Randomized, Double-Blind Trial of Guanfacine Extended Release in Children With Attention-Deficit/Hyperactivity Disorder: Morning or Evening Administration

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Objective: To examine the efficacy and tolerability of guanfacine extended release (GXR) administered in the morning or evening in children with attention-deficit/hyperactivity disorder (ADHD). **Method:** In this multicenter, double-blind, placebo-controlled, dose-optimization study, children 6 to 12 years of age with ADHD were randomized to receive GXR (1–4 mg/d) in the morning and placebo in the evening (GXR AM), placebo in the morning and GXR in the evening (GXR PM), or twice-daily placebo. The primary efficacy measure was the ADHD Rating Scale–IV (ADHD-RS-IV). **Results:** A total of 333 child participants received study drug in the following cohorts: GXR AM (n = 107), GXR PM (n = 114), or placebo (n = 112). Mean (standard deviation) changes from baseline to week 8 (visit 10 or last observation carried forward) in ADHD-RS-IV total scores were significant for both GXR treatment groups combined (GXR all-active: –20.0 [12.97]) and separately (GXR AM: –19.8 [12.95]; GXR PM: –20.1 [13.04]) compared with placebo (–11.0 [12.93]; $p < .001$ for all). Most spontaneously-elicited treatment-emergent adverse events were mild or moderate in severity; the most common was somnolence (GXR all-active: 44.3%; GXR AM: 46.7%; GXR PM: 42.1%; placebo: 12.5%). **Conclusions:** GXR administered either in the morning or evening was associated with significant and clinically meaningful improvements in ADHD symptoms. The levels of response and tolerability observed with GXR were similar regardless of time of dosing (morning versus evening), indicating that once-daily GXR monotherapy is effective whether administered in the morning or evening. Clinical trial registration information—Tolerability and Efficacy of AM and PM Once Daily Dosing With Extended-release Guanfacine Hydrochloride in Children 6–12 With Attention-Deficit/Hyperactivity Disorder (ADHD) (The ADHD Tempo Study); http://clinicaltrials.gov/; NCT00997984. J. Am. Acad. Child Adolesc. Psychiatry, 2013;52(9):921–930. **Key Words:** attention-deficit/hyperactivity disorder (ADHD), α_{2A}-agonist, guanfacine extended release (GXR), nonstimulant

Attention-deficit/hyperactivity disorder (ADHD), one of the most common neurobehavioral disorders of childhood, affects an estimated 9.5% of children and adolescents aged 4 to 17 years in the United States.[1] ADHD is characterized by a persistent and developmentally inappropriate inattention and/or hyperactivity–impulsivity, associated with a wide range of impairments.[2,3] Although treatment with psychostimulants is considered first-line pharmacotherapy for ADHD,[4] not all patients are responsive to or can tolerate stimulant therapy.[5,6] Decreased appetite and initial insomnia are frequent adverse events (AEs) associated with stimulants.[7] Currently, there are 3 nonstimulants approved for the treatment of ADHD: guanfacine extended release (GXR) and clonidine extended-release, both α_{2A}-adrenoceptor agonists, and atomoxetine, a selective norepinephrine reuptake inhibitor.

Guanfacine extended release (GXR) is approved both as monotherapy and as adjunctive therapy to

CG Clinical guidance is available at the end of this article.

psychostimulants for the treatment of ADHD in children and adolescents aged 6 to 17 years.[8] The efficacy and safety of GXR monotherapy for the treatment of ADHD in children and adolescents were established in 2 pivotal phase III, randomized, double-blind, placebo-controlled, short-term studies.[9,10] In these studies, GXR (1–4 mg/d or 2–4 mg/d) or placebo was administered in the morning; subjects who received GXR demonstrated significant reductions on the ADHD Rating Scale–IV (ADHD-RS-IV). Sedation and somnolence were among the most commonly reported AEs in these and other studies of α_2-adrenoceptor agonists.[9-19] Other commonly observed AEs included headache, fatigue, and upper abdominal pain.[9,10]

To date, controlled trials of GXR monotherapy have examined the effects of morning medication administration only. Anecdotal reports suggest that administration of GXR monotherapy is sometimes recommended in the evening by clinicians, perhaps to attempt to mitigate problems in tolerability (e.g., somnolence, sedation), or because evening administration may be more convenient or helpful for parents or children. The efficacy and safety of morning or evening administration of adjunctive treatment with GXR has been examined in a phase III study of children and adolescents with ADHD exhibiting suboptimal responses on psychostimulants alone.[20] In that study, both morning and evening dosing of GXR (1–4 mg/d), respectively, coadministered with psychostimulants, demonstrated significantly greater improvements in ADHD-RS-IV total scores compared with placebo plus psychostimulant.[20]

The objective of the current study was to assess the efficacy and tolerability of once-daily GXR (1–4 mg/d) monotherapy administered either in the morning or evening versus placebo in the treatment of ADHD in children 6 to 12 years of age. It was hypothesized that either morning or evening administration of GXR would be superior to placebo in reducing ADHD symptoms. In addition, although the study was not designed or powered to address this issue, it was of clinical interest to learn whether there were any indications of differences in efficacy and/or tolerability of GXR when it is given at 1 time or another.

METHOD

Participants

Participants were outpatient children aged 6 to 12 years with a primary diagnosis of ADHD with combined subtype or hyperactive/impulsive subtype, as defined by the *DSM-IV-TR*,[21] based on psychiatric evaluation using the Kiddie-Schedule for Affective Disorders and Schizophrenia–Present and Lifetime version (K-SADS-PL). Children were required to have a baseline ADHD-RS-IV total score ≥28 and a Clinical Global Impressions–Severity of Illness Scale score ≥4. Exclusion criteria included any current controlled or uncontrolled comorbid psychiatric diagnosis (except oppositional defiant disorder), including any severe comorbid Axis II disorders or Axis I disorders (e.g., posttraumatic stress disorder, bipolar illness, psychosis, pervasive developmental disorder, obsessive compulsive disorder, substance abuse disorder, or other symptomatic manifestations) that could confound efficacy or safety assessments, or for which GXR treatment might be contraindicated; at risk for suicide currently or in the past; history or presence of cardiac abnormalities or a primary sleep disorder; body weight <55 lbs or body mass index >95th percentile; and use of another investigational product within 30 days of baseline.

The study protocol was approved by local institutional review boards or independent ethics committees before study initiation. This study was conducted in accordance with the International Conference on Harmonisation of Good Clinical Practice, under the principles of the Declaration of Helsinki. Written permission was provided by parents or legal guardians, and subjects provided additional assent if applicable.

Study Design

This was an 8-week, double-blind, randomized, placebo-controlled, dose-optimization study conducted at 47 sites in the United States and Canada. Screening for eligibility occurred at visit 1. Eligibility was confirmed at baseline (visit 2), and subjects were randomized on a 1:1:1 schedule to 1 of 3 treatment arms, as follows: administration of GXR in the morning, upon awakening, and matching placebo in the evening, at approximately 7 PM ± 1.5 hours (GXR AM); placebo in the morning and GXR in the evening (GXR PM); or placebo in the morning and evening (placebo). The study consisted of a 5-week dose-optimization period (visits 2–7; days 1–35), a 3-week dose-maintenance period (visits 8–10; days 36–56), and a 9-day dose-taper period. During dose optimization, a starting dose of 1 mg/d was titrated upward in 1-mg increments after a minimum of 1 week at the previous dose, based on clinical response and tolerability, up to a maximum of 4 mg/d. The optimal dose was defined as the dose that produced a clinically significant reduction in ADHD symptoms (≥30% reduction in ADHD-RS-IV total score from baseline) with an acceptable level of side effects. Subjects were maintained on their optimal dose for an additional 3 weeks (dose maintenance), during which efficacy and

safety were assessed weekly and the dose could not be increased. A single 1-mg dose reduction was allowed during either dose optimization or dose maintenance based on tolerability. After study completion or early withdrawal, subjects had their dose of study drug tapered in 1-mg increments over a period of 9 days. The final efficacy evaluation was scheduled at visit 10.

Assessments

The primary efficacy measure was the investigator-administered ADHD-RS-IV rating scale. The ADHD-RS-IV is composed of 18 items based on *DSM-IV-TR* criteria, scored from 0 (behavior occurring never or rarely) to 3 (behavior occurring very often), yielding a total score ranging from 0 to 54, with higher scores representing greater severity.[22]

Safety assessments included assessments of adverse events (AEs), vital signs, laboratory test results, physical examination findings, and ratings on the Pediatric Daytime Sleepiness Scale. Administered at each visit up to the final efficacy evaluation, this scale comprised 8 items rated by children (with parental assistance if necessary) and scored from 0 (never) to 4 (always). Higher scores indicate greater daytime sleepiness. Spontaneously elicited AEs, coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 12.1, were evaluated at each study visit. Treatment-emergent AEs were defined as AEs that started or worsened during the period between the day of a subject's first dose of study drug and through the third day after treatment was stopped. Serious AEs (SAEs) were defined as any untoward medical occurrence at any dose that resulted in death, was life-threatening, required inpatient hospitalization or prolonged hospitalization, was a congenital abnormality/birth defect, or was an important medical event in the investigator's judgment.

Data Analyses

The full analysis set (FAS) was used for efficacy and safety analyses, and comprised all subjects who were randomized and received at least 1 dose of study medication. The primary efficacy analysis was performed on the change from baseline to end of treatment. Secondary analyses included visit by visit measurements of change. A last observation carried forward (LOCF) approach (excluding baseline) was used when efficacy assessments were incomplete owing to early withdrawal from the study or missing data. The mean change in the ADHD-RS-IV total score from baseline at visit 10, LOCF (end of treatment), was examined using an analysis of covariance (ANCOVA) model, with treatment group as the effect of interest and baseline score as the covariate. To protect the family-wise significance level of 0.05, a hierarchical approach was used to test the following 3 comparisons, in the order specified: GXR all-active group (GXR AM and GXR PM combined) was compared with placebo results; GXR AM group results were compared with placebo results; and GXR PM group results were compared with placebo results. Only if a significant difference was found in the immediately preceding analysis was the next comparison formally assessed (e.g., a significant difference in analysis 1 was required to perform analysis 2; a significant difference in analysis 2 was required to perform analysis 3).

The same analysis of covariance (ANCOVA) model was used to evaluate mean changes from baseline in the ADHD-RS-IV Hyperactivity/Impulsivity and Inattention subscale scores. Least squares (LS) means and effect sizes were calculated from the ANCOVA models for the change from baseline in ADHD-RS-IV total and subscale scores. Summary statistics were used to compare safety assessments between groups.

To detect an effect size $\geq$0.4 between the GXR all-active and placebo groups ($\geq$90% power and 2-sided $\alpha = 0.05$) for the primary efficacy measure (ADHD-RS-IV total score) using a 2-sample t test with a 1:1:1 allocation ratio to GXR AM, GXR PM, and placebo, ADHD-RS-IV data were necessary from 315 subjects (105 subjects in each arm). To account for an estimated 5% of subjects dropping out without a postbaseline efficacy assessment, 333 subjects (111 per treatment arm) were to be randomized.

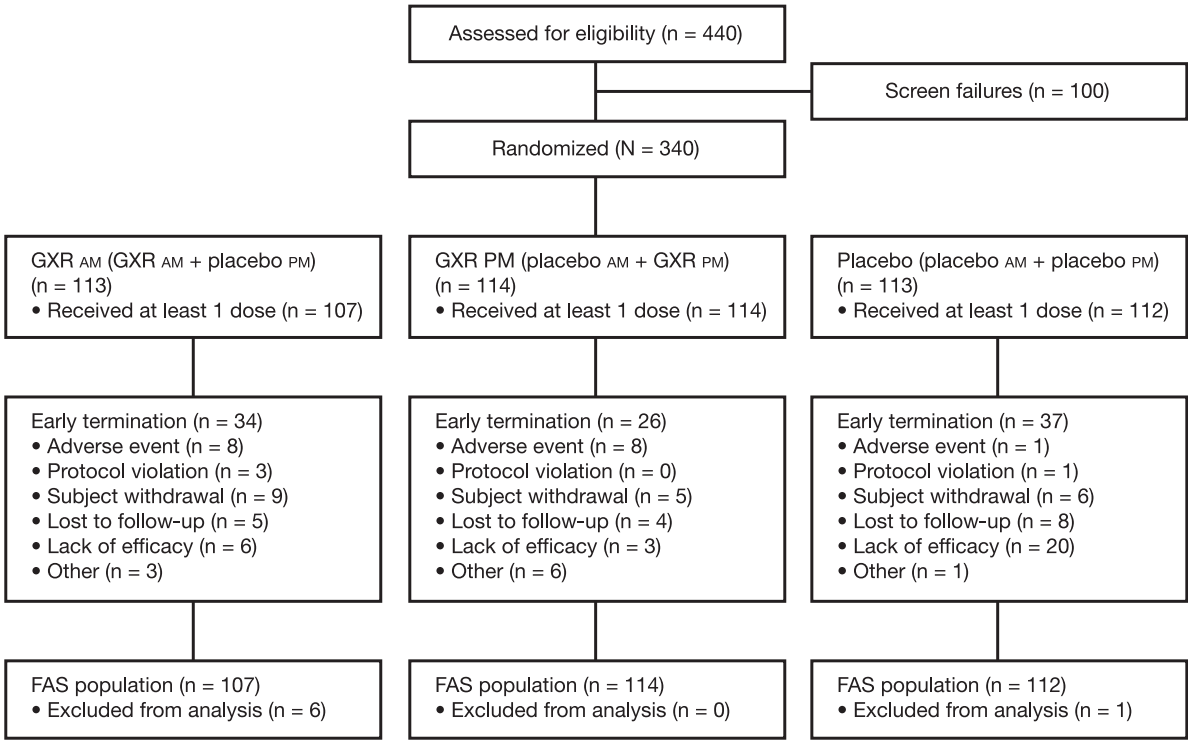
RESULTS

Subject Disposition

The study was conducted between November 2009 and September 2010. A total of 440 subjects were screened, and 340 subjects were randomized. The FAS included 333 subjects: 107 in the GXR AM group, 114 in the GXR PM group, and 112 in the placebo group (Figure 1); 7 subjects with predominantly inattentive subtype (an exclusion criterion) were inadvertently randomized to treatment groups (GXR AM, n = 3; GXR PM, n = 3; placebo, n = 1). Upon discovery, these protocol violators were reported to the Medical Monitor, and it was decided that all 7 subjects should remain in the FAS, in line with good statistical practice, when considering intent-to-treat analyses. A total of 72.6% subjects (247 of 340) completed the dose-maintenance period (visit 10), and 71.5% (243 of 340) of subjects continued through the dose-taper period (visit 11). Three subjects in the GXR AM group and 1 subject in the placebo group discontinued because of protocol violations. Baseline demographic characteristics were similar across study groups (Table 1). Most subjects were male (70.6%) and white (57.1%), and the mean (SD) age was 9.1 years (1.77 years).

The mean (SD) optimal dose of GXR was 2.9 (0.95) mg/d for the all-active group, 2.9 (0.92) mg/d

FIGURE 1 Study flow diagram. Note: FAS = full analysis set; GXR = guanfacine extended release.



for the GXR AM group, and 3.0 (0.98) mg/d for the GXR PM group. The mean (SD) weight-adjusted optimal dose of GXR was 0.084 (0.03) mg/kg for the all-active group, 0.083 (0.03) mg/kg for the GXR AM group, and 0.085 (0.03) mg/kg for the GXR PM group. The minimum and maximum weight-adjusted doses for all groups were 0.02 mg/kg and 0.16 mg/kg, respectively.

Efficacy

At baseline, mean (SD) ADHD-RS-IV total scores were similar across all treatment groups: 41.7 (6.52) for GXR all-active, 41.7 (6.39) for GXR AM, 41.6 (6.66) for GXR PM, and 42.9 (6.21) for placebo. At visit 10, LOCF (end of treatment), subjects receiving GXR demonstrated significantly greater reductions in mean ADHD-RS-IV total scores compared with the placebo group, regardless of the time of GXR administration (Figure 2A). Mean (SD) changes from baseline to visit 10, LOCF, were –20.0 (12.97), –19.8 (12.95), –20.1 (13.04), and –11.0 (12.93) for the all-active, GXR AM, GXR PM, and placebo groups, respectively ($p < .001$ for all 3 GXR groups versus placebo). Although statistically significant differences in ADHD-RS-IV total scores between GXR treatment groups and placebo were evident by visit 3 compared with baseline, the separation between GXR and placebo continued to increase in magnitude through visit 10, LOCF. Effect sizes for the placebo-adjusted LS mean differences at visit 10, LOCF, across GXR treatment groups were 0.77, 0.75, and 0.78 for the all-active, GXR AM, and GXR PM groups, respectively. When baseline weight was included as a covariate, effect sizes for the placebo-adjusted LS mean differences at visit 10, LOFC (end of treatment), across GXR treatment groups remained unchanged for the all-active, GXR AM, and GXR PM groups.

Baseline mean (SD) ADHD-RS-IV Hyperactivity/Impulsivity subscale scores were also similar across all 3 treatment groups: 19.6 (4.78) for GXR all-active, 19.6 (4.81) for GXR AM, 19.7 (4.78) for GXR PM, and 20.3 (4.39) for placebo. At visit 10, LOCF, subjects on GXR demonstrated significantly greater reductions in mean ADHD-RS-IV Hyperactivity/Impulsivity subscale scores compared with subjects given placebo, regardless of time of GXR administration (Figure 2B). Mean (SD) changes from baseline to visit 10, LOCF, were –10.0 (6.77), –9.9 (6.81), –10.2 (6.77), and –5.3 (6.71) for the all-active, GXR AM, GXR PM, and placebo groups, respectively ($p < .001$ for all 3 GXR groups versus placebo). Effect sizes for the

TABLE 1 Baseline Characteristics of Study Patients

Characteristic[a]	All-Active [GXR AM + GXR PM] (n = 221)	GXR AM (n = 107)	GXR PM (n = 114)	Placebo (n = 112)
Age, y, m (SD)	9.2 (1.76)	9.1 (1.77)	9.3 (1.76)	8.9 (1.78)
Sex, n (%)				
Male	150 (67.9)	72 (67.3)	78 (68.4)	85 (75.9)
Female	71 (32.1)	35 (32.7)	36 (31.6)	27 (24.1)
Race, n (%)				
White	134 (60.6)	66 (61.7)	68 (59.6)	56 (50.0)
African American	73 (33.0)	38 (35.5)	35 (30.7)	47 (42.0)
Asian	1 (0.5)	1 (0.9)	0	1 (0.9)
American Indian or Alaska Native	1 (0.5)	0	1 (0.9)	0
Other	12 (5.4)	2 (1.9)	10 (8.8)	8 (7.1)
Body weight, lb, m (SD)	79.20 (20.20)	77.95 (19.44)	80.38 (20.91)	75.79 (17.57)
BMI, kg/m^2, m (SD)	18.09 (2.38)	17.92 (2.42)	18.25 (2.35)	17.96 (2.33)
ADHD subtype, n (%)				
Predominately inattentive[b]	6 (2.7)	3 (2.8)	3 (2.6)	1 (0.9)
Predominately hyperactive–impulsive	5 (2.3)	3 (2.8)	2 (1.8)	1 (0.9)
Combined subtype	210 (95.0)	101 (94.4)	109 (95.6)	110 (98.2)
Time since ADHD diagnosis, y, m (SD)	1.8 (2.19)	1.5 (2.12)	2.0 (2.24)	1.6 (2.13)

Note: ADHD = attention-deficit/hyperactivity disorder; BMI = body mass index; GXR = guanfacine extended release; y=years.

[a] *No statistically significant differences were observed between groups for any characteristic.*

[b] *Predominately inattentive subtype was exclusionary. However, 7 subjects with predominantly inattentive subtype were inadvertently randomized to treatment groups (GXR AM, n = 3; GXR PM, n = 3; placebo, n = 1).*

placebo-adjusted LS mean differences at visit 10, LOCF, for all GXR treatment groups were similar: 0.78, 0.77, and 0.78 for the all-active, GXR AM, and GXR PM groups, respectively.

For the ADHD-RS-IV Inattention subscale, baseline mean (SD) scores were 22.0 (3.51) for GXR all-active, 22.2 (3.30) for GXR AM, 21.9 (3.71) for GXR PM, and 22.6 (3.25) for placebo. At visit 10, LOCF, subjects who received GXR also demonstrated significantly greater improvement in mean ADHD-RS-IV Inattention subscale scores compared with subjects who received placebo, regardless of the time of GXR administration (Figure 2C). Mean (SD) changes from baseline to visit 10, LOCF were –9.9 (7.12), –9.9 (7.05), –10.0 (7.21), and –5.7 (7.01) for the all-active, GXR AM, GXR PM, and placebo groups, respectively ($p < .001$ for all 3 GXR groups versus placebo). Effect sizes at visit 10 (end of treatment), LOCF, for all GXR treatment groups were 0.68, 0.65, and 0.70 for the all-active, GXR AM, and GXR PM groups, respectively.

Safety

Treatment-emergent AEs were reported by 81.4% (180 of 221) of subjects in the all-active group, 79.4% (85 of 107) of the GXR AM group, 83.3% (95 of 114) of the GXR PM group, and 57.1% (64 of 112) of the placebo group (Table 2). For subjects receiving GXR, most AEs that emerged during treatment were of mild (36.7% of subjects) or moderate (40.7% of subjects) severity; 9 subjects (4.1%) reported severe AEs (4 and 5 subjects in the GXR AM and GXR PM groups, respectively). Three subjects (1.4%) receiving GXR reported SAEs, which were determined by the investigators to be related to GXR: 1 subject each in the GXR AM and GXR PM groups experienced syncope of mild/moderate intensity, and 1 subject in the GXR PM group experienced self-injurious/suicidal ideation. All 3 subjects with SAEs were withdrawn from the study, and the SAEs resolved posttreatment. Neither of the subjects who experienced SAEs of syncope (both 12-year-old males) had a history of syncope or presyncope, and baseline electrocardiograms were normal. The subject who received GXR AM experienced syncope on day 28, which resolved the same day. The subject who received GXR PM experienced a syncopal event with abdominal cramps and constipation on day 25; the investigator believed that the episode of syncope was related to a vasovagal reaction triggered by straining and pain associated with defecation. The subject who experienced suicidal ideation was an 11-year-old female with no history of suicidal ideation or other psychiatric disorders.

FIGURE 2 Mean change from baseline in attention-deficit/hyperactivity disorder (ADHD) Rating Scale–IV (ADHD-RS-IV) scores by visit. Note: (A) Total score. (B) Hyperactivity/Impulsivity subscale. (C) Inattention subscale. All *p* values are based on type III sum of squares from an analysis of covariance (ANCOVA) model. GXR = guanfacine extended release; LOCF = last observation carried forward; LS = least squares; SEM = standard error of the mean.[a]$p < .05$ versus placebo based on change from baseline (visit 2). [b]$p < .01$ versus placebo based on change from baseline (visit 2). [c]$p < .001$ versus placebo based on change from baseline (visit 2).

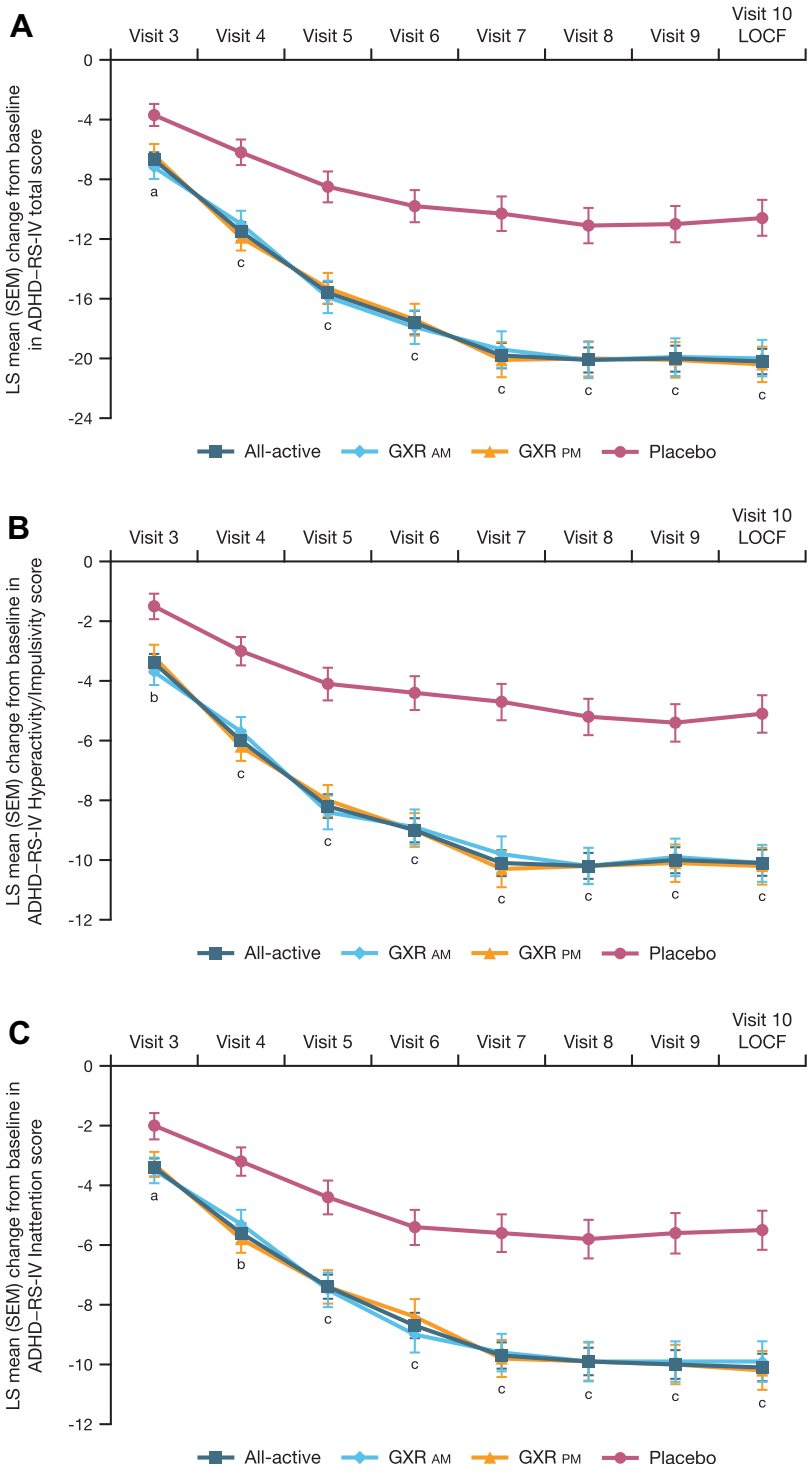


TABLE 2 Treatment-Emergent Adverse Events Occurring in ≥5% of Subjects

Adverse event, n (%) of subjects	All-Active (n = 221)	GXR AM (n = 107)	GXR PM (n = 114)	Placebo (n = 112)
Somnolence	98 (44.3)	50 (46.7)	48 (42.1)	14 (12.5)
Headache	37 (16.7)	19 (17.8)	18 (15.8)	12 (10.7)
Sedation	32 (14.5)	15 (14.0)	17 (14.9)	3 (2.7)
Abdominal pain upper	27 (12.2)	7 (6.5)	20 (17.5)	8 (7.1)
Fatigue	24 (10.9)	11 (10.3)	13 (11.4)	3 (2.7)
Irritability	16 (7.2)	8 (7.5)	8 (7.0)	3 (2.7)
Nausea	12 (5.4)	6 (5.6)	6 (5.3)	1 (0.9)
Upper respiratory tract infection	12 (5.4)	8 (7.5)	4 (3.5)	11 (9.8)
Diarrhea	11 (5.0)	4 (3.7)	7 (6.1)	4 (3.6)
Dizziness	11 (5.0)	6 (5.6)	5 (4.4)	3 (2.7)
Vomiting	11 (5.0)	7 (6.5)	4 (3.5)	2 (1.8)
Insomnia	9 (4.1)	6 (5.6)	3 (2.6)	4 (3.6)
Decreased appetite	9 (4.1)	6 (5.6)	3 (2.6)	3 (2.7)
Enuresis	7 (3.2)	1 (0.9)	6 (5.3)	1 (0.9)
Increased appetite	2 (0.9)	0	2 (1.8)	6 (5.4)

Note: GXR = guanfacine extended release.

On day 21, she was reported to have been upset at the loss of privileges and stated that she wanted to cut herself and had been thinking of suicide. Her mother reported that the subject had never voiced an intention of harming herself before and that the subject denied having an action plan. An accelerated down-titration (taper) was initiated; the events were considered resolved on the day that they occurred, and arrangements were made to initiate counseling. There was no suicidal ideation or behavior at the follow-up visit. Another subject who reported suicidal ideation in the follow-up period (off study treatment for 13 days) was hospitalized for a complete assessment. The investigator reported that the ideation event was "not related" to the study drug. This is the only known case of hospitalization during the study.

superiorIn all, 7.2% of subjects (16 of 221) who received GXR discontinued because of treatment-emergent AEs (8 subjects each in the GXR AM and GXR PM groups, respectively); no subjects receiving placebo discontinued because of AEs that emerged during treatment. AEs of somnolence, sedation, or hypersomnia that emerged during treatment were reported by 55.7% of subjects (123 of 221) in the all-active group, 57.0% (61 of 107) in the GXR AM group, 54.4% (62 of 114) in the GXR PM group, and 15.2% (17 of 112) in the placebo group. These events were mostly mild (all-active, 57.4%; GXR AM, 62.4%; GXR PM, 52.4%; placebo, 75%) or moderate (all-active, 37.9%; GXR AM, 31.8%; GXR PM, 44.0%; placebo, 25%) in severity. The majority of somnolence, sedation, or hypersomnia treatment-emergent AEs resolved before the start of the taper period (78.1% for GXR all-active and 90% for placebo), and the incidence of discontinuations because of these events was 4.1% in the all-active group, 4.7% in the GXR AM group, 3.6% in the GXR PM group, and 0% in the placebo group.

Results from the self-report Pediatric Daytime Sleepiness Scale showed minimal differences between the GXR all-active, GXR AM, and GXR PM groups. Placebo-adjusted LS mean change scores from baseline to visit 10, LOCF (end of treatment; 95% confidence interval [CI]), were 1.1 (–0.2, 2.4) in the all-active, 0.4 (–1.1, 1.9) in the GXR AM, and 1.7 (0.2, 3.2) in the GXR PM groups; differences between GXR all-active and GXR AM compared with placebo were not significant (both $p > .1$, ANCOVA), whereas the difference between GXR PM and placebo was significant, suggesting that there was less daytime sleepiness with placebo ($p = .02$, ANCOVA).

At visit 10, LOCF (end of treatment), subjects receiving GXR (all-active group) demonstrated a mean decrease from baseline in supine pulse, supine systolic blood pressure, and supine diastolic blood pressure (–3.8 bpm, –1.9 mm Hg, and –1.5 mm Hg, respectively). Subjects receiving placebo demonstrated mean changes in the same measures of 1.0 bpm, –0.5 mm Hg, and –0.3 mm Hg, respectively.

DISCUSSION

In this study, GXR monotherapy administered either in the morning or evening was associated

with significantly greater ADHD symptom improvement compared with placebo. Significant reductions were observed in ADHD-RS-IV total scores as well as in Hyperactivity/Impulsivity and Inattention subscale scores. These findings are consistent with previous phase III studies with morning administration, which established the efficacy and safety of GXR monotherapy in children and adolescents with ADHD.[9,10] In these phase III trials, effect sizes ranged from 0.43 to 0.62 (1–4 mg/d GXR) in 1 study[10] and from 0.64 to 0.86 (2–4 mg/d GXR) in the other.[9] In the current study, at the median optimal dose level of 3 mg/d, the treatment effect size for the all-active GXR group was 0.77. Although this value is consistent with the effect size ranges established in the previous GXR monotherapy studies referenced above,[9,10] the effect size in this study is at the top of that range, possibly owing to the dose-optimized design. It is also possible that the effect size may have been affected by the study sample selection, which was limited to children with hyperactivity/impulsivity symptoms and did not include those with primarily inattentive symptoms.

No notable differences in efficacy were observed between the 2 GXR arms, and a similar safety and tolerability profile was demonstrated. Treatment effect sizes were also comparable between morning and evening administration of GXR. These results suggest that GXR monotherapy had a positive effect on ADHD symptoms regardless of the time of drug administration. In a previous study,[20] GXR administered in the morning or evening in combination with a psychostimulant resulted in significantly greater reductions in ADHD-RS-IV scores compared with placebo. Thus, GXR taken in the morning or evening, as monotherapy or in combination with a psychostimulant, yields a positive effect on ADHD symptoms. These data may have clinical impact, as the most convenient time of administration for ADHD medication may vary for different children and their families.

The design of the current study was similar to that of a previous placebo-controlled study[23] with another nonstimulant medication, atomoxetine, in which children 6 to 12 years of age with ADHD were randomized to receive treatment in the morning or evening. In that study, atomoxetine was administered for approximately 6 weeks at a dose titrated between 0.8 mg/kg/d and 1.4 mg/kg/d, depending on tolerability. At 6 weeks, subjects who received AM atomoxetine showed significant improvements in ADHD-RS-IV total scores compared with placebo ($p < .001$; effect size = 0.7); the decrease in ADHD-RS-IV total scores with PM dosing of atomoxetine was not statistically significantly different from placebo. However, both AM (61%) and PM (57%) atomoxetine dosing resulted in significantly higher response rates (predefined as a ≥25% decrease on the ADHD-RS-IV total score) compared with placebo (35%; $p < .001$). In the current study, both AM and PM dosing of GXR were associated with significant improvements in ADHD-RS-IV total scores compared with placebo. The fact that the efficacy of GXR did not differ between evening and morning administration is consistent with the longer half-life of GXR.

The tolerability profile in the current study was similar to that reported in previous investigations of GXR and other nonstimulants. The overall incidence of treatment-emergent AEs in the all-active group (81.4%) was comparable to that observed in the previous phase III studies of GXR monotherapy (74%[10] and 84%[9]) and clonidine XR monotherapy (83%),[16] and most treatment-emergent AEs were of mild or moderate severity. Consistent with previous studies of nonstimulants, somnolence was the most common treatment-emergent AE experienced by those who received GXR (44.3%), and the combination of somnolence, sedation, or hypersomnia events was reported by 55.7% of subjects in the all-active group. Most of these events were mild in intensity and resolved before the dose-taper period. Fatigue was reported in 10.9% of subjects on GXR in this study, which was comparable with previous studies of GXR monotherapy (9%[10] and 18.1%[9]) and clonidine XR monotherapy (14.3%).[16] Because of potential sedative effects, some clinicians have recommended evening administration of α_{2A}-agonists. Although this study did not demonstrate notable differences in the incidence of somnolence or collective somnolence, sedation, or hypersomnia events between GXR AM and GXR PM treatment arms, particular individuals may find greater benefit and/or tolerability from either morning or evening administration of GXR. There were no clinically relevant laboratory abnormalities associated with GXR treatment. The modest decline in pulse and blood pressure observed with GXR treatment is consistent with the known safety profile of GXR.[9,10]

There are several limitations to the sample and methodology in this study that should be considered. Although the efficacy and safety profiles of GXR administered in the morning or evening appeared to be similar, the study was not adequately powered to detect small differences between the GXR AM and GXR PM treatment arms. We limited the drug administration times to 2 time points: morning or evening. To formally assess whether any circadian fluctuations in symptomatology exist across AM and PM dosing regimens, systematic testing would be necessary, such as pharmacokinetic/pharmacodynamic data obtained across different times of day and/or clinical ratings obtained in laboratory classroom studies. Another limitation in the current study is that subjects were not required to complete a self-report or structured scale of AEs, which may have resulted in underreporting of side effects related to tolerability. Furthermore, possible existence of rater bias or halo effects of the rating scales must also be considered as possible limitations. Because there was a high rate of somnolence observed in the GXR groups, there is a possibility that the blind could have been broken, thereby potentially affecting the observed effect size. Finally, although there were no significant differences in baseline characteristics across the treatment groups, when interpreting the results of this study it is important to take into consideration the fact that the subject cohort consisted predominantly of white males and may not generalize to other samples where there is more ethnic or gender diversity.

CG Clinical Guidance

- Once-daily guanfacine extended release (GXR) monotherapy is effective in improving attention-deficit/hyperactivity disorder (ADHD) symptoms whether administered in the morning or in the evening.
- Somnolence is the most common treatment-emergent adverse event associated with GXR; it is transient in the majority of cases.
- Evening GXR dosing produces a similar tolerability profile compared with morning GXR dosing.
- Decisions about when to dose GXR can be made based on the individual needs of patients and families.

To summarize, findings from this study suggest that GXR monotherapy is effective when administered in the morning or in the evening, and therefore can be administered for ADHD symptom improvement either in the AM or PM, with no expected difference in the magnitude of clinical effect. These results extend the findings of a previous study examining morning and evening GXR as an adjunct to stimulant treatment.[20] &

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