Guanfacine Extended Release in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder: A Placebo-Controlled Trial

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ABSTRACT

Objective: This study compared the efficacy of guanfacine extended release (GXR), a selective α_{2A}-adrenoceptor agonist, with placebo in children and adolescents with attention-deficit/hyperactivity disorder (ADHD). **Method:** This double-blind, 9-week, dose-ranging, parallel-design, multicenter trial randomized 6- to 17-year-olds with ADHD to once-daily oral GXR in 1-, 2-, 3-, and 4-mg doses or placebo. Primary outcome was change in total ADHD Rating Scale–IV score from baseline to endpoint. Secondary outcomes included changes in scores of hyperactive/impulsive and inattentive subscales; clinician and parent ratings; duration of clinical effect; and safety measures. **Results:** Statistically significant reductions in ADHD Rating Scale-IV scores were observed from baseline to endpoint at all doses of GXR, with effect sizes ranging from 0.43 to 0.62. In subjects receiving GXR, mean heart rate and systolic and diastolic blood pressure decreased as the dose of GXR increased and then returned toward baseline during the dose-maintenance and dose-tapering phases of the trial. Most frequent treatment-emergent adverse events (≥5%) were somnolence, headache, fatigue, sedation, dizziness, irritability, upper abdominal pain, and nausea. Somnolence, sedation, and fatigue adverse events emerged within the first 2 weeks of dosing and generally resolved by study end. **Conclusions:** Guanfacine extended-release was effective in reducing symptoms of ADHD. Adverse events were mild to moderate, did not interfere with improvements in attention, and rarely led to discontinuation. *J. Am. Acad. Child Adolesc. Psychiatry,* 2009;48(2):155–165. **Key Words:** α_2-adrenoceptor agonist, attention-deficit/hyperactivity disorder, ADHD, guanfacine, nonstimulant. Clinical trial registration information—Safety and Efficacy of SPD503 in Treating ADHD in Children and Adolescents Aged 6–17. URL: *http://clinicaltrials.gov*. Unique identifier: NCT00150618.

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Attention-deficit/hyperactivity disorder (ADHD) affects up to 10% of children in the United States.[1] Its precise etiology remains unknown, although it is clear that most effective therapies for the disease facilitate catecholamine neurotransmission.[2,3] Although stimulants remain the mainstay of ADHD therapy, many patients do not respond to or cannot tolerate treatment with psychostimulants.[4,5] This state of affairs calls for the development of alternative effective and safe nonstimulant ADHD therapies.

The α_2-adrenoceptor agonists clonidine and guanfacine have been used off label as alternative therapies for ADHD. Clonidine's short duration of action, marked sedation, and hypotension have historically limited

its use.[6] Guanfacine has emerged as a selective α_2-adrenoceptor agonist that acts preferentially on postsynaptic α_{2A}-adrenoceptors, which are believed to play a role in attentional and organizational functions in the prefrontal cortex.[7,8] Wang et al.,[9] Li et al.,[10] and Arnsten[11] have suggested that α_{2A} stimulation increases delay-related firing of prefrontal cortex neurons, a cellular measure of underlying working memory and behavioral inhibition. In nonhuman primates, guanfacine has been shown to specifically improve delay-related firing,[3] perhaps explaining improvement in some ADHD symptoms found in open-label studies[12–14] and small controlled trials.[4,15]

Immediate-release guanfacine has a short duration of action, therefore requiring multiple daily doses for ADHD treatment.[4,15,16] The absorption characteristics of immediate-release guanfacine are not ideal because peak plasma concentration is achieved rapidly and declines precipitously with considerable interindividual variation.[17,18] These characteristics have prompted development of a new formulation, guanfacine extended release (GXR), to achieve a broader and flatter plasma concentration profile so that therapeutic concentrations can be sustained over longer periods with reduced peak-to-trough fluctuation.[19]

This is the second of two similarly designed short-term pivotal phase III studies of GXR as monotherapy in children and adolescents with ADHD.[20] A distinguishing feature of the present study relative to the first phase III study was the inclusion of a weight-restricted 1-mg dose group so that once-daily oral doses of GXR 1, 2, 3, and 4 mg could be compared with placebo in 6- to 17-year-olds diagnosed with ADHD.

METHOD

Study Design

This study was conducted at 51 sites in the United States from March to October 2004. It was conducted in accordance with the Declaration of Helsinki (2000). Each subject's legal guardian provided written informed consent, and each patient provided assent, with procedures approved by each participating institution's institutional review board.

The study was divided into screening, washout, double-blind treatment, and follow-up periods during 16 weeks (Fig. 1). The double-blind period lasted 9 weeks: dose escalation (3 weeks), a stable dose evaluation period (3 weeks), then dose tapering (3 weeks).

Male and female subjects ages 6 to 17 years with a *DSM-IV-TR* diagnosis of ADHD and a minimum baseline score of 24 on the ADHD Rating Scale-IV (ADHD-RS-IV)[21] were enrolled. At screening, investigators conducted a psychiatric evaluation with the *DSM-IV-TR* criteria for ADHD and the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime diagnostic interview[22] and performed a complete medical history and physical examination. Subjects were excluded for any current severe Axis I or Axis II disorders or any other current uncontrolled comorbid psychiatric diagnosis (excluding oppositional defiant disorder), weight of less than 55 lb (25 kg), morbid obesity (body mass index ≥35), current use of medications that affect blood pressure (BP) or heart rate (except for ADHD therapies, which were discontinued during the washout period), hypertension or orthostatic hypotension, abnormal electrocardiogram or vital signs, previous treatment of ADHD with GXR, or intolerance of guanfacine.

After screening, eligible patients underwent a washout period during which all ADHD and other psychoactive medications were discontinued for 1 week or at least 5 times the half-life of the medication before the subject began the treatment period. The subjects were randomized to placebo or GXR 1, 2, 3, or 4 mg/day at the end of the baseline visit (visit 0). Randomization was stratified by baseline weight: less than 75 lb, 75 lb or greater to but less than 110 lb, and 110 lb or greater. The GXR 1-mg group was limited to subjects weighing less than 110 lb (<50 kg). Each patient was given preprepared weekly drug kits containing four tablet bottles, each representing one of four GXR doses or matching placebo. Because the true identity of each pill depended on the randomization regimen and remained unknown to clinicians and the subjects, the subjects were required to take one tablet from each bottle daily in the morning. At the end-of-study visit, eligible subjects had the option to enroll in a 25-month open-label extension study. Those who enrolled completed end-of-study assessments for the present study, which doubled as the baseline visit for the extension study. Subjects who did not enroll in the open-label extension study were required to return to the clinic for a final follow-up visit (visit 10) 2 to 4 days immediately after drug discontinuation for collection of BP and body weight measurements and to assess adverse events (AEs) and concomitant medication use. Overall, the subjects were followed for 30 (±2) days after their last dose of study drug. A telephone contact (visit 11) was initiated by the research site to collect any new serious AEs (SAEs), and to follow up on any unresolved AEs.

Assessment Measures

The primary outcome was change in ADHD-RS-IV total score from baseline to endpoint. *Endpoint* was defined as the last post-randomization treatment week of the double-blind treatment period for which a valid ADHD-RS-IV score was obtained. The ADHD-RS-IV was administered to parents or caregivers by clinicians with scoring based on 18 items of behavior symptoms grouped into subscales of hyperactivity/impulsivity and inattentiveness, each with a value of 0 (no symptoms) to 3 (severe symptoms); the total score ranged from 0 to 54.[21] The ADHD-RS-IV Hyperactivity/Impulsivity and Inattentiveness subscale scores were also examined.

Secondary outcomes were as follows:

1. The Conners' Parent Rating Scale-Revised: Short Form (CPRS-R), completed by the subjects' parents/caregivers before dosing at approximately 6 A.M. and after dosing at approximately 10 A.M., 2 P.M., 6 P.M., and 8 P.M., on the last washout day and the days preceding visits 4 to 6
2. The Clinical Global Impressions-Improvement (CGI-I) administered by the clinicians at visits 1 to 6
3. The Parent Global Assessment (PGA) collected at baseline and visits 4 through 6

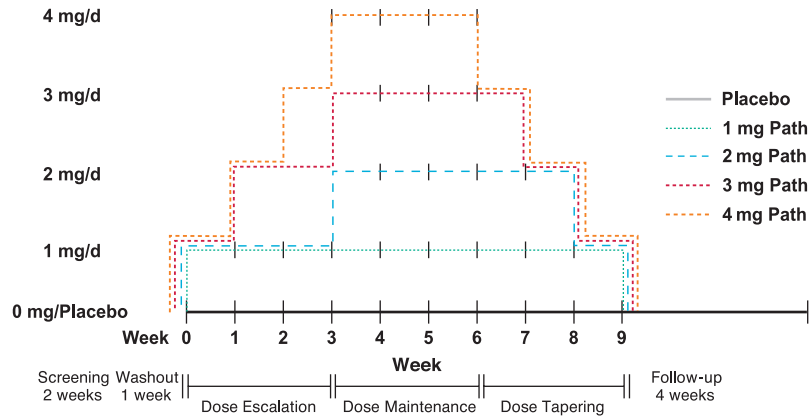

Fig. 1 Study design: subjects were randomized to receive guanfacine extended release started at the dosage of 1 mg/day, and the dosage was escalated to match the subject's randomized dose during a 3-week period. At the end of week 3 (day 22), all of the subjects started receiving the appropriate randomized dose, then continued at that dose through the maintenance period (weeks 4–6) until the start of week 7, when dosages were tapered downward by 1 mg/day weekly through week 9.

The CPRS-R scale contains 27 questions relating to the child's behavior. The respondents were asked to base their ratings on behaviors immediately preceding the assessment time, such that the 6 P.M. assessment reflected behavior during the after-school period and the 8 P.M. assessment reflected behavior from dinnertime through bedtime. The 6 A.M. assessment was used to determine whether the effects of GXR extended for the 24 hours until the next dose was given.

The CGI-S assesses the severity of a subject's condition, whereas the CGI-I assesses clinical change. At screening and baseline, the investigator rated the severity of the subject's ADHD symptoms on a 7-point scale ranging from 1 (no symptoms) to 7 (very severe symptoms). At visits 1 to 6, the investigator assessed the subject's change in clinical status relative to the symptoms at baseline using the CGI-I scale, a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). The PGA is an analog of the CGI-S and CGI-I designed to capture the parent's/caregiver's opinions of their child's disease severity and improvement from baseline.

Analyses by randomized dose group, actual dose group, weight-adjusted actual dose group, and age group were performed; however, the study was only powered to test hypotheses based on the entire age group rather than age subgroups. *Actual dose* refers to the dose of medication a subject was taking at the time of the assessment. A subject's weight-adjusted actual dose at any time was the actual dose (in milligrams) divided by the subject's baseline weight (in kilograms) or screening weight (if baseline unavailable) and is grouped in ranges: placebo and GXR—0.01 to 0.04, 0.05 to 0.08, 0.09 to 0.12, and 0.13 to 0.16 mg/kg.

Safety profile assessments at every visit included vital signs (BP, pulse, breathing rate, and body weight). Orthostatic BP was measured at screening and visits 4 and 6; and temperature at screening and visit 9. Clinical laboratory tests consisted of complete blood count with differential, chemistry, and urinalysis. They were administered at screening (and repeated at baseline if screening had not occurred within the previous 3 weeks) and at the completion of the double-blind period (visit 9). Twelve-lead ECGs were administered at screening, baseline (a minimum of three ECGs were performed at the beginning, middle, and end of baseline visit to ensure appropriate baseline values), visits 3 and 6, and end of study. The ECG findings included QT interval, QT interval for heart rate according to Bazett factor and Fridericia factor (QT_cB), the latter preferred in pediatric evaluations.[23] Additional safety assessments included Pediatric Daytime Sleepiness Scale[24] at screening, baseline, and through the end of study. Assessments of AEs using the Medical Dictionary for Regulatory Activities, version 5.1 (MedDRA: Maintenance and Support Service Organization, Reston, VA) and collection of data on use of concomitant medication were done at each visit. An AE was defined as treatment emergent if it started or worsened during the period between a subject's randomization and the third day (inclusive) after treatment was stopped. AEs with missing start dates were assumed to be treatment emergent unless the stop date occurred before the first dose date.

Data Analysis

Randomizing 60 subjects to each group was determined necessary to allow detection of an effect size of 0.60 between a single active group and the placebo group at 90% power and a significance level of .05 (two-sided) using a two-sample *t* test.

Analysis of the primary efficacy outcome was performed on the intent-to-treat population, defined as all subjects who are randomized to treatment and have a baseline and at least 1 postrandomization primary efficacy measurement recorded during dose escalation or dose maintenance.

For continuous efficacy parameters, hypothesis testing was performed using analysis of covariance (ANCOVA). The results from any modeling were presented in terms of least squares (LS) means for all treatment groups, the difference in LS means between active groups and placebo, two-sided 95% confidence intervals for the difference between active groups and placebo, and *p* values for the differences between active groups and placebo. The primary analysis was performed using endpoint values (last on-treatment value before dose tapering captured for each patient), which is analogous to the last observation carried forward method. Analyses of covariance were also performed for observed data at each visit, and the assumptions of all models were checked and verified. The ANCOVA model included treatment group (the effect of interest) and the corresponding baseline score (i.e., the covariate). Site was not included as a factor in the ANCOVA models because the randomization was not stratified by site. The interpretation of results from the ANCOVA modeling was based on type III sums of squares.

The null hypothesis stated that there were no differences among the five groups of the subjects who received different dosages (GXR

1, 2, 3, and 4 mg/day), including placebo, with the alternative of nonzero differences among them. For the ANCOVA, the type I error for rejecting a null hypothesis was set at .05. Effect sizes were calculated by dividing the changes in LS mean scores by the square root of the mean square error, as determined by the ANCOVA model.

Using the ANCOVA model, ADHD-RS-IV (total, subscale, subgroup) and CPRS-R data were evaluated using a hierarchical testing procedure. Starting with the dosage of 4 mg/day, if the difference, compared with placebo, was significant, the analysis continued with a test of significance at the next lowest dose; if not significant, no further comparisons were considered significant. Furthermore, for the CPRS-R data, the duration of effect for each active dose group was determined as the time point after the 2 P.M. dose at which the last significant result was observed. Furthermore, the duration of effect for a lower active dose group could not exceed that observed for a higher active dose group.

The CGI-I and PGA results were evaluated by means of the nonparametric Cochran-Mantel-Haenszel test performed separately for placebo and each GXR dose. The seven scores were dichotomized into "clinical improvement" ("very much improved" or "much improved") and "no improvement" (remaining categories).

RESULTS

Subject Demographics and Disposition

The safety population, which included all of the subjects who received at least 1 dose of study drug, included 241 subjects ages 6 to 12 years (75%), 80 subjects ages 13 to 17 years (25%), and 1 subject who was enrolled 3 days before his sixth birthday. The mean age was 11 (SD 3) years. There were 233 male subjects (72%) and 89 female subjects (28%). The ethnic origin of the safety population was 67% white (n = 214), 17% black (n = 56), 9% Hispanic (n = 28), 2.8% Asian or Pacific Islander (n = 9), 0.3% Native American (n = 1), and 4.3% other (n = 14). The mean weight was 44 (SD 16) kg and ranged from 25 to 108 kg. The GXR 1-mg/day treatment group, however, was limited to the subjects weighing less than 50 kg (110 lb). The numbers of subjects in the safety population grouped by ADHD subtype were 82 (26%) for inattentive, 6 (2%) for hyperactive/impulsive, and 234 (73%) for combined. A total of 18 subjects (5.6%) in the safety population had comorbid oppositional defiant disorder. The mean baseline ADHD-RS-IV score for the intent-to-treat population was 40.1 (SD 8.65).

Of the 329 enrolled subjects, 324 were randomized to treatment, with early terminations and dispositions by treatment group listed in Figure 2. Reasons for early termination were similar between the placebo and treated groups.

Efficacy: ADHD-RS-IV

There were no notable differences in baseline scores for ADHD-RS-IV, the primary outcome, across all groups. All GXR dose groups showed statistically and clinically significant decreases in ADHD-RS-IV total score from baseline to endpoint, which was defined as

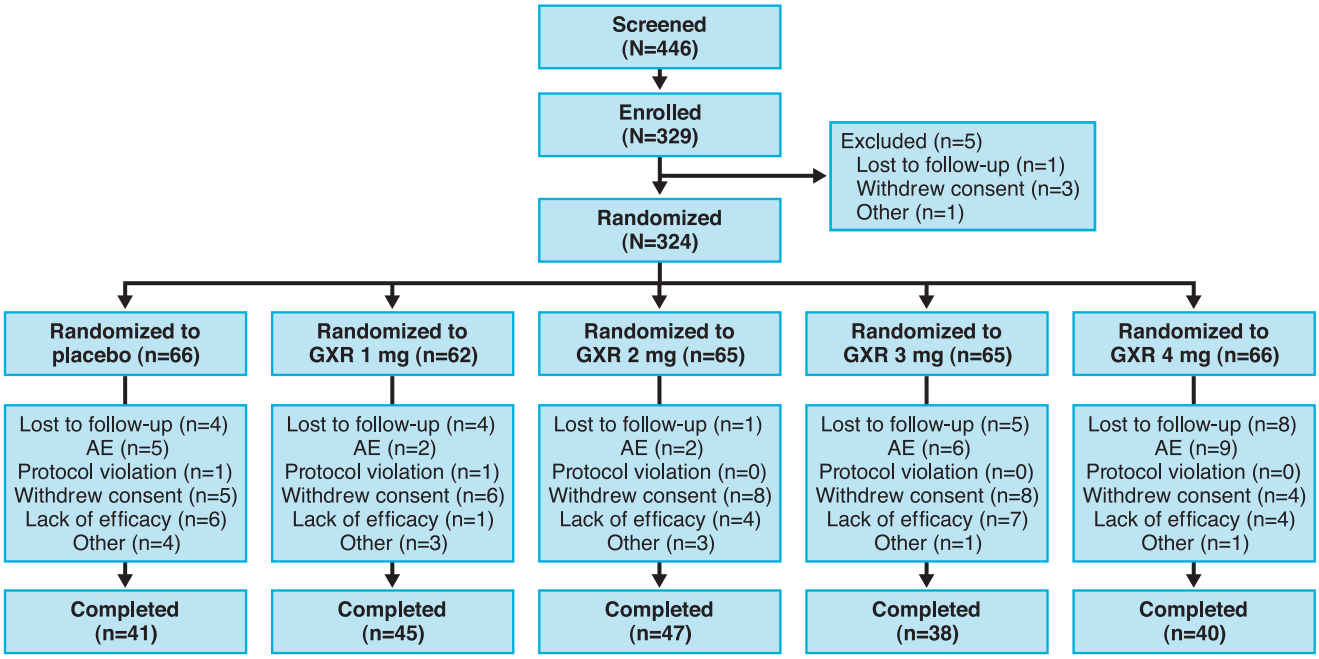

Fig. 2 Subject disposition.

the last postrandomization treatment week of the dose-escalation or dose-maintenance phase for which a valid ADHD-RS-IV score was obtained. The placebo-adjusted LS mean (SD) endpoint changes from baseline in the GXR 1-, 2-, 3-, and 4-mg/day randomized dosage groups were −6.75 (p = .0041), −5.41 (p = .0176), −7.34 (p = .0016), and −7.88 (p = .0006), respectively. The mean reduction in ADHD-RS-IV total scores from baseline to endpoint across all GXR randomized dosage groups was −19.6 (SD 13.9) compared with −12.2 (SD 13.0) for placebo. There were consistent statistically significant changes in LS means from baseline to endpoint for GXR at all randomized dose levels compared with placebo (Fig. 3A). For the entire sample examined by weight-adjusted actual dose, a dose-response effect was suggested by the placebo-adjusted LS mean endpoint improvements from baseline for each GXR dose range (Fig. 3B). The differences between LS mean ADHD-RS-IV score for GXR randomized doses compared with placebo were significant at most follow-up visits and endpoint (Fig. 4). At visit 1 and at all time points thereafter, the mean ADHD-RS-IV total score decreased, indicating improvement in symptoms with prompt onset of effect for all randomized dose groups compared with the placebo group.

When examined by age group, younger subjects (ages 6–12 years, mean weight 84.6 lb) who received GXR demonstrated significant improvement from baseline to endpoint when compared with placebo for all GXR randomized dose groups. The placebo-adjusted LS mean endpoint changes from baseline for the GXR 1-, 2-, 3-, and 4-mg/day randomized dosage groups were –9.08 (p = .0007), –5.44 (p = .45), –10.29 (p = .0003), and –10.77 (p < .0001), respectively. In contrast, for older subjects (ages 13–17 years, mean weight 130.1 lb, n = 80), there was no significant improvement from

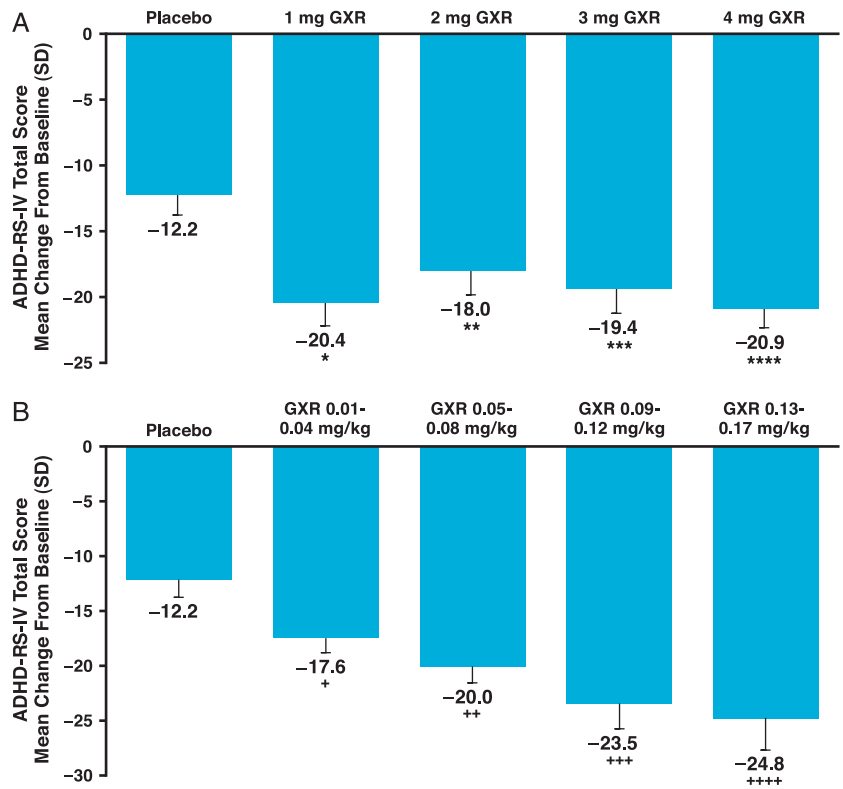

Fig. 3 The ADHD Rating Scale-IV total score mean changes from baseline by randomized dose (A) and weight-adjusted actual dose (B; intent-to-treat population; N = 306). Endpoint obtained from last postrandomization treatment week of dose-escalation and dose-maintenance phases for which a valid ADHD-Rating Scale-IV score was obtained. For subjects not dispensed a dose at a visit, assessment is presented under last reported dose. p values are pairwise comparisons of placebo-adjusted least squares mean changes from baseline to endpoint between the dose groups and placebo based on analysis of variance model for baseline value with treatment as a fixed effect. (A) Placebo (n = 63), guanfacine extended release (GXR) 1 mg/day (weight-restricted group) (n = 57), 2 mg/day (n = 63), 3 mg/day (n = 60), and 4 mg/day (n = 63). $^{*}p$ = .004; $^{**}p$ = .018; $^{***}p$ = .0016; $^{****}p$ = .0006. (B) Placebo (n = 63), GXR 0.01 to 0.04 mg/kg (n = 112), 0.05 to 0.08 mg/kg (n = 84), 0.09 to 0.12 mg/kg (n = 33), 0.13 to 0.16 mg/kg (n = 14). ^{+}p = .01; ^{++}p = .0004; ^{+++}p = .001; ^{++++}p = .003.

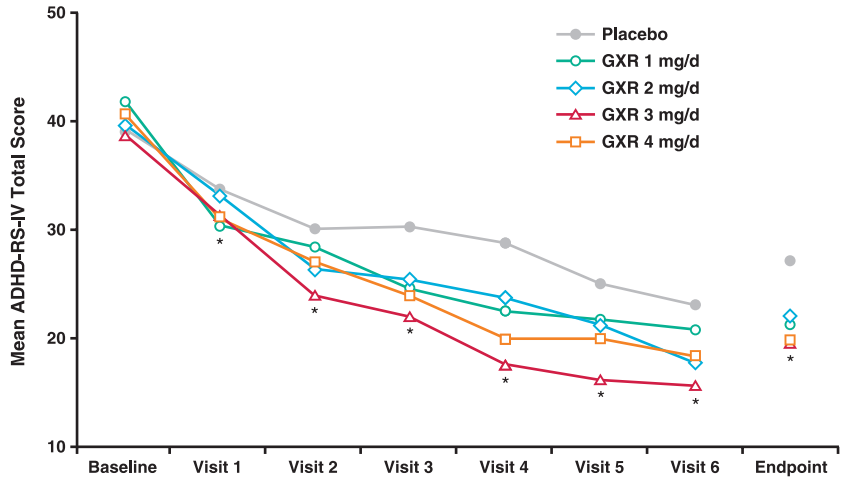

Fig. 4 Mean ADHD Rating Scale-IV total score by randomized dose and visit (intent-to-treat population; $N = 306$). Endpoint obtained from the last week of dose-escalation or dose-maintenance phases for which a valid ADHD Rating Scale-IV score was obtained. Placebo ($n = 63$), guanfacine extended release (GXR) 1 mg ($n = 57$), 2 mg ($n = 63$), 3 mg ($n = 60$), and 4 mg ($n = 63$). *$p < .05$ versus placebo for visit 1 (1 and 4 mg/day), visit 2 (2, 3, and 4 mg/day), visit 3 (all doses), visit 4 (all doses), visit 5 (3 and 4 mg/day), visit 6 (2, 3, and 4 mg/day), and endpoint (all doses). During the dose-escalation phase of the study (visits 1–3), the subjects were not necessarily receiving their randomized dose. All of the subjects were receiving their randomized doses starting at week 4.

baseline to endpoint in any GXR randomized treatment group when compared with placebo. The placebo-adjusted LS mean endpoint changes from baseline in the GXR 1-, 2-, 3-, and 4-mg/day randomized dosage groups were 1.06 ($p = .8$), –5.43 ($p = .2$), –0.24 ($p = .95$), and 0.26 ($p = .95$), respectively.

Post hoc analysis of the ADHD-RS-IV treatment effect size by randomized dosage was 0.53 for the 1-mg/day (weight-restricted) group, 0.43 for the 2-mg/day group, 0.58 for the 3-mg/day group, and 0.62 for the 4-mg/day group. For weight-adjusted actual dose (milligrams/kilogram), the effect size was 0.41 for the 0.01- to 0.04-mg/kg group, 0.60 for the 0.05- to 0.08-mg/kg group, 0.71 for the 0.09- to 0.12-mg/kg group, and 0.89 for the 0.13- to 0.16-mg/kg group.

Reductions in ADHD-RS-IV Inattentiveness and Hyperactivity/Impulsivity subscale scores were also significant at all GXR randomized doses compared with placebo. Placebo-adjusted mean baseline-to-endpoint changes for symptoms of inattentiveness were significant: –4.2 for 1 mg/day (weight-restricted group, $p = .002$), –3.0 for 2 mg/day ($p = .02$), –3.5 for 3 mg/day ($p = .007$), and –4.0 for 4 mg/day ($p = .002$). Similarly, hyperactivity/impulsivity symptoms improved for all of the subjects at each GXR randomized dosage; placebo-adjusted mean baseline to endpoint changes were –2.7 for 1 mg/day ($p = .028$), –2.5 for 2 mg/day ($p = .03$), –3.9 for 3 mg/day ($p = .001$), and –4.0 for 4 mg/day ($p = .0008$).

Efficacy: Secondary Outcomes

The parent/caregiver completed the CPRS-R five times each day on the last day of the washout period and the days immediately preceding visits 4 through 6. Using placebo-adjusted LS mean differences in change from baseline at endpoint in CPRS-R total scores, the 4-mg/day GXR dose demonstrated significant efficacy at 8 hours (−10.2; $p = .004$) and 12 hours (−7.5; $p = .04$) postdose but not at 14 hours (−6.1; $p = .1206$). Although the 3-mg/day GXR dosage group demonstrated significant improvements in CPRS-R results at 8 (−11.8; $p = .002$), 12 (−9.6; $p = .01$), and 14 hours (−9.8; $p = .0156$) postdose, given the hierarchical testing procedure previously described, the 3-mg GXR dose was considered to have a duration of 12 hours. The 2-mg/day GXR dosage group demonstrated significant efficacy as measured by improvements in CPRS-R scores at 8 hours (−9.0; $p = .01$) postdose but not at 12 hours (−5.5; $p = .13$). For the weight-restricted GXR 1-mg/day group, the placebo-adjusted LS mean differences in CPRS-R at 8, 12, 14, and 24 hours were −12.8 ($p = .0004$), −11.4 ($p = .002$), −10.4 ($p = .0077$), and −8.9 ($p = .02$), respectively. Given the hierarchical testing method used, the duration of the 1-mg/day GXR dosage could not exceed the duration of the 2-mg/day GXR dosage and was therefore assessed to be 8 hours. It should be noted, however, that all comparisons for the 1-mg/day dosage could be significant because a weight restriction was used in assigning subjects to receive that dose.

Based on CGI-I scores completed by the investigators at visits 1 through 6, percentages of the subjects showing clinical improvement were 30% (placebo), 54% (GXR 1 mg/day, weight-restricted group), 43% (GXR 2 mg/day), 55% (GXR 3 mg/day), and 56% (GXR 4 mg/day). Placebo-GXR differences were significant for GXR 1 (p = .007), 3 (p = .006), and 4 mg/day (p = .004), but not for 2 mg/day (not significant; p = .1404). Improvements in PGA scores were 30% (placebo), 51% (GXR 1 mg/day), 36% (GXR 2 mg/day), 62% (GXR 3 mg/day), and 57% (GXR 4 mg/day). The PGA differences were significant for GXR 1 (p = .030), 3 (p = .002), and 4 mg/day (p = .0063), but not for 2 mg/day (not significant, p = .4982).

Safety Profile: AEs

The overall frequency of treatment-emergent AEs (TEAEs) with GXR (74%) was similar to that with placebo (76%; Table 1). The rate of all severe TEAEs was similar between the placebo group (4.5%; 3 of 66 subjects) and all the active randomized groups (3.9%; 10 of 256 subjects), and was low overall. Mild to moderate TEAEs occurring in 5% or greater in the subjects taking GXR were somnolence, headache, fatigue, sedation, dizziness, irritability, upper abdominal pain, and nausea. The discontinuation rate for any given TEAE was similar for placebo (7.6%) and all GXR groups (7.4%). Few TEAEs occurred in 5% or greater of the subjects by weight-adjusted actual dose. The most common reason for discontinuation (the ''other'' category) included inability to swallow pills and nonadherence (Fig. 2).

TABLE 1
Treatment-Emergent Adverse Events in 5% or Greater of All of the Subjects (Safety Population)

Characteristic	Placebo (n = 66), n (%)	All Active Randomized GXR Doses (n = 256), n (%)
Total subjects[a] (%)	50 (76)	189 (74)
Somnolence	8 (12)	69 (27)
Headache	7 (11)	53 (21)
Fatigue	2 (3)	24 (9)
Upper abdominal pain	6 (9)	16 (6)
Dizziness	4 (6)	15 (6)
Sedation	3 (5)	15 (6)
Irritability	3 (5)	14 (6)
Nausea	1 (2)	13 (5)
Vomiting	4 (6)	7 (3)
Nasopharyngitis	4 (6)	5 (2)

[a] Subjects may have experienced more than one treatment-emergent adverse event. GXR = guanfacine extended release.

Somnolence, sedation, and fatigue (SSF; Table 1) were reported within 2 weeks of dosing initiation and typically resolved by study end. More subjects receiving the highest weight-adjusted GXR dose (0.13–0.16 mg/kg) experienced fatigue but not somnolence or sedation, compared with placebo. The rate of fatigue in subjects receiving 0.13 to 0.16 mg/kg of GXR was 6.3% (3.0% for placebo), the rate of somnolence was 6.3% (12.1% for placebo), and the rate of sedation was 0% (4.5% for placebo). Somnolence and fatigue were the most common TEAEs leading to discontinuation (n = 8 and n = 5, respectively), although the likelihood of early discontinuation for SSF was low in the study population (5.9% for all, 3.1% for somnolence, 0.8% for sedation, and 2.0% for fatigue). Pediatric Daytime Sleepiness Scale measurements showed no significant differences in reported sleepiness between the subjects taking placebo and the GXR groups (dosage versus placebo: p = .05 [1 mg/day]; p = .66 [2 mg/day]; p = .17 [3 mg/day]; p = .24 [4 mg/day]).

Safety Profile: Laboratory Results, Vital Signs, Pulse Rate, ECG Findings, and Height and Weight

No clinically meaningful changes in laboratory assessments were observed for any of the study subjects. Guanfacine extended release was not associated with abnormal changes in height or weight. Vital signs are reported based on actual GXR doses received. In the subjects who received GXR, systolic BP (SBP), diastolic BP (DBP), and pulse rate (PR) decreased as the actual dose increased (weeks 0–3) and then increased (returning toward baseline) during dose maintenance and tapering (weeks 4–9).

At weeks 4–6, all of the subjects reached their full target randomized dose. At these time points, the range of mean changes from baseline for seated SBP for the placebo group was −1.30 to −0.48 mmHg and −7.38 to 0.54 mmHg for the GXR randomized dose groups, with the −7.38 mmHg average change corresponding to the 4-mg/day group and the 0.54 mmHg average change corresponding to the 1-mg/day group. The range of mean changes from baseline at weeks 4 to 6 for seated DBP for the placebo group was −0.69 to

0.79 mmHg and −5.43 to 1.24 mmHg for the GXR randomized dosage groups, with the average change of −5.43 mmHg corresponding to the 4-mg/day group and the average change of 1.24 mmHg corresponding to the 1-mg/day group. In general, SBP and DBP returned to levels above baseline at the end of the dose-tapering period (week 9). At weeks 4 to 6, the range of mean changes from baseline for seated PR was −1.61 to 1.48 beats per minute (bpm) for the placebo group and −9.51 to −1.29 bpm for the GXR randomized dosage groups, with the average change of −9.51 bpm corresponding to the 4-mg/day group and the average change of −1.29 bpm corresponding to the 2-mg/day group. These fluctuations from baseline to endpoint were modest and not considered clinically meaningful.

Outliers were defined using pediatric criteria derived from normal data in the 95th percentiles of the child and adolescent populations—specifying the lower and upper limits of PR and of normal SBP and DBP. In 6- to 12-year-olds at the end of the double-blind treatment phase (week 6), 10% of the placebo subjects had SBP of less than 90 mmHg compared with 24% for all of the GXR doses. None of the placebo subjects had DBP of less than 50 mmHg, whereas 9% of the GXR subjects had DBP of less than 50 mmHg. Three weeks after the double-blind treatment phase ended, outlying BP was similar between the placebo and the GXR-treated subjects.

By the end of the double-blind treatment phase (visit 6), PR of 100 bpm or greater was higher in the placebo group (9%) compared with subjects treated with GXR 2 mg/day (4%), 3 mg/day (5%), and 4 mg/day (7%), but not for the 1-mg/day group (15%). At end of taper (week 9), PR of 100 bpm or greater was 2% with placebo, 5% with GXR 1 mg/day, 0% with 2 mg/day, 14% with 3 mg/day, and 0% with 4 mg/day. Mean PRs at week 6 (pretaper) were 75.0 bpm in the placebo group, and 75.5, 68.1, 68.4, and 64.7 bpm for the GXR 1-, 2-, 3-, and 4-mg/day treatment groups, respectively. None of these findings were considered clinically significant. No abnormality of PR or BP was reported as an SAE.

When all of the subjects were receiving their maximal dose (visit 6), mean change in QTcF interval (milliseconds) from baseline was –0.3 (SD 16.3) for placebo, 4.3 (SD 12.7) for GXR 1 mg/day, 2.4 (SD 12.3) for GXR 2 mg/day, 7.1 (SD 12.8) for GXR 3 mg/day, and 9.7 (SD 15.9) for GXR 4 mg/day. No subject had an outlier of prolonged QRS interval of 120 milliseconds or greater, QT interval of 480 milliseconds or greater, QTcF interval of 500 milliseconds or greater, or QTcF increase from baseline of 60 milliseconds or greater during the study. No ECG abnormality was reported as an SAE or cited as a reason for GXR discontinuation. For all tracings throughout the study, no subject in the placebo group had a heart rate of 50 bpm or less, whereas one subject each in the 1-mg/day (0.5%) and 2-mg/day (1.0%) GXR dosage groups, seven subjects (6.9%) and three subjects (6.7%) who received the 3-mg/day and 4-mg/day GXR dosages experienced a heart rate of 50 bpm or less. The ECG abnormalities considered clinically significant and related or possibly related to GXR were first-degree atrioventricular block (PR interval = 266 milliseconds at visit 6) and symptomatic sinus bradycardia (PR = 64 bpm, dizziness with standing), each occurring in one subject.

There were two subjects who experienced three SAEs: one in the 3-mg/day GXR group experienced a concussion and convulsions (both considered unrelated to study drug); and one in the placebo group experienced a lower limb fracture considered unrelated to study drug.

DISCUSSION

This phase III randomized controlled trial of GXR conducted in children and adolescents with ADHD found that all GXR dosages (1, 2, 3, and 4 mg/day) were significantly more efficacious than placebo on the primary endpoint, change in ADHD-RS-IV score from baseline to endpoint. These results support previously reported data on the efficacy and safety of GXR in pediatric patients with ADHD.[20] Guanfacine extended release was effective in reducing both inattentive and hyperactive/impulsive symptoms of ADHD as reflected by reductions in ADHD-RS-IV subscale scores. These data are also consistent with previous studies of GXR and suggest that symptom improvement was not due to sedative or hypotensive effects of guanfacine as once postulated[4] but instead stemmed from attentional enhancement as a selective α_{2A}-adrenoceptor agonist.

The improvements in mean ADHD-RS-IV score in the subjects receiving GXR were similar to other nonstimulant medications used to treat ADHD. Studies of atomoxetine have demonstrated an effect size of 0.6 to 0.8 when the medication was dosed at 1 to 2 mg/kg.[25–28] However, it is noteworthy that at

0.13 mg/kg and higher, the effect size for GXR approximates that found for stimulants in similarly designed large-scale clinical trials.[29,30] Moreover, at 0.13 mg/kg and higher, the effect size of GXR exceeds those found for other nonstimulant treatments including bupropion,[31] modafinil,[32] and clonidine, a less selective α_2-adrenoceptor agonist.[33]

Post hoc analyses of data from the present study indicated a dose-response relation, with the most significant improvements in ADHD-RS-IV scores seen at higher milligram per kilogram doses. In addition, subjects given GXR showed improvements in ADHD symptoms compared with patients in the placebo group, as measured by mean total ADHD-RS-IV score, beginning at week 1 when all of the subjects were receiving 1 mg/day GXR as part of the dose-escalation phase.

As observed in the previous study,[20] changes in ADHD-RS-IV mean total score from baseline to endpoint were significant for all GXR doses in the younger age group (6–12 years) but not for the older age group (13–17 years). However, the study was not designed or powered to test for significant differences by age. It is possible that the lack of efficacy in this population, which has a heavier weight, may have been related to a lower weight-corrected dosing distribution. The low number of subjects (i.e., 76 of 306) and the higher placebo response for the older age group may also have contributed to the lack of significant findings. More work is needed to evaluate the safety and efficacy of higher doses of GXR in adolescent patients.

Results of the present study support an 8-hour duration of effect for the 1- and 2-mg/day dosages and a 12-hour duration for the 3- and 4-mg/day dosage groups as measured by parental assessments on the CPRS-R. Although future studies are required to further elucidate the duration of GXR effect, once-daily dosing of GXR seems efficacious throughout the day.

AEs were generally mild to moderate, although GXR was associated with a greater rate of SSF events compared with placebo. The highest frequency of SSF occurred within the first 2 weeks of treatment, and most events resolved by the end of dose escalation. Furthermore, the concurrent improvement of ADHD-RS-IV Inattentive subscale scores suggests that GXR efficacy was maintained regardless of SSF. Examination of AEs by weight-adjusted GXR dose did not consistently support a dose-dependent increased rate of SSF. In general, SSF events resolved by end of study, were mostly mild to moderate in severity, and most did not result in discontinuation of study drug.

In the subjects receiving GXR, heart rate, SBP, and DBP decreased as the dose of GXR increased and then returned to baseline during dose-maintenance and dose-tapering phases. These modest decreases were most apparent in the 6- to 12-year-old group, where a greater proportion of GXR—compared with placebo subjects—had SBP and DBP readings lower than the 95th percentile for age. There were two cases of hypotension that led to study discontinuation and two cases of ECG abnormalities that were clinically significant (first-degree atrioventricular block and sinus bradycardia), but otherwise, there were no other cardiac findings that were characterized as clinically significant. Neither of the ECG abnormalities led to study discontinuation, and no ECG abnormality was reported as an SAE.

Limitations of the present study include a narrow treatment period (9 weeks) and a rigid dose-escalation period that, except for the 1-mg dose group, was performed without consideration of the patient's weight. Data regarding the severity of ADHD symptoms were not collected during the dose-tapering period of the study (the last 3 weeks of the double-blind period), although AEs were assessed throughout the study. The relatively small number of adolescents in the present study limited the evaluation of the efficacy of GXR by age group. Furthermore, teacher ratings were not obtained, preventing the evaluation of the effects of GXR on classroom behavior and comparison of the present study with some studies on the efficacy of stimulants. This study used the 27-item CPRS-R administered five times in a day as a measure of duration of clinical effect and as a secondary measure of efficacy. Although this scale has not been validated to measure symptom change throughout the day, it has been used in such a manner in other studies.[34,35]

The present study used a fixed-dose design, thereby limiting the recommendations that can be made regarding dosing. Available clinical data suggest that GXR treatment in children with ADHD should be initiated at a dosage of 1 mg daily. The dose can be adjusted in increments of 1 mg/week to a maximum of 4 mg daily.

Despite limitations, the present study adds to an increasing clinical database that supports the use of GXR, a selective α_{2A}-adrenergic receptor agonist, in the treatment of children and adolescents with ADHD. The

nonstimulant GXR, given once daily in the present study, improved all core symptoms of ADHD throughout the day, eliminating the need for redosing and/or dosing during school time. These findings warrant additional studies to establish the long-term efficacy and tolerability of GXR in children and adolescents with ADHD.

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