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Title:

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Long-Term, Open-Label Extension Study of Guanfacine Extended Release in Children and Adolescents with ADHD

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ABSTRACT

Introduction: Guanfacine is a noradrenergic agonist that is believed to improve symptoms of attention-deficit/hyperactivity disorder (ADHD) through selective actions at α_{2A} -adrenoceptors in the prefrontal cortex. A recent double-blind, multicenter trial supports the efficacy and safety of guanfacine extended release (GXR) for pediatric ADHD. This long-term, open-label extension was conducted to study the safety profile and effectiveness of GXR for up to 2 years.

Methods: Subjects were 240 children 6–17 years of age with a diagnosis of ADHD who participated in the preceding randomized trial. GXR was initiated at 2 mg/day and titrated as needed in 1-mg increments to a maximum of 4 mg/day to achieve optimal clinical response.

Results: The most common adverse events were somnolence (30.4%), headache (26.3%), fatigue (14.2%), and sedation (13.3%). Somnolence, sedation, and fatigue were usually transient. Cardiovascular-related adverse events were uncommon, although small reductions in mean blood pressure and pulse rate were evident at monthly visits. ADHD Rating Scale, Version IV, total and sub-

FOCUS POINTS

- Guanfacine is a noradrenergic agonist that is believed to improve symptoms of attention-deficit/hyperactivity disorder (ADHD) through selective actions at α_{2A} -adrenoceptors in the prefrontal cortex.
- Evidence from short-term studies support the efficacy and safety of guanfacine extended release (GXR) in the treatment of ADHD.
- Results from the present open-label long-term extension study indicate that GXR 2–4 mg/day was generally safe for up to 24 months of treatment.
- This study also found long-term (up to 2 years) effectiveness of GXR in the treatment of ADHD.
- Although somnolence, sedation, and fatigue events were the most common adverse events reported in this study, they were not typically persistent or severe.
- Small decreases from baseline in mean blood pressure and pulse rate were noted, but few subjects experienced clinically significant cardiovascular-related events.

scale scores improved significantly from baseline to endpoint for all dose groups ($P < .001$ for all comparisons, intent-to-treat population).

Conclusion: Long-term treatment with GXR was generally safe for up to 24 months of treatment, and effectiveness was maintained over this treatment period.

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Affiliations and Disclosures: Please see page 1055 for biographies and disclosure information.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a chronic disorder, estimated to affect 8% to 10% of school-aged children.¹ It often persists into adulthood and usually requires long-term treatment.^{2,3} Although stimulant therapy has been the mainstay of ADHD treatment,⁴ some subjects do not respond to stimulants or are unable to tolerate the associated side effects.⁵⁻⁷ Guanfacine is a nonstimulant noradrenergic agonist that is believed to improve ADHD symptoms via selective effects at α_{2A} -adrenoceptors in the prefrontal cortex.⁸⁻¹⁰ In short-term, open-label,^{11,12} and small double-blind trials,^{13,14} immediate-release guanfacine has demonstrated efficacy in reducing ADHD symptoms.

A recently developed extended-release formulation of guanfacine (guanfacine extended release [GXR]; SPD503; Shire Development Inc, Wayne, PA) allows convenient once-daily dosing and reduces peak-to-trough fluctuations in guanfacine levels, which may improve its safety profile and clinical effect. The safety and efficacy of GXR (1, 2, 3, and 4 mg/day) in children and adolescents with ADHD have been examined in two large, double-blind pivotal trials: a 9-week dose-ranging study of GXR at 1, 2, 3, or 4 mg/day and an 8-week fixed-dose escalation study of GXR at 2, 3, or 4 mg/day.^{15,16} In both studies, GXR significantly improved Attention-Deficit/Hyperactivity Disorder Rating Scale, Version IV (ADHD-RS-IV) scores compared with placebo and commonly reported treatment-emergent adverse events (AEs) were generally mild to moderate in intensity.^{15,16} At the completion of the 8-week fixed-dose escalation study, participating subjects were eligible to enter this open-label extension designed to assess the long-term safety and effectiveness of GXR.

METHODS

Subjects

Subjects who participated in the preceding 8-week double-blind, placebo-controlled study were eligible for the open-label extension study if they completed at least 2 weeks of the previous trial without experiencing any clinically important AEs. Subjects who intended to participate in this extension study were titrated to a 2-mg/day dose of GXR as they neared the end of participation in the previous trial, either because of completion of the study or a decision to end participation in the previous trial early and enroll

in the extension study. All subjects started GXR 2 mg/day for the first week of the open-label extension study, regardless of prior treatment allocation in the previous study.

The study was conducted at 45 outpatient sites in the United States from March 11, 2003, until July 21, 2005. The previous trial enrolled subjects 6–17 years of age with a primary diagnosis of ADHD according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision*. Intellectual functioning at age-appropriate levels (as deemed by the investigator) was also required. Subjects with uncontrolled comorbid psychiatric disorders (except for oppositional defiant disorder), who had symptoms that contraindicated treatment with GXR or that could confound efficacy or safety assessments, were excluded. Other exclusion criteria included weight <25 kg; morbid obesity; hypertension; pregnancy; QTc interval >440 msec; positive urine drug screen; history of nonfebrile seizure in the past 2 years; tic disorder; family history of Tourette disorder; inadequately treated thyroid dysfunction; treatment with medication that affects blood pressure, heart rate, or central nervous system function (eg, psychotropics, sedating antihistamines [newer agents permitted >72 hours before a visit], sympathomimetic agents); and any concurrent condition that could confound study results or increase risk to the subject.

The study protocol was approved by the institutional review boards at all study centers. The study was performed in accordance with the Declaration of Helsinki (2000) and the International Conference on Harmonisation guideline. Written informed consent was obtained from each subject's parent or legal guardian, and written assent was obtained from each subject.

Study Design and Treatment

The extension protocol was originally designed as a 12-month study, but was amended to allow the option of continuing for an additional 12 months. Visits were scheduled weekly for the first month (to allow safety profile and efficacy assessments during titration) and monthly thereafter for up to 22 additional months. During the final month (month 24 for subjects who completed the entire study), visits occurred at weekly intervals to allow down-titration and assessment. Subjects also attended two clinic visits after drug discontinuation (at 2–4 days post-drug and 28–32 days post-drug) to further assess safety parameters.

GXR was taken as a single tablet each morning. All subjects started GXR 2 mg daily for the first week of the open-label extension study. This dose could then be titrated upward in 1-mg increments weekly to a maximum of 4 mg/day to achieve an optimally effective dose per the investigator's judgment. Further dose adjustments could be made at any visit as necessary.

During the final month of the study, downward titration occurred in weekly 1-mg decrements, with all subjects receiving a 1-mg/day dose during the last week of treatment. Downward titration occurred at month 24 for subjects who opted for the second 12-month extension and at month 12 for subjects ending the study at the original 12-month cutoff.

Study Assessments

The primary objective of the study was to continue assessing the safety profile of GXR by analyzing AEs, clinical laboratory tests (hematology, chemistry, urinalysis), vital signs, 12-lead electrocardiograms (ECGs), changes in physical examination or concomitant medications, and study withdrawal data. AEs were reported as a response to a nonleading question asked by the investigator, such as "How are you feeling today?" Any symptoms or conditions reported during assessments deemed to be clinically significant by the investigator were also assessed as AEs. The investigator then decided if the event was related to the study drug. Vital signs were taken at all visits. ECGs and laboratory assessments were obtained at baseline, months 3, 6, 9, 12, and 18, and endpoint. Additional laboratory assessments were taken at months 1 and 24.

The key secondary objective was assessment of long-term effectiveness. Efficacy was evaluated at each visit with the ADHD-RS-IV, which assesses symptoms using an 18-item scale with each item rated from 0 (no symptoms) to 3 (severe symptoms) based on *DSM-IV-TR* criteria.¹⁷ Other efficacy measurements included scores on the ADHD-RS-IV Inattention and Hyperactivity/Impulsivity subscales, the Parents' Global Assessment (PGA) scale, and the Child Health Questionnaire-Parent Form 50 (CHQ-PF50). The PGA captures parents' impressions of their child's behavioral improvement from baseline on a 7-point scale that ranges from "very much improved" to "very much worse," while the CHQ-PF50 measures physical and psychosocial well-being in pediatric subjects. The PGA was assessed at baseline, and both the PGA and the

CHQ-PF50 were completed by parents at 3, 6, 9, and 12 months for 12-month participants, and at 3, 6, 9, 13, 18, and 24 months for 24-month participants.

Statistical Methods

A sample size calculation was unnecessary because only subjects from the preceding double-blind study were eligible to enter the open-label extension study. Safety analyses were performed for all subjects who enrolled in the study and received at least one dose of extension-study medication (safety population). Efficacy analyses were performed for the intent-to-treat population, which included all subjects who had a baseline ADHD-RS-IV score from the preceding study and at least one valid ADHD-RS-IV score after the baseline visit in the open-label extension study.

Descriptive statistics were used to summarize safety results and results from the PGA. Two-sided, one-sample *t*-tests were performed on changes from baseline in ADHD-RS-IV and CHQ-PF50 scores. Baseline for efficacy and safety analyses was defined as the baseline from the previous double-blind study prior to receipt of study drug. Because GXR decreases heart rate, confounding the assessment of a possible drug effect on the QT interval, Bazett's correction (QTcB) and Fridericia's correction (QTcF) factors were used to evaluate changes in QT intervals.

Endpoint was defined as the last valid assessment recorded after the baseline visit while still on study drug. All analyses presented in this report were prospectively planned except for the analysis of incidence, duration, and onset of sedative events (combining somnolence, sedation, and fatigue [SSF]).

RESULTS

Subjects

Two hundred forty of the 345 children and adolescents enrolled in the previous study were rolled over into this extension study. Mean age at the start of the antecedent study was 10.5 years, and the majority of subjects were male (76.7%) and white (69.6%). Most (72.5%) were diagnosed with the ADHD combined subtype (Table 1). The disposition of study subjects is shown in Figure 1.

Safety Profile

Mean duration of exposure to GXR prior to tapering was 8.8±8.1 months; 32 subjects were exposed for a full 24 months, although two sub-

jects discontinued the study prematurely despite being treated for ≥ 720 days: one withdrew consent after 720 days and one left town suddenly after 724 days exposed. The medication adherence rate was 97.7% in the safety population. Adherence was a measure of the proportion of scheduled study drug taken between the dates of the first and last doses.

A total of 198 subjects did not complete the study; the most common reason for discontinuation was withdrawal of consent (67/198; 34%). About one quarter (26%) of the study withdrawals were related to AEs.

Somnolence, headache, fatigue, and sedation were the most frequently reported treatment-emergent AEs (Table 2). The highest rates of study discontinuation due to an AE ($\geq 2\%$) were for somnolence (3.8%), weight increase (2.9%), and fatigue (2.1%). SSF events (somnolence,

sedation, and fatigue) were usually mild or moderate in severity. When examined by actual dose at event onset, somnolence and sedation, but not fatigue, appeared dose related.

SSF events were typically reported early in treatment but did not persist. The median onset day was day 15 of the extension study, which was within the first 3 weeks of dosing. Median duration (defined as the total number of days between the first and last reports of the SSF event) was 50 days. The prevalence rate was highest during the first month of the study and generally diminished over subsequent months (Figure 2). Overall, eight subjects (3.3% of the total population) had unresolved events that did not result in study discontinuation, and 16 subjects (6.7% of the total population) discontinued because of SSF.

No deaths were reported during the study. Nine subjects reported 11 serious AEs, defined as any untoward medical occurrence that is life-threatening or results in hospitalization, prolongation of hospitalization, significant disability, or death. Three of these events were considered possibly or probably related to study drug: one event of orthostatic hypotension and two events of syncope. In one case of syncope, the subject experienced syncope while riding in a hot bus. Severe treatment-emergent AEs, defined as incapacitating with inability to work or to complete

TABLE 1.
Subject and Disease Characteristics

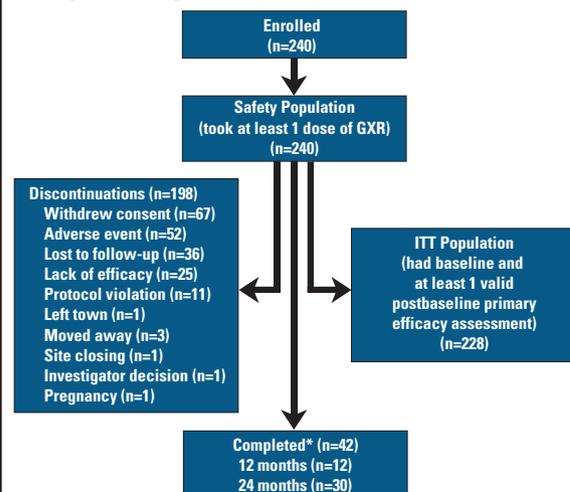
<i>Characteristic</i>	<i>Safety Population (All GXR)</i>
Age (years), mean	10.5 \pm 2.6
6–12 years, n (%)	188 (78.3)
≥ 13 years, n (%)	52 (21.7)
Gender, n (%)	
Male	184 (76.7)
Female	56 (23.3)
Ethnic origin, n (%)	
White	167 (69.6)
Black	30 (12.5)
Hispanic	25 (10.4)
Other	18 (7.5)
Weight (kg), mean	44.0 \pm 16.5
Height (m), mean	1.45 \pm 0.2
ADHD subtype, n (%)	
Inattentive	63 (26.3)
Hyperactive-impulsive	3 (1.3)
Combined	174 (72.5)
Years since ADHD diagnosis, mean	2.25 \pm 2.9
ADHD-RS-IV total score at baseline,* mean	37.4 \pm 9.4

* From baseline (prior to randomization) in the previous study for the ITT population only (n=228).

GXR=guanfacine extended release; ADHD=attention-deficit/hyperactivity disorder; ADHD-RS-IV=Attention-Deficit/Hyperactivity Disorder Rating Scale, Version IV; ITT=intent to treat.

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FIGURE 1.
Subject disposition



* Subjects were considered completed if they participated for 12 or 24 months and completed end-of-study visits.

GXR=guanfacine extended release; ITT=intent to treat.

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usual activities, were experienced by 33 subjects. Severe treatment-emergent AEs that occurred in more than one subject in all the active GXR dose groups included constipation (2/240 subjects), lethargy (2/240 subjects), influenza (2/240 subjects), sinusitis not otherwise specified (2/240 subjects), headache (5/240 subjects), sedation (2/240 subjects), somnolence (7/240 subjects), and aggression (3/240 subjects).

TABLE 2.
Treatment-Emergent Adverse Events Reported by $\geq 5\%$ of Safety Population

<i>Characteristic</i>	No. (%) of Subjects with Event
	<i>All GXR Groups (n=240)</i>
<i>Any</i>	209 (87.1)
<i>Nervous system</i>	
Dizziness	17 (7.1)
Headache	63 (26.3)
Sedation	32 (13.3)
Somnolence	73 (30.4)
<i>General</i>	
Fatigue	34 (14.2)
Lethargy	14 (5.8)
Pyrexia	20 (8.3)
<i>Gastrointestinal</i>	
Abdominal pain upper	26 (10.8)
Nausea	14 (5.8)
Vomiting	20 (8.3)
Diarrhea NOS	12 (5.0)
<i>Infections</i>	
Upper respiratory tract infection	25 (10.4)
<i>Investigations</i>	
Weight increased	21 (8.8)
<i>Psychiatric</i>	
Irritability	13 (5.4)
Insomnia	12 (5.0)
<i>Respiratory</i>	
Cough	29 (12.1)
Nasal congestion	15 (6.3)
Nasopharyngitis	19 (7.9)
Pharyngitis	25 (10.4)

GXR=guanfacine extended release; NOS=not otherwise specified.

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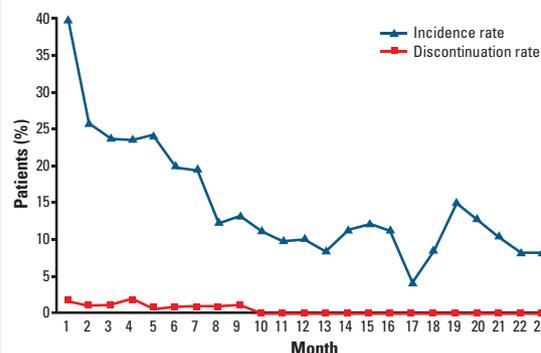
Modest reductions in mean blood pressure were evident during treatment with GXR, with the largest reduction occurring after the first month of the study. Blood pressure returned to near baseline at 24 months, when dose was tapered down. Changes in pulse rate followed a similar pattern (Figure 3). Changes from baseline to endpoint in systolic blood pressure, diastolic blood pressure, and pulse rate were -0.8 mmHg, -0.4 mmHg, and -1.9 beats per minute (bpm), respectively (Figure 4).

Mean changes in pulse rate and QRS intervals were generally unremarkable across study visits. From baseline to endpoint, mean change in heart rate was -7.8 bpm.

Mean change in QTcF intervals from baseline to endpoint for subjects treated with GXR was -0.1 msec. QTcB intervals were shortened from baseline to endpoint with a mean change of -8.0 msec. In an analysis of outliers, no subject had a QRS interval ≥ 120 msec, QTcB or QTcF interval ≥ 500 msec, or a QTcB or QTcF increase from baseline ≥ 60 msec at any scheduled ECG assessment while on study drug. Two subjects had pulse rate intervals ≥ 200 msec during the study.

Three subjects had abnormal, clinically significant ECGs as judged by the investigator. Two subjects had bradycardia: one was judged related

FIGURE 2.
Incidence and discontinuation rates for treatment-emergent SSF events by month (safety population)*



* Percentage of subjects=number of subjects with an SSF (whether it was first reported or a continuing event) or number of subjects discontinued for an SSF event during that month divided by number of subjects still enrolled in the study during that month. At 1 month, n=240; at 12 months, n=79; and at 24 months, n=33.

SSF=somnolence, sedation, and fatigue.

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to GXR treatment and resolved and the other was considered possibly related to GXR treatment and also resolved. (The second subject was discontinued from the study as described below.) The third subject had junctional escape complexes, which were judged to be possibly related to GXR treatment and which resolved. No ECG abnormality was reported as a serious AE.

Cardiovascular-related AEs with GXR were uncommon. Hypotension was reported by seven subjects (2.9%) and bradycardia was reported by five subjects (2.1%). Two subjects were discontinued because of treatment-emergent abnormal ECGs. One subject had worsening of a sinus arrhythmia, which resolved off study drug. The other experienced asymptomatic bradycardia (heart rate: 46 bpm) and the heart rate returned to normal range after study drug discontinuation. Both were judged related to GXR treatment. Two subjects were discontinued for hypotension and two for orthostatic hypotension: all four events were judged related to GXR treatment and all resolved. One subject was discontinued for syncope, which was judged possibly related to GXR treatment and which resolved. Rebound hypertension was reported for two subjects.

No unexpected changes occurred in mean height or weight. Figure 5 depicts increases from baseline at 6-month intervals. Gains by month in weight and height appeared linear and proportional to one another. Seventeen subjects (7.1%) reported weight increase possibly or probably

related to study drug, and 7 (2.9%) discontinued for this event. Weight decrease was not reported. Appetite increase was reported by 2.1% of subjects (5/240), appetite decrease by 3.3% (8/240), and anorexia by 0.8% (2/240). No subjects discontinued for appetite-related events.

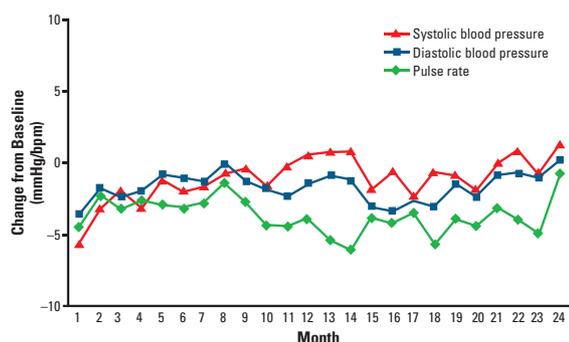
Clinical laboratory analysis was performed at baseline and months 1, 3, 6, 9, 12, 18, 24, and endpoint. Mean changes from baseline were unremarkable. There were no consistent trends suggesting excessive suppression or elevation of human growth hormone or cortisol levels. One subject discontinued because of a laboratory abnormality (moderate thrombocytopenia, platelet count of 97,000/ μ L, possibly related to study medication, while taking GXR 4 mg/day). The condition resolved prior to drug discontinuation and was not considered a serious AE.

Effectiveness

For the primary effectiveness outcome, mean ADHD-RS-IV total score was significantly reduced from baseline to endpoint (Table 3). Reductions were apparent at 1 month and were sustained for up to 24 months for those subjects who continued in the study for 2 years (Figure 6). Significant decreases in ADHD-RS-IV total scores were also achieved in the 6–12-years and \geq 13-years age groups.

Mean reductions in scores from baseline to endpoint were also significant for both the Inattention and the Hyperactivity/Impulsivity subscales of the

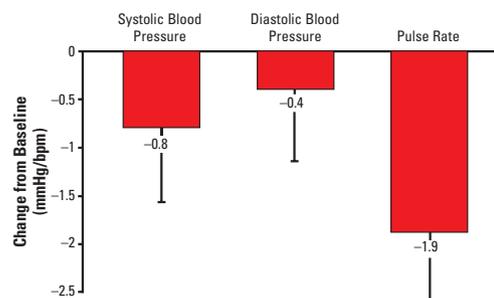
FIGURE 3.
Change from baseline (of the preceding study, prior to randomization) in blood pressure and pulse rate by month (safety population)



bpm=beats per minute.

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FIGURE 4.
Mean changes from baseline to endpoint in blood pressure and pulse rate (safety population; all GXR groups)*



* Change from baseline of the preceding study (prior to randomization) to the last valid measurement while the subject was on study drug (endpoint) in the current study.

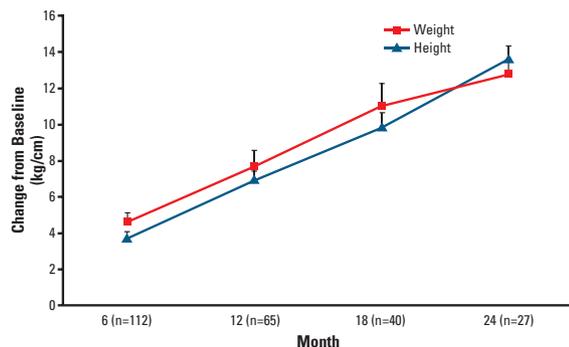
GXR=guanfacine extended release; bpm=beats per minute.

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ADHD-RS-IV (Table 3). Similar to ADHD-RS-IV total scores, significant decreases in both subscales of the ADHD-RS-IV were achieved in the 6–12-years and the ≥ 13 -years age groups. Mean change on the Inattention subscale was -9.1 ± 7.6 ($P < .001$) for the 6–12-years age group and -11.2 ± 7.3 ($P < .001$) for the ≥ 13 -years age group. Mean change on the Hyperactivity/Impulsivity subscale was -8.4 ± 6.9 ($P < .001$) for the 6–12-years group and -9.0 ± 6.2 ($P < .001$) for the ≥ 13 -years age group.

Improvement in PGA scores was gauged conservatively by comparing the percentage of subjects rated as “very much improved” or “much improved” with that of subjects rated as “minimally improved,” “no change,” “minimally worse,” “much worse,” or “very much worse.” Based on this, 58.6% of subjects (95/162) were improved (all dose groups combined) at endpoint compared with baseline of the preceding study. Among subjects 6–12 years of age at the time of enrollment, 57.3% (71/124) were improved at endpoint compared with baseline of the preceding study. For subjects ≥ 13 years of age at the time of enrollment, 63.2% (24/38) were improved at endpoint compared with baseline of the preceding study. For the CHQ-PF50, physical summary scores did not change significantly from baseline to endpoint overall or in any dose or age group. However, psychosocial summary scores were significantly improved overall, in all dose groups and in both the 6–12-years and the ≥ 13 -years age groups.

FIGURE 5.
Change from baseline in weight and height at 6-month intervals (safety population)*



* Change from baseline of the preceding study; number of subjects with weight recorded for each month; height was recorded in fewer subjects.

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DISCUSSION

The present open-label study was designed to assess the safety profile as well as the effectiveness of GXR during up to 24 months of treatment in subjects who participated in a previous 8-week double-blind trial. Results from this study indicate that GXR 2–4 mg/day was generally safe over a long-term (2-year) period. Adherence to study medication was nearly 100%. The majority of discontinuations over this 2-year study period were not related to AEs. The most common cause of discontinuation was withdrawal of consent. The attrition rate reported in this study was similar to rates from other open-label, long-term ADHD treatment studies (~3% per month of study)^{6,18-21} and reflects the difficulties and inconveniences associated with long-term study participation in a pediatric and adolescent population. Subjects and their caregivers who completed this 2-year study were required to attend at least 38 clinic visits and complete hundreds of safety and efficacy assessments—a significant challenge for families.

SSF events were the most common AEs reported in this study, but were not typically persistent or severe. Most were reported within the first few weeks of treatment, were mild or moderate in intensity, did not result in discontinuation from the study, and resolved during continued treatment with GXR. Transient seda-

TABLE 3.
Change From Baseline to Endpoint in ADHD-RS-IV Score (ITT)*

	All GXR Groups (n=227)†
Total score, mean (SD)	-18.1‡ (13.0)
By subscale, mean (SD)	
Inattention	-9.5‡ (7.6)
Hyperactivity/Impulsivity	-8.5‡ (6.8)
By age (total score), mean (SD)	
6–12 years	-17.5‡ (13.2)
≥ 13 years	-20.2‡ (12.0)

* Change from baseline in the preceding study to the last valid assessment in the current study (endpoint).

† Does not include one subject from the full ITT population (n=228) who had a baseline evaluation but no postbaseline assessments while on treatment.

‡ $P < .001$ vs baseline.

ADHD-RS-IV=Attention-Deficit/Hyperactivity Disorder Rating Scale, Version IV; ITT=intent to treat.

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tion early in the course of treatment has also been reported in other studies of guanfacine for ADHD treatment.^{11-13,22}

Small decreases from baseline in mean blood pressure and pulse rate were noted at study visits, but few subjects experienced clinically significant cardiovascular-related events. Cardiovascular events requiring subject discontinuation have been reported rarely or not at all in previous guanfacine studies,^{11-14,22} although prior studies of immediate-release guanfacine for ADHD were generally small and of short duration.

This study found a weight increase of 13.0 lb and a height increase of 2 inches over 2 years during GXR treatment. Weight increase has not been reported in previous ADHD studies with guanfacine,^{13,14,16,22} although the previous maximum study duration was only 20 weeks. In contrast, chronic use of stimulants has been associated with impaired or delayed growth, although its clinical relevance is debated.^{18,19,23,24} In addition, in long-term studies of ADHD, decreased appetite/anorexia, insomnia, and weight loss are typically among the most frequently reported events for stimulants.^{4-6,21,25}

Reduction in ADHD-RS-IV total scores from the previous study baseline score was evident at the 1-month visit, and improvement was sustained throughout the study period and for up to 24 months in subjects who remained on treatment. Changes from baseline to endpoint were also statistically significant for all dose

groups (2–4 mg/day) for both the Inattention and the Hyperactivity/Impulsivity subscale scores. Improvement in the Inattention scores suggests that GXR improves symptoms at least in part through specific effects on attention rather than through secondary effects related to sedation. The magnitude of the reduction in ADHD-RS-IV total scores from baseline to endpoint is similar to what was reported in the preceding double-blind study.¹⁶ Analysis by age group indicated GXR was effective for children (6–12 years of age) and adolescents (13–17 years of age).

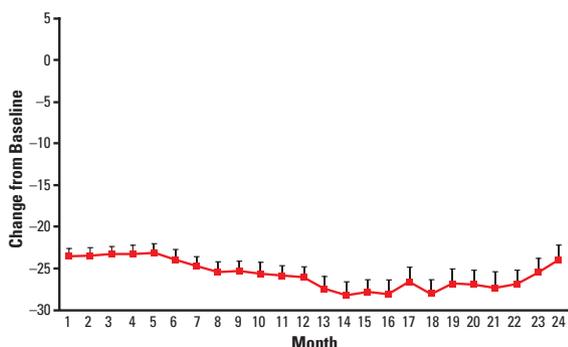
The conclusions from this study are subject to its methodologic limitations. The study was open-label, and, as such, results could have been affected by observer bias. In addition, only subjects who participated in a previous placebo-controlled, double-blind study without experiencing any clinically important AEs were eligible for entry into the current study, thus potentially producing an artificial enhancement of the safety profile. The safety profile supported by this study may also have been affected by the method used to assess AEs. Although AEs were assessed both through open-ended questions as well as through any clinically important symptoms or conditions reported during the assessment, some AEs may have been missed that might have been captured using a more structured interview. However, the approach that was taken was chosen to avoid bias in eliciting AEs.

Regarding the efficacy profile, some subjects who did not respond to GXR in the controlled study may have chosen to discontinue from the controlled study and/or not to participate in the current open-label study. This may have biased the effectiveness results. Other limitations reported for this study are typical for long-term safety studies of ADHD treatments, particularly for studies lasting ≥ 2 years.^{5-7,20} Recruiting and retaining subjects in a long-term, placebo-controlled study when effective therapy is available can be extremely difficult.

CONCLUSION

Despite its potential limitations, this 2-year open-label study of GXR indicates that GXR was generally safe, with clinical benefits maintained over the study period. The present study adds to and extends the existing evidence supporting the use of GXR in the treatment of children and adolescents with ADHD. The sustained safety and effectiveness of GXR, over the course of 2 years,

FIGURE 6.
Change from baseline in mean ADHD-RS-IV total scores by month (ITT)*



* Change from baseline of the preceding study (prior to randomization).
ADHD-RS-IV=Attention-Deficit/Hyperactivity Disorder Rating Scale, Version IV; ITT=intent to treat.

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supports GXR as a viable alternative ADHD treatment for patients, including those patients for whom stimulant treatment is not appropriate. **CNS**

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