94 in the 2-mg group (95% CI: −14.80 to −1.08; $P = .0184$), −9.84 in the

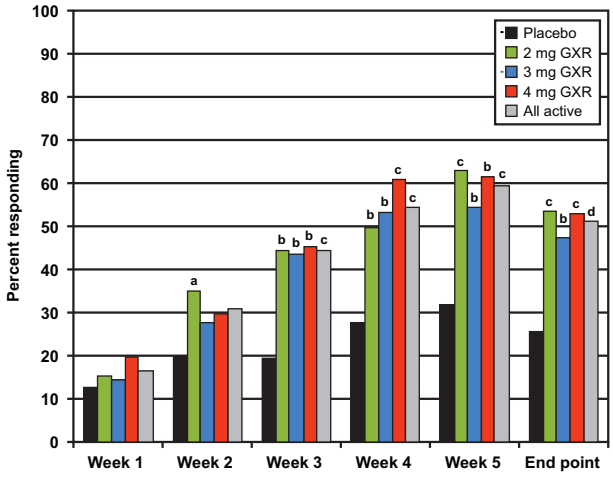

FIGURE 5
Responder analysis based on proportion (%) of patients with 30% improvement in ADHD-RS and CGI-I = 1 or 2 (ITT population). Shown are *P* values versus placebo. [a] $P < .05$; [b] $P < .01$; [c] $P < .001$; [d] $P < .0001$.

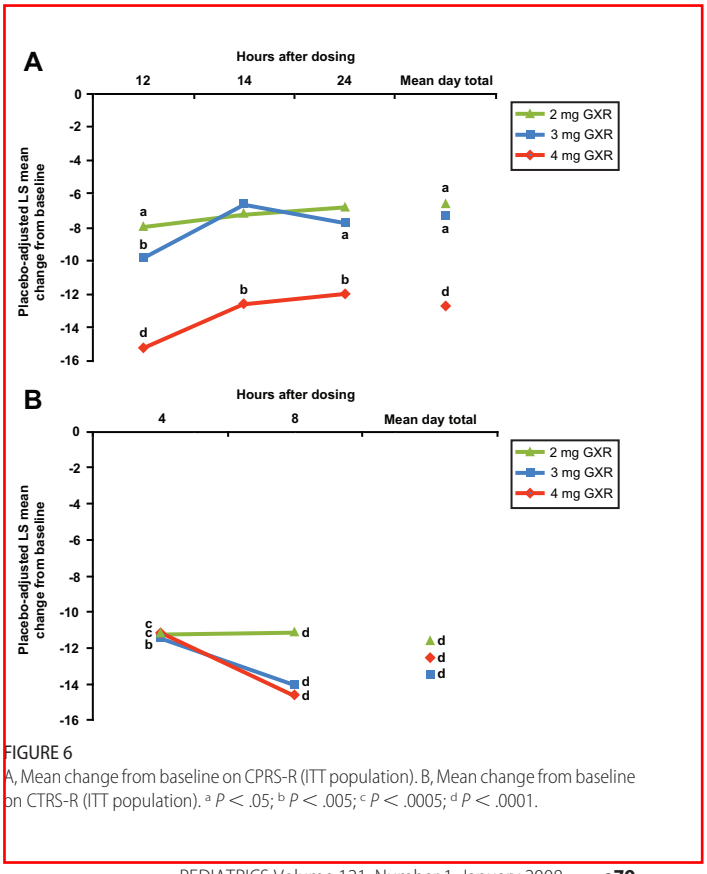

FIGURE 6
A, Mean change from baseline on CPRS-R (ITT population). B, Mean change from baseline on CTRS-R (ITT population). [a] $P < .05$; [b] $P < .005$; [c] $P < .0005$; [d] $P < .0001$.

TABLE 4 **TEAEs Occurring in ≥5.0% of Any Treatment Group and Twice the Placebo Rate: Safety Population**

Parameter	Placebo ($n = 86$), *n* (%)	GXR 2 mg ($n = 87$), *n* (%)	GXR 3 mg ($n = 86$), *n* (%)	GXR 4 mg ($n = 86$), *n* (%)
Total patients who experienced TEAEs[a]	55 (64.0)	67 (77.0)	76 (88.4)	75 (87.2)
Abdominal pain, upper	5 (5.8)	9 (10.3)	14 (16.3)	14 (16.3)
Dry mouth	1 (1.2)	2 (2.3)	8 (9.3)	5 (5.8)
Nausea	2 (2.3)	6 (6.9)	5 (5.8)	5 (5.8)
Fatigue	3 (3.5)	16 (18.4)	18 (20.9)	13 (15.1)
Lethargy	3 (3.5)	5 (5.7)	7 (8.1)	8 (9.3)
Pyrexia	3 (3.5)	2 (2.3)	0 (0.0)	6 (7.0)
Appetite decreased not otherwise specified	2 (2.3)	5 (5.7)	8 (9.3)	5 (5.8)
Dizziness	2 (2.3)	4 (4.6)	5 (5.8)	9 (10.5)
Sedation	3 (3.5)	8 (9.2)	11 (12.8)	14 (16.3)
Somnolence	3 (3.5)	21 (24.1)	29 (33.7)	33 (38.4)
Irritability	3 (3.5)	9 (10.3)	2 (2.3)	5 (5.8)

[a] Patients may have experienced >1 TEAE.

3-mg group (95% CI: −16.86 to −2.84; $P = .0030$), and −15.17 in the 4-mg group (95% CI: −22.22 to −8.12; $P < .0001$). Placebo-adjusted LS mean end point changes from baseline were also significant at 14 hours (−12.55; 95% CI: −20.06 to −5.04; $P = .0003$) and 24 hours (−11.94; 95% CI: −19.35 to −4.52; $P = .0005$) in the 4-mg group and at 24 hours (−7.68; 95% CI: −15.08 to −0.28; $P = 0.0398$) in the 3-mg group.

All groups of children taking GXR showed significant improvement through the same day (8 hours after dosing) on the CTRS-R, compared with placebo. Placebo-adjusted LS mean end point changes from baseline at 4 hours and 8 hours after dosing were −11.21 (95% CI: −17.67 to −4.76; $P = .0002$) and −11.10 (95% CI: −17.08 to −5.13; $P < .0001$) in the 2-mg group, −11.45 (95% CI: −18.28 to −4.62; $P = .0003$) and −14.07 (95% CI: −20.28 to −7.87; $P < .0001$) in the 3-mg group, and −11.18 (95% CI: −18.06 to −4.30; $P = .0005$) and −14.59 (95% CI: −20.71 to −8.46; $P < .0001$) in the 4-mg group.

Safety Results

GXR was safe and generally well tolerated in daily dosages of 2 mg, 3 mg, and 4 mg, compared with placebo. The average length of exposure to GXR was 42 days. The most commonly reported TEAEs were somnolence, fatigue, upper abdominal pain, and sedation (Table 4). Most of the commonly reported TEAEs were mild or moderate in intensity. Severe TEAEs were experienced by 24 patients, all of whom received GXR. Severe TEAEs experienced by >1 patient included sedation ($n = 7$), somnolence ($n = 6$), fatigue ($n = 4$), headache ($n = 2$), vomiting ($n = 2$), and insomnia ($n = 2$). The most commonly reported TEAEs that led to discontinuation in patients who received GXR were somnolence (4.2%), sedation (3.5%), and headache (1.5%). Two patients who received GXR had serious AEs, asthma aggravated and pneumothorax, both of which were unrelated to the study drug. There were no deaths.

The majority of sedative events (somnolence, sedation, or fatigue) were mild or moderate in intensity, related to the study drug, and resolved within the duration of the study (Table 5). The median day of onset of fatigue was within the first week of dosing, whereas the median days of onset for somnolence and sedation were within the first 2 weeks of dosing. The median duration of sedative events was longer for patients who were taking GXR (17–24, 11–30, and 8–14 days for somnolence, sedation, and fatigue, respectively) than for those who were taking placebo (5 days for somnolence, sedation, and fatigue). For somnolence and sedation, incidence rates increased with increasing randomized dosages of GXR. When sedative events were examined by actual and weight-adjusted actual dose at event onset, incidence rates remained suggestive of a dosage relationship to GXR dosage for somnolence only. The incidence of somnolence in patients who were receiving GXR 1-mg, 2-mg, 3-mg, and 4-mg actual doses was 12.7%, 11.4%, 20.9%, and 17.5%, respectively. The incidence of somnolence in GXR 0.01 to 0.04 mg/kg, 0.05 to 0.08 mg/kg, 0.09 to 0.12 mg/kg, and 0.13 to 0.17 mg/kg dose groups was 15.8%, 17.5%, 27.6%, and 13.6%, respectively.

TABLE 5 **Sedative TEAEs (Somnolence, Sedation, or Fatigue)**

Parameter	Placebo ($n = 86$)	GXR		
		2 mg ($n = 87$)	3 mg ($n = 86$)	4 mg ($n = 86$)
No. of events	9	58	77	77
Patients with AE, %	9 (10.5)	40 (46.0)	53 (61.6)	54 (62.8)
Mild	6 (7.0)	19 (21.8)	29 (33.7)	17 (19.8)
Moderate	3 (3.5)	20 (23.0)	18 (20.9)	28 (32.6)
Severe	0 (0.0)	1 (1.1)	6 (7.0)	9 (10.5)
Onset day				
Mean	9.0	6.9	9.6	10.9
Median	1.0	2.5	8.0	10.5
Range	0–28	1–34	1–42	0–37
Duration of event, d				
Mean	8.6	18.2	24.3	22.4
Median	5.0	16.0	22.5	23.0
Range	1–33	3–44	1–62	1–55
Patients with unresolved AEs, %	2 (2.3)	5 (5.7)	10 (11.6)	4 (4.7)

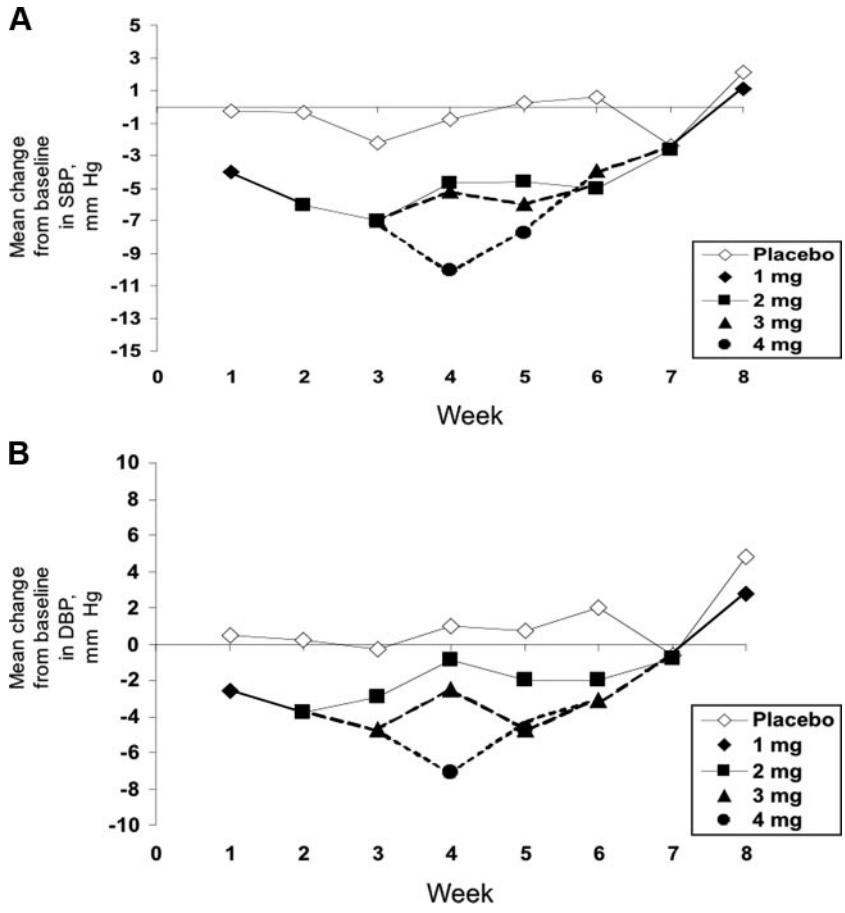

FIGURE 7
A, Mean change from baseline in SBP according to actual GXR dose. B, Mean change from baseline in DBP according to actual GXR dose.

In patients who received GXR, systolic BP (SBP), diastolic BP (DBP), and pulse rate decreased as their actual dosages increased, then increased as dosages stabilized and tapered down (weeks 5–8). The greatest mean changes from baseline in SBP and DBP for patients who were receiving GXR 2-mg, 3-mg, and 4-mg actual doses were −7.0 mm Hg (week 3) and −3.8 mm Hg (week 2), −7.0 mm Hg (week 3) and −4.7 mm Hg (weeks 3 and 5), and −10.1 mm Hg (week 4) and −7.1 mm Hg (week 4), respectively (Fig 7). The greatest mean changes from baseline in pulse rate for patients who were receiving GXR 2-mg, 3-mg, and 4-mg actual doses were −5.7 beats per minute (bpm) (week 3), −8.1 bpm (week 3), and −8.0 bpm (week 4), respectively.

Mean changes in PR and QRS intervals from baseline were unremarkable for patients who received GXR compared with those who received placebo. Because this drug alters heart rate, Fridericia's correction was deemed more reliable than Bazett's correction.[30] ECG measurements were taken at week 3 and thus included patient results for the 1-, 2-, and 3-mg groups but not the 4-mg group. Mean changes in QTcF intervals from baseline to week 3 for patients who were receiving placebo and GXR 2-mg and 3-mg actual doses were 3.7, 6.1, and 9.1 milliseconds, respectively. No patient had a QRS interval ≥120 milliseconds, QT interval ≥480 milliseconds, QTcF interval ≥500 milliseconds, or QTcF increase from baseline ≥60 milliseconds at any time during the study. No ECG abnormality was reported as a serious AE. Seven patients discontinued the study because of ECG abnormalities: 4 because of QTc interval prolongation (1 in each treatment group; none was considered to be clinically significant), 1 because of a QTc of >440 milliseconds at screening (placebo group), 1 because of sinus bradycardia (3-mg group), and 1 because of a pretreatment "left anterior hemiblock" (4-mg group). None of these findings was considered clinically meaningful.

Mean changes in height and weight from baseline to end point were unremarkable in all treatment groups. There was no evidence of any pattern or trend of excessive suppression or elevation of cortisol or human growth hormone in patients who were treated with GXR versus those who were treated with placebo, either in group mean changes or in individual values.

DISCUSSION

GXR given at dosages of 2, 3, and 4 mg/day was found to be effective compared with placebo, having met the primary and secondary efficacy end points of statistically significant improvement in ADHD-RS-IV total scores and hyperactivity/impulsivity and inattentiveness subscale and in CPRS-R, CTRS-R, CGI-I, and PGA scores in children with ADHD (6–17 years) with improvements observed in both symptoms of hyperactivity and inattention. A dosage response was suggested by analysis of ADHD-RS-IV total scores by randomized dosage and

most strongly supported by actual dosage adjusted for patients' body weight. Posthoc analyses showed that lighter patients who received higher weight-adjusted dosages of GXR had the most improvement in ADHD-RS-IV total scores. In additional analyses of CPRS-R and CTRS-R scores by time of the day to examine the duration of effect of GXR, significant improvement was demonstrated for all GXR groups at 8 and 12 hours after the morning dose, respectively, and for the 2-mg and 4-mg groups through the 24-hour time point.

Although this study was not adequately powered to detect significant differences among age subgroups, a secondary age subgroup analysis for ADHD-RS-IV total scores showed greater efficacy of GXR for 6- to 12-year-old patients compared with 13- to 17-year-old patients. The lack of significant change from baseline to end point in any GXR group for patients aged 9 to 12 and 13 to 17 years, compared with placebo, may have been attributable to the small size of the subgroup (lack of power) and higher placebo response. In addition, because 13- to 17-year-old patients weigh more, a higher dosage may be required for optimal efficacy, and the dosage administered to this group may have been too low. Additional study is needed to evaluate adequately the safety and efficacy of GXR in adolescent patients.

The lack of significance in patients with the inattentive subtype of ADHD may have been attributable to the small size of this group. In addition, patients with the inattentive subtype had lower baseline scores on the ADHD-RS-IV (84 patients with a mean of 29.54), compared with the combined subtype (235 patients with a mean of 40.23), which may not have provided a sufficient evaluation range considering the elevated placebo response that was observed in this group. The sample size was powered to test the entire ITT population rather than subgroups; therefore, conclusions that may be drawn for GXR regarding diagnostic subtypes in this study are limited.

In this study, improvements in ADHD-RS-IV total scores with GXR treatment by randomized dosage were consistent with those reported for other emerging nonstimulant medications for ADHD, such as atomoxetine and modafinil.[31–35] The treatment effect sizes in the GXR groups were 0.58, 1.19, and 1.34, for the 0.05 to 0.08 mg/kg, 0.09 to 0.12 mg/kg, and 0.13 to 0.17 mg/kg groups, respectively. In placebo-controlled trials, atomoxetine treatment (~1.0 to 2.0 mg/kg per day) in children and adolescents with ADHD has been associated with treatment effects sizes of 0.6 to 0.8.[31–34] A similar treatment effect size of 0.69 was reported with modafinil treatment in a recent placebo-controlled trial in children and adolescents with ADHD.[35] Furthermore, a posthoc responder analysis showed that patients who were treated with any dosage of GXR were more likely than patients who were treated with placebo to achieve a 30% improvement in ADHD-RS score or CGI-I score of 1 or 2 for any given week. At end point, >50% of patients met these criteria for any active dosage of GXR. These findings are comparable with those reported for atomoxetine with 5 weeks of treatment.[36]

Although GXR was relatively well tolerated at all dosages in this study (1–4 mg), sedation-related AEs were prominent. Most sedative events generally emerged within the first 2 weeks of dosing, resolved within 2 to 3 weeks, and did not result in discontinuation of the study drug. Previous studies of guanfacine immediate release also found that sedative and hypotensive effects tend to occur early in treatment and are transient in children and adolescents with ADHD.[16,27,28] In this study, analyses of safety results by actual dosage and weight-adjusted actual dosage of GXR showed that the incidence of somnolence seems to be dosage related, increasing with higher weight-adjusted dosages of GXR. Because patients in this study were randomly assigned to treatment groups without regard to body weight, some lighter patients may have received higher weight-adjusted dosages of GXR that may have contributed to the higher incidence of sedation among these patients.

GXR was not associated with any clinically relevant trends in clinical chemistry or physical examination results. For most patients, the clinical impact on BP and pulse was minor. The maximum mean changes in BP from baseline occurred at week 4 for the 4-mg group (SBP: −10.1 mm Hg; DBP: −7.1 mm Hg), and the maximum mean change from baseline in pulse was −8 bpm, which occurred at week 3 for the 3-mg group and at week 4 for the 4-mg group. Furthermore, no ECG abnormality was reported as a serious AE. Changes in mean QTcF from baseline in GXR-treated patients ranged from −3.3 to 9.1 milliseconds. No patient had a QRS interval ≥120 milliseconds, QT interval ≥480 milliseconds, QTcF interval ≥500 milliseconds, or QTcF increase from baseline ≥60 milliseconds at any ECG assessment.

These results should be viewed in light of some limitations. A fixed-dosage escalation design was used in this study to ensure that an adequate number of patients were included in each dosing group for efficacy and safety assessments; however, this design may have pushed younger or lighter patients to receive higher dosages than they might receive in clinical practice. A less aggressive dosage escalation of GXR may have resulted in fewer AEs, particularly in the 4-mg group.

Despite these considerations, GXR given at doses of 2, 3, and 4 mg/day was found to be effective, compared with placebo, as assessed by total ADHD-RS-IV, CPRS-R, CTRS-R, CGI-I, and PGA scores, and was generally well tolerated in children with ADHD, aged 6 to 17 years. Long-term follow-up and confirmatory trials are needed to evaluate more fully the effectiveness and safety of GXR in children and adolescents with ADHD, including the use of GXR in patients with other behavioral comorbidities and in combination with stimulant therapies.

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