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Long-Term Safety and Efficacy of Guanfacine Extended Release in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder

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Abstract

Objective: Short-term, controlled studies of extended-release guanfacine (GXR), a selective α_{2A}-adrenoreceptor agonist, demonstrate efficacy in treating attention-deficit/hyperactivity disorder (ADHD) symptoms as monotherapy. This 2-year open-label study was conducted to further assess the long-term safety and efficacy of GXR.
Methods: Study participants, aged 6–17 years with ADHD, had previously been exposed to GXR therapy alone or in combination with psychostimulants in one of two antecedent trials. In this study, doses were titrated to 1, 2, 3, or 4 mg/day of GXR alone or in combination with a psychostimulant. Safety and efficacy data collected at clinic visits over 24 months provided further evidence of the overall safety and efficacy of GXR for treating ADHD.
Results: The majority of adverse events (AEs) were mild to moderate, and few patients discontinued the study because of an AE. Efficacy measures demonstrated significant improvement beginning in the first month and lasting through the end of the 24-month treatment period. Throughout the entire 2-year study, 202 subjects (77.1%) discontinued and 60 (22.9%) completed the study.
Conclusions: Overall, these data support that GXR monotherapy is generally safe and effective for treating ADHD.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is characterized in children by developmentally inappropriate behaviors, including inattention, hyperactivity, and impulsivity. These behaviors may manifest as impairment in school performance, intellectual functioning, and social skills, among others (Brown et al. 2001; Biederman and Faraone 2005). In addition, an ADHD diagnosis can predict clinically meaningful risks for co-morbidity with other psychiatric disorders and for substance abuse, which can further complicate effective treatment (Brown et al. 2001; Olfson 2004; Biederman and Faraone 2005).

Stimulants, including methylphenidate and amphetamines, have been the primary treatment for ADHD for many decades (Olfson 2004; Biederman and Faraone 2005). However, there remains a need for effective nonstimulant treatment options for patients who may need a combined approach to treatment, who either have a suboptimal response to or cannot tolerate stimulant medications, or who prefer a nonstimulant. Although substantial research supports the efficacy and overall safety of stimulants in treating the symptoms of ADHD, approximately 30% of patients experience inadequate symptom relief and/or the development of treatment-limiting side effects (Scahill et al. 2001; Biederman et al. 2008). Nonstimulant medications can be used in place of stimulants in patients who do not adequately respond to or cannot tolerate stimulants, or when either the patient or the parent prefers alternatives to stimulant treatment (Olfson 2004; Biederman and Faraone 2005). Alternatively, nonstimulant medications may be combined with stimulants when response is suboptimal, or as a means to achieve and balance adequate symptom response and the emergence of dose-limiting side effects, or to treat co-morbid disorders (Biederman and Faraone 2005; Adler et al. 2006; Pliszka et al. 2006). Current clinical guidelines recommend monotherapy with stimulants or atomoxetine as first-line pharmacologic treatments for ADHD (Pliszka et al. 2006; American Academy of Child and Adolescent Psychiatry 2007). However, despite limited data from controlled trials and the lack of approval by

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the U.S. Food and Drug Administration (FDA), combination pharmacotherapy is fairly common in clinical practice in this population (Adler et al. 2006).

In the past, case-level data have raised safety concerns regarding certain combinations, for instance, the combination of clonidine and methylphenidate (Popper 1995; Swanson et al. 1995), although a later assessment of those cases concluded that they do not provide substantial support of an adverse interaction between the two drugs (Fenichel 1995). A more recent study also found no evidence of differences between the effects of clonidine and methylphenidate when given together compared with either agent given alone on electrocardiogram (ECG) measures or overall rates of AEs (Daviss et al. 2008).

Guanfacine is a selective α_{2A}-adrenoreceptor agonist that is believed to improve cognition via action in the prefrontal cortex (Arnsten et al. 1988; Uhlén et al. 1991; Arnsten et al. 1996). Recent data have shown that stimulation of the α_{2A}-adrenoreceptor, in the prefrontal cortex, as occurs with guanfacine, results in a strengthening of cortical networks (Wang et al. 2007). Clonidine, another α_2-adrenoreceptor agonist, has been shown to be effective in reducing symptoms of ADHD when measured by some scales (e.g., the Conners' Abbreviated Symptom Questionnaire for Parents, the Children's Global Assessment Scale) but not by others (e.g., the Conners' Teachers' Abbreviated Symptom Questionnaire) (Connor et al. 1999; Connor et al. 2000; Hazell et al. 2003; Palumbo et al. 2008). Studies have shown that guanfacine, in comparison with clonidine, is less likely to produce sedation or hypotension, possibly due to a greater selectivity for the α_{2A}-adrenoreceptor subtype (Arnsten et al. 1988; Uhlén et al. 1991; Newcorn et al. 1998).

Immediate-release guanfacine was shown in small studies to be effective in reducing ADHD symptoms (Chappell et al. 1995; Hunt et al. 1995; Scahill et al. 2001). An extended-release formulation of guanfacine (GXR) (SPD503, Shire Development Inc., Wayne, PA) is in development, with the goal of significantly reducing peak-to-trough fluctuations, thus potentially improving the safety profile while maintaining therapeutic drug levels. Furthermore, the extended-release formulation permits once-daily dosing. Randomized, double-blind, placebo-controlled short-term studies have demonstrated the efficacy of GXR monotherapy for treating symptoms of ADHD (Biederman et al. 2008; Sallee et al. 2008).

The goal of this study was to further evaluate the long-term safety and efficacy of GXR as monotherapy or in combination with psychostimulants in children and adolescents aged 6–17 years with ADHD.

Methods

Study design and eligibility

This multicenter, open-label study (SPD503-305) was conducted in 48 U.S. centers from June, 2004, to December, 2006, and was designed to assess the safety of GXR treatment for up to 24 months in children and adolescents aged 6–17 years with ADHD. All subjects signed informed consent/assent after a full explanation of study requirements following procedures approved by each participating site's respective Institutional Review Board. Subjects enrolled in this study were previously exposed to GXR in either of 2 antecedent trials (SPD503-205 or SPD503-304), as shown in Fig. 1. Clinical study SPD503-205 (study 1) was a phase 2 open-label, uncontrolled 9-week study to assess the safety of co-administration of GXR with psychostimulants to children and adolescents with ADHD (Clinical Trial NCT00151996) (Spencer et al. 2008). SPD503-304 (study 2) was a phase 3 multicenter, double-blind, dose-ranging, forced-dose titration, 16-week pivotal trial to assess the efficacy and safety of GXR versus placebo for treatment of ADHD in children and adolescents (Clinical Trial NCT00150618) (Sallee et al. 2008).

Subjects were eligible for the present study if they satisfied all entry criteria and completed all visits up through visit 9 in either of the antecedent trials, or had withdrawn from study 2 due to lack of efficacy after visit 4. Furthermore, subjects could not be experiencing any adverse events (AEs) that would preclude further exposure to GXR. Subjects from study 1 had to weigh >65 pounds; subjects from study 2 had to weigh >55 pounds. Nonpregnant subjects of child-bearing potential agreed to comply with applicable contraceptive measures. Written, informed consent was obtained from all subjects' parents or legally authorized representatives. Documentation of the subject's assent was also attained, indicating that the subject was aware of the investigational nature of the study and the required procedures and restrictions. Exclusion criteria included uncontrolled co-morbid psychiatric diagnosis (except oppositional defiant disorder) with significant symptoms, a body mass index of $\geq$35, a specific cardiac condition or family history deemed unsafe for continuation in the study, orthostatic hypotension or hypertension measurements outside the 95th percentile for age, weight, and gender, or other clinically significant laboratory abnormalities. Further exclusion criteria included concurrent use of medications that would affect blood pressure or heart rate, or a positive urine drug test with the exception of psychostimulant drug for those subjects from study 1 who chose to continue receiving their psychostimulant in the current study.

Dosing

Subjects received GXR once daily at a dosage of 1, 2, 3, or 4 mg. All subjects were tapered off study medication from the antecedent trial, began the present study at a titration dose of 1 mg/day, and were titrated to their optimal dose by 1 mg/day increments at weekly intervals during the first 4 weeks of the study. Optimal dose was defined as a clinically significant reduction in ADHD symptoms with minimal side effects. As a general rule, subjects were considered optimized if, after having at least a 30% reduction from baseline in ADHD Rating Scale Version IV (ADHD-RS-IV) total symptom scores, they were considered to have reached their optimum dose in the opinion of the clinician. Subjects who had not achieved at least a 30% reduction in ADHD-RS-IV total symptom scores were escalated to a higher dose level if judged appropriate by the investigator based on clinical experience.

Subjects were maintained at their optimal dose throughout the remainder of the study (until month 24) when GXR was tapered off by 1-mg/day decrements at weekly intervals. Subjects who previously participated in study 1 could receive GXR as monotherapy or co-administered with their same psychostimulant medication (amphetamine or methylpheni-

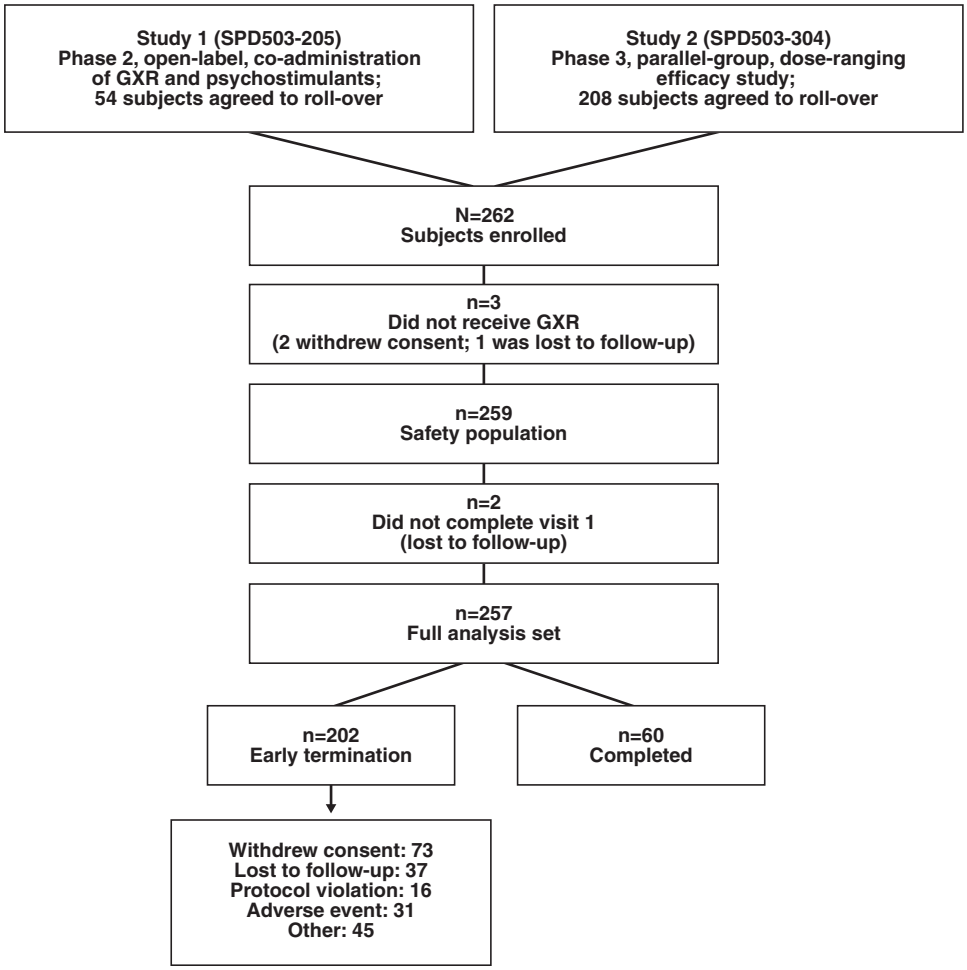

FIG. 1. Subject disposition. GXR = guanfacine extended release.

date). Investigators could adjust the dosage of GXR or psychostimulant for efficacy throughout the 24-month open-label investigation.

Study populations and evaluations

There were 32 planned clinic visits and a follow-up phone contact over the 25-month duration of the study. At visit 0, inclusion and exclusion criteria were reviewed to ensure that all subjects continued to meet eligibility criteria. Safety analysis was performed on the safety population, which was composed of all enrolled subjects ($N = 262$) except 3 subjects, who did not receive study medication ($n = 259$); of those 3 subjects, 2 withdrew consent and 1 was lost to follow up. Additional analyses of safety data were performed separately on the monotherapy subgroup ($n = 206$) and the psychostimulant co-administration subgroup ($n = 53$); however, this study was neither designed nor powered to evaluate differences between the subgroups, and these subgroups were not randomized but rather reflect enrollments from two different antecedent studies. The main efficacy analysis was conducted on the full analysis set, which included all subjects with an efficacy assessment from baseline in the antecedent study and at least one primary efficacy measurement recorded after the baseline of the current study ($n = 257$).

Safety

Safety was assessed via AE reports, vital signs, height and weight measurements, laboratory tests, physical examinations, ECGs, concomitant medications, the Pediatric Daytime Sleepiness Scale (PDSS), and evaluation of early discontinuation data. Descriptive statistics were used for the PDSS and clinical laboratory tests. Qualitative analysis for abnormalities of laboratory tests was performed using the shift-table method, which analyzed the shift from baseline values of the antecedent studies to end-of-treatment values in the number and percentage of subjects with normal and abnormal findings.

Diastolic blood pressure (DBP) and systolic blood pressure (SBP), pulse, and results from physical examinations were summarized descriptively. Vital sign outlier limits included pulse measurements of $\leq$50 or $\geq$100 beats per minute (bpm), postural orthostatic DBP decrease $\geq$15 mmHg or SBP decrease of $\geq$30 mmHg, seated SBP of $<$90 or $>$120 mmHg for 6 to 12 year olds and $<$100 or $>$140 mmHg for 13 to 17 year olds, or a seated DBP of $<$50 or $>$80 mmHg for 6 to 12 year olds and $<$60 or $>$90 mmHg for 13 to 17 year olds. ECGs were conducted at the baseline of the antecedent study, the baseline of the open-label extension study, and visits 6, 9, 12, 15, 21, and at follow up (visit 31). ECG outlier criteria were defined as follows: heart rate $\leq$50 bpm or $\geq$100 bpm, PR interval

≥200 msec, QT interval ≥480 msec, QRS interval ≥120 msec, QTcF ≥500 msec, QTcB ≥500 msec, and QTcF and QTcB change from baseline of the antecedent study of ≥30 msec to <60 msec or ≥60 msec. PDSS data were collected at every visit except for visits 31 and 32. For the safety analyses presented here, comparisons were made using baseline values from the antecedent studies.

Efficacy

The main efficacy measure was the ADHD-RS-IV total score collected at each monthly visit and the main efficacy outcome was the ADHD-RS-IV total score change from the baseline of the antecedent study at end point. The ADHD-RS-IV was developed to measure the behavior of children with ADHD and consists of 18 items, each scored from 0 (no symptoms) to 3 (severe symptoms). The total score ranges from 0 to 54. End point was defined as the last nonmissing valid assessment after baseline of the open-label extension study while the subject was on study drug. The analysis of the end point is thus numerically equivalent to the analysis of the last observation carried forward. The ADHD-RS-IV actual score and change from the baseline of the antecedent study in the full analysis set were evaluated overall, by therapy group (i.e., monotherapy and psychostimulant coadministration), by age group (6–12 and 13–17 years of age), and by actual dose and weight-adjusted actual dose prior to dose tapering at the end of the study.

Secondary efficacy measures included the investigator-rated Clinical Global Impressions of Improvement (CGI-I), the Parent Global Assessment (PGA) scale, the Child Health Questionnaire–Parent Form 50 (CHQ-PF50), and the Conners' Parent Rating Scale–Revised (CPRS-R) short form. The CGI scale is a global evaluation of baseline symptom severity and improvement over time. At baseline, the investigator used the CGI–Severity (CGI-S) to rate severity of symptoms on a 7-point scale ranging from 1 (no symptoms) to 7 (very severe symptoms). At each visit thereafter, the investigator used the CGI-I to rate the improvement relative to baseline on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). The PGA is a variant of the CGI scales of severity and improvement. For the PGA, the parent/caregiver rated their child's behavior at baseline of the antecedent study and assessed changes in behavior and symptoms relative to these baseline ratings. The CHQ-PF50 is designed to measure physical and psychosocial well being in children aged ≥5 years. Two summary scores were obtained using 14 Core Health Concepts, one score for physical well being and the other for psychosocial well being. GXR duration of effect was monitored via the CPRS-R short form, which assesses a cross section of ADHD-related symptoms and problem behaviors. The CPRS-R was completed by parents and contained four subscales (i.e., oppositional, cognitive problems, hyperactivity, ADHD index). The CPRS-R evaluations were designed to permit an analysis of the duration of effect of GXR throughout the day by assessing scores at 12, 14, and 24 hours postdose. Parents answered 27 questions regarding their child's behavior immediately preceding the assessment times. Analyses of efficacy measures were made relative to baseline of the antecedent study.

Compliance with the study drug was determined by tablet counts. Subjects were requested to return unused study drug at each visit, and those who had taken 80–120% of their prescribed amount were considered compliant. Statistical analysis was performed using SAS® version 9.1. Because this was an open-label extension study, a power analysis was not performed.

Results

Subject disposition and demographics

As shown in Fig. 1, a total of 262 eligible subjects from the antecedent studies enrolled in the current study: 54 from study 1 (psychostimulant co-administration) and 208 from study 2 (GXR monotherapy). The full analysis comprised 257 subjects who received the drug and had at least one

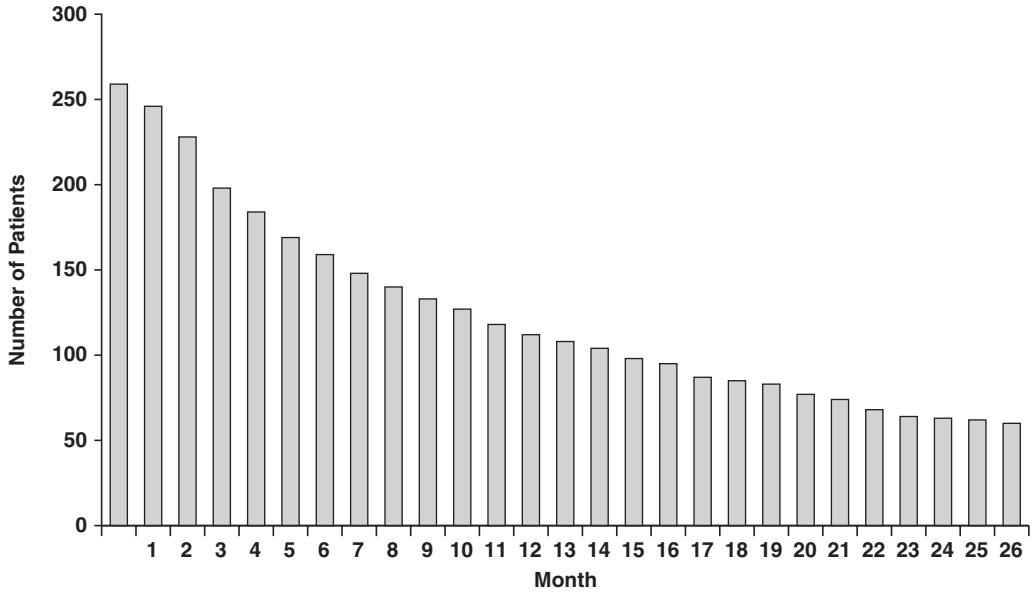

FIG. 2. Number of patients remaining in study by month.

primary efficacy measurement after the baseline of the open-label extension study. Throughout the entire 2-year study, 202 subjects (77.1%) discontinued and 60 (22.9%) completed the study (Fig. 2). The most common reason for early discontinuation was withdrawal of consent ($n = 73$, 27.9%). Over the 24-month treatment period, only 27 subjects (10.3%) terminated early due to lack of efficacy.

Early discontinuation occurred in 171 of 208 (82.2%) subjects in the monotherapy subgroup and 31 of 54 subjects (57.4%) receiving a co-administered psychostimulant. Withdrawal of consent was the most frequent reason for discontinuation in both subgroups. Other reasons for early termination in at least 10% of subjects in the monotherapy subgroup were lost to follow up (13.5%; 28 of 208 subjects), AE (13.5%; 28 of 208 subjects), or lack of efficacy (12.5%; 26 of 208 subjects). In the combination therapy subgroup, 16.7% of subjects (9 of 54) were lost to follow up, 5.6% of subjects (3 of 54) discontinued due to AEs, and 1.9% of subjects (1 of 54) discontinued due to lack of efficacy.

Subject demographics are shown in Table 1. The majority of subjects had the ADHD combined subtype (73.0%). Overall mean (standard deviation [SD]) years since diagnosis was 2.5 (2.9), although the mean time since diagnosis was 4.0 years (2.6 years) in the group of 53 subjects who received co-administered psychostimulants. The mean (SD) ADHD-RS-IV total symptom score at baseline of the antecedent study was 38.3 (10.1). Overall, mean symptom scores were similar across the 1, 2, 3, and 4 mg/day GXR dose groups. However, although significance testing was not performed, the mean total symptom score at baseline was numerically higher in the GXR monotherapy subgroup (40.6, SD 8.5) compared with the psychostimulant co-therapy subgroup (29.3, SD 10.9).

Table 1. Subject Demographics

Characteristics	*Overall* (n = *259*)	*Monotherapy* (n = *206*)	*Co-administered psychostimulants* (n = *53*)
Age (years)			
Mean (SD)	10.7 (2.6)	10.6 (2.7)	11.2 (1.8)
Median	10.0	10.0	11.0
Min, max	6, 17	6, 17	7, 15
Age category, *n* (%)			
6–12 years	191 (73.7)	151 (73.3)	40 (75.5)
≥13 years	68 (26.3)	55 (26.7)	13 (24.5)
Gender, *n* (%)			
Male	188 (72.6)	148 (71.8)	40 (75.5)
Female	71 (27.4)	58 (28.2)	13 (24.5)
Ethnic origin, *n* (%)			
White	180 (69.5)	142 (68.9)	38 (71.7)
Black	39 (15.1)	30 (14.6)	9 (17.0)
Hispanic	25 (9.7)	20 (9.7)	5 (9.4)
Asian or Pacific Islander	8 (3.1)	7 (3.4)	1 (1.9)
Other	7 (2.7)	7 (3.4)	0
Weight (pounds)			
Mean (SD)	96.6 (33.2)	95.4 (34.0)	101.2 (29.8)
Median	90.0	88.0	95.0
Min, max	55, 237	55, 237	61, 180
Height (inches)			
Mean (SD)	57.5 (5.7)	57.1 (5.9)	59.2 (4.4)
Median	58.0	57.40	60.0
Min, max	40.7, 71.3	40.7, 71.3	52, 70.3
ADHD subtype, *n* (%)			
Inattentive	62 (23.9)	51 (24.8)	11 (20.8)
Hyperactive	8 (3.1)	5 (2.4)	3 (5.7)
Combined	189 (73.0)	150 (72.8)	39 (73.6)
Years since ADHD diagnosis			
Mean (SD)	2.5 (2.9)	2.2 (2.8)	4.0 (2.6)
Median	1.6	0.8	4.0
Min, max	0, 12.2	0, 12.2	0, 10.1
Mean (SD total symptom score at baseline)	38.3 (10.1)	40.6 (8.5)	29.3 (10.9)

SD = Standard deviation; ADHD = attention-deficit/hyperactivity disorder.

Safety: Adverse events

Treatment-emergent AEs (TEAEs) were reported by 87.3% of subjects overall. TEAEs were reported in 87.4% of subjects in the monotherapy subgroup and 86.8% of subjects in the combination therapy subgroup. Over the long-term treatment period, discontinuations due to TEAEs occurred in 12.0% of subjects (31 of 259 subjects) in the overall safety population, 13.6% (28 of 206) subjects in the monotherapy subgroup, and 5.7% (3 of 53) subjects in the combined therapy subgroup. The majority of AEs leading to discontinuations were mild to moderate in intensity.

According to investigators, 73.4% of overall TEAEs were considered possibly or probably related to study medication. The incidence of possibly/probably related TEAEs was 77.2% in the monotherapy subgroup and 58.5% in the combined therapy subgroup. Twenty-two treatment-emergent serious AEs occurred in 16 (6.2%) subjects in the safety population. As discussed in further detail below, 5 of these subjects reported syncope. The next most common treatment-emergent serious AEs were head injury, loss of consciousness, and suicidal ideation, all of which were reported by 2 subjects each. Twenty-one of the 22 serious AEs resolved and one remains unknown because the patient was lost to follow up. Thirteen of the serious AEs were judged not related to study medication by investigators. Severe TEAEs were reported in 21 of 259 (8.1%) subjects overall, 9.2% of subjects in the monotherapy subgroup, and 3.8% of subjects in the combination therapy subgroup.

The most commonly reported TEAEs are shown in Table 2. Although not among the most common TEAEs, hypotension was reported in 13 subjects (5.0%), decreased DBP was found in 9 subjects (3.5%), decreased blood pressure in 7 subjects (2.7%), and decreased SBP in 6 subjects (2.3%) of the safety population. Three of the subjects who had decreased SBP also had decreased DBP. The most common TEAEs were similar in the GXR monotherapy subgroup relative to the overall group (Table 2). Decreased appetite (13.2%), irritability (13.2%), and pharyngitis (11.3%) were among the most common TEAEs that differed in the subgroup co-administered psychostimulants relative to monotherapy or the overall safety population (Table 2).

Safety:Syncope

Five subjects (all from the monotherapy subgroup) reported syncope. All syncopal events were deemed serious adverse events (SAEs) and were considered by the investigators possibly or probably related to study medication. All of the episodes were brief and resolved. Confounding factors may have been associated with at least some episodes of syncope. In one case, a female subject reported a history of "black-out spells" and lightheadedness prior to use of study drug. At the time of the syncopal event, she had not yet eaten breakfast or taken her daily dose of GXR. At the time of this event, the subject also had a mild fever and moderate dehydration. She had also experienced vomiting, diarrhea, and gastroenteritis the day before the event. In another instance, the syncopal event occurred while the subject was at church. Subsequently, there were additional reports of other people fainting at the church, possibly related to the heat. Another subject felt dizzy and fainted while playing soccer on a 90-degree day. The syncopal episode resolved the same day without medical treatment. The fourth subject who experienced syncope had taken her daily dose of GXR 10 minutes after awakening and on an empty stomach. The subject fainted a few minutes later during an argument with her father. The syncope resolved the same day without treatment. In the remaining case of syncope, the subject fainted after standing for an extended length of time. The investigator judged that the event was related to both dehydration and prolonged standing.

Safety: Somnolence, sedation, or fatigue events

The incidence of somnolence, sedation, or fatigue events is summarized in Fig. 3. The majority of somnolence, sedation, or fatigue events were moderate or mild in severity and resolved by end of treatment. The median day of onset for a somnolence, sedation, or fatigue event was within the first 3 weeks of treatment (17 days). Figure 4 depicts the overall incidence and severity of somnolence, sedation, or fatigue events over the course of the study. The frequency of som-

Table 2. Most Common Treatment Emergent Adverse Events Occurring in ≥10% of the Safety Population of Each Therapy Subgroup

Adverse event	*Safety population,* N = *259,* n *(%)*	*Monotherapy,* n = *206,* n *(%)*	*Psychostimulant co-therapy,* n = *53,* n *(%)*
Somnolence	79 (30.5)	78 (37.9)	—
Headache	63 (24.3)	51 (24.8)	12 (22.6)
Upper respiratory tract infection	46 (17.8)	33 (16.0)	13 (24.5)
Nasopharyngitis	37 (14.3)	29 (14.1)	8 (15.1)
Fatigue	36 (13.9)	31 (15.0)	—
Upper abdominal pain	33 (12.7)	25 (12.1)	8 (15.1)
Sedation	29 (11.2)	26 (12.6)	—
Pharyngitis	—	—	6 (11.3)
Decreased appetite	—	—	7 (13.2)
Irritability	—	—	7 (13.2)

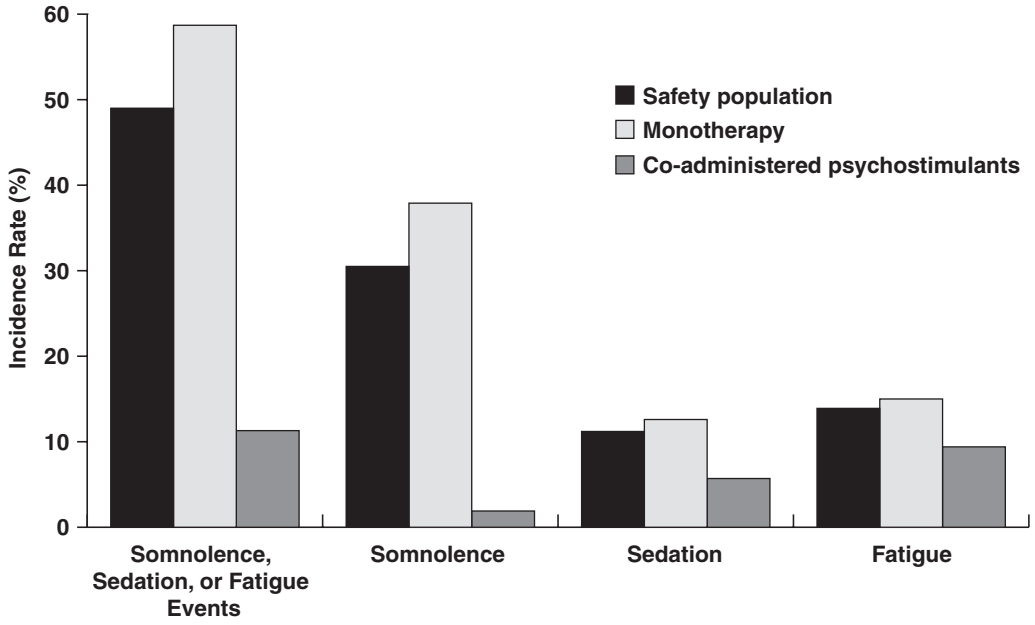

FIG. 3. Incidence of treatment-emergent somnolence, sedation, or fatigue events (safety population). Somnolence, sedation, or fatigue events were reported by 49% (127 of 259) of subjects in the safety population, 58.7% of subjects (121 of 206) administered monotherapy and 11.3% of subjects (6 of 53) administered guanfacine extended release with a psychostimulant.

nolence, sedation, or fatigue events steadily declined during the first 6 months of treatment from 37.8% to 15.8% and remained below 15.8% for the remainder of the study with the exceptions of visits 13 (15.9%) and 14 (17.1%).

Safety:Vital signs

There were small changes from baseline to end point in pulse, DBP, and SBP. Over the long-term treatment period, there were no overt trends in vital sign measurements over time or across actual doses at time of assessments. The mean (SD) change in pulse at the end of treatment in the safety population was −0.1 (14.7) bpm and the range of mean changes in the all active treatment group (excluding end point) varied from −3.5 bpm to −0.2 bpm. In the monotherapy subgroup there was a −0.8 (14.7) bpm mean decrease in pulse rate, whereas in the combination therapy subgroup there was a 2.6 (14.4) bpm mean increase.

Overall, there was a mean (SD) increase in SBP of 1.2 (12.4) mmHg at end of treatment, with a range of means in the all active treatment group (excluding end point) of −3.8 mmHg to +4.7 mmHg. At the end of treatment, there was a mean (SD) increase in DBP of 0.9 (10.0) mmHg (range −2.7 to +2.5 mmHg in the all-active group). Mean (SD) changes from baseline of the antecedent study to end point in SBP and DBP were 6.6 (11.3) mmHg and 4.6 (9.9) mmHg.

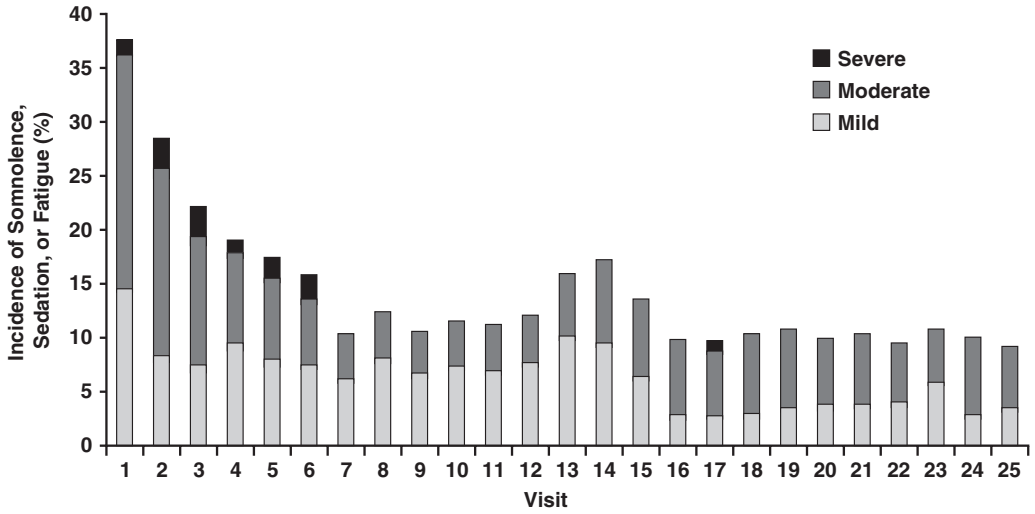

FIG. 4. Incidence of somnolence, sedation, or fatigue by visit (safety population). The frequency of sedative events steadily declined during the first 6 months of treatment and remained near that level throughout most of the study. Visit 25 includes all data after visit 24.

Reports of vital sign outliers from the safety population demonstrated that most pulse outliers were due to pulse increases, and most blood pressure outliers were due to decreases in blood pressure. Pulse rates of <50 bpm were reported in 15 subjects (5.9%) in contrast with 77 subjects (30.1%) of the safety population who demonstrated pulse rates of >100 bpm. SBP measures of <90 mmHg were reported in 46.8% of subjects aged 6–12 years and <100 mmHg in 61.8% of older subjects, aged 13–17 years. In contrast, elevated SBP (>120 mmHg) was reported in 23.9% of the younger subjects and 13.2% of adolescents (>140 mmHg). DBP outliers followed a similar pattern. Decreased DBP (<50 mmHg) was observed in 27.7% of children and in 67.6% of adolescents (<60 mmHg). Conversely, increased DBP of >80 mmHg or >90 mmHg was reported in 16% of 6- to 12-year-old subjects and 5.9% of 13- to 17-year-old subjects, respectively.

Mean weight gain from baseline of the antecedent study to end point was 15.4 pounds.

Only 2.3% (6 of 259 subjects) of subjects experienced increases in weight deemed possibly related or related to study medication. Mean height increase from baseline of the antecedent study to end point was 2.7 inches.

Safety: ECG

No ECG abnormality was considered by investigators as a serious AE. Twenty eight subjects had new, abnormal ECGs at end point; only 2 were considered clinically significant by the investigators. In the first subject, advanced atrioventricular block was initially reported as a serious AE and subsequently changed to a nonserious conduction disorder not otherwise specified (NOS) after further tests and evaluation. The subject's pulse rate and QRS intervals never met outlier criteria during the study, and QTcF intervals never exceeded 366 msec. This subject had shown intraventricular delay on ECGs at baseline of the antecedent study and at baseline of the open-label extension study. This is the only subject to have discontinued the study due to an ECG abnormality. The second subject with a clinically significant ECG displayed sinus bradycardia in month 3. The subject's baseline heart rate was 63 bpm but repeat measures in month 3 showed a heart rate of 45 and 46 bpm, and an end-of-study rate of 76 bpm. The subject did not report any other symptoms at the time of the event.

Further analysis of ECG outlier criteria demonstrated that throughout the duration of the study, no subject had a QRS interval ≥120 msec, a QT interval ≥480 msec, a QTcB or QTcF interval ≥500 msec, or a QTcB or QTcF increase from baseline of ≥60 msec. Thirty subjects had a QTcF change from baseline measure between ≥30 and <60 msec, and the same QTcB change from baseline criterion was met by 21 subjects. A heart rate ≤50 bpm was observed in 15 subjects and an increased heart rate of ≥100 bpm was recorded in 9 subjects.

Efficacy: Main efficacy measure; ADHD-RS-IV scores

Overall mean (SD) ADHD-RS-IV total score at baseline of the antecedent study was 38.3 (10.1). There were no notable differences in baseline (SD) ADHD-RS-IV total scores between dose groups (1 mg, 38.6 [7.3]; 2 mg, 35.8 [10.7]; 3 mg, 38.4 [11.1]; and 4 mg, 39.5 [9.1]). At baseline, the mean (SD) ADHD-RS-IV total score was 29.3 (10.9) for the population of subjects co-administered psychostimulants and 40.6 (8.5) for the monotherapy subgroup.

The mean (SD) ADHD-RS-IV score at end point across all active GXR dose groups was 18.1 (12.4), representing a reduction of more than 50% from the mean baseline score. Mean (SD) changes in ADHD-RS-IV total score from baseline to end point showed statistically significant improvement: overall, −20.1 (13.5) ($p < 0.001$), and for all GXR dose groups, −23.8 (12.3), −22.5 (12.3), −20.0 (14.0), and −18.4 (13.7) for the 1-, 2-, 3-, and 4-mg dose groups, respectively ($p < 0.001$ for each). GXR monotherapy yielded a significant reduction in ADHD-RS-IV mean score (overall group final mean [SD] score was 19.4 [12.9], mean score reduction was −21.2 [13.9], $p < 0.001$), and significant (SD) score reductions were demonstrated in each monotherapy dose group: 1 mg = −24.3 (12.8), 2 mg = −24.3 (11.5), 3 mg = −22.1 (14.2), and 4 mg = −18.0 (14.6); $p < 0.001$ for all. Similarly, in the smaller group of subjects who received psychostimulant co-therapy, the overall ADHD-RS-IV mean [SD] total score also showed a significant reduction from baseline to end point (overall group final mean score was 13.2 [8.5], mean score reduction was −16.1 [11.0], $p < 0.001$). Statistically significant [SD] improvements were seen in the co-therapy subgroups receiving 2, 3, and 4 mg of GXR (−14.4 [12.7], $p = 0.006$; −12.5 [10.2], $p < 0.001$; −19.7 [10.2], $p < 0.001$, respectively). There was a −21.5 (SD 13.4) point mean score reduction observed in the 1 mg GXR combination therapy subgroup; however, statistical significance was not attained, most likely due to the small sample size ($n = 2$) of this group.

GXR therapy elicited early improvement based on a mean (SD) ADHD-RS-IV total score reduction of −15.8 (11.0) achieved for the overall full analysis set at the first assessment after baseline of the open-label extension study (visit 1, week 1) and for each GXR dose group; (1 mg = −19.3 [9.6], 2 mg = −17.2 [10.2], 3 mg = −16.5 [12.1], 4 mg = −13.9 [10.2]). Efficacy was sustained throughout the 24-month study as determined by ADHD-RS-IV scores at each monthly evaluation up to and including end point.

Similar results were obtained when data from the full analysis set were analyzed based on weight-adjusted actual doses. Mean (SD) changes in ADHD-RS-IV total score from baseline to visit 1 were −12.2 (11.8), −16.5 (12.7), and −21.4 (12.4) for the 0.01- to 0.04-mg/kg, 0.05- to 0.08-mg/kg, and 0.09- to 0.12-mg/kg dose groups, respectively. The earliest time point that included subjects in the 0.13- to 0.17-mg/kg dose group was not until the month 1 visit, at which point this dose group demonstrated a −27.7 (9.4) mean (SD) reduction in ADHD-RS-IV total score. At end point, mean ADHD-RS-IV total scores were significantly ($p < 0.001$) reduced from baseline in each weight-adjusted dose group. Mean (SD) changes were −18.9 (12.1) for the 0.01-to 0.04-mg/kg group, −19.8 (14.7) for the 0.05- to 0.08-mg/kg group, −25.5 (14.3) for the 0.09- to 0.12-mg/kg group, and −20.8 (15.5) for the 0.13- to 0.17-mg/kg group. Results from this analysis are shown in Fig. 5.

Efficacy: Additional outcomes (CPRS-R, CGI-I, PGA, and CHQ-PF50)

CPRS-R mean changes from baseline to end point were statistically significant in the overall treatment group (−18.2; $p<0.001$). Similar results were obtained when analyzing the

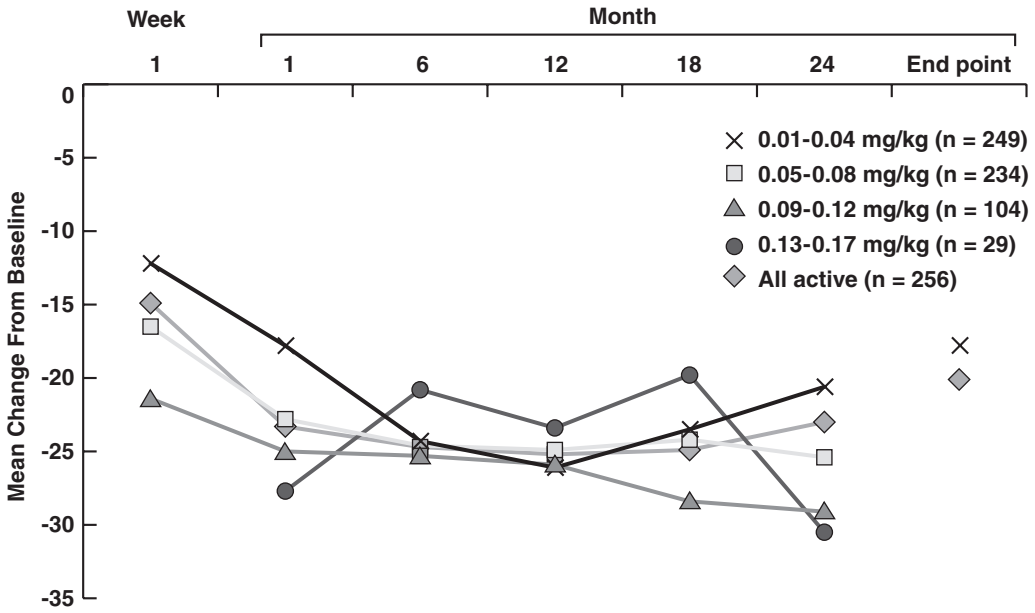

FIG. 5. ADHD-RS-IV total score by weight-adjusted actual dose (full analysis set). The earliest time point that included subjects in the 0.13- to 0.17-mg/kg dose group was the month 1 visit. At end point, mean ADHD-RS-IV total scores were significantly ($p < 0.001$) reduced from baseline in each weight-adjusted dose group. End point is the last valid ADHD-RS-IV total score obtained postbaseline and on treatment. ADHD-RS-IV = Attention-Deficit/Hyperactivity Disorder Rating Scale Version IV.

monotherapy and combination therapy subgroups separately. The overall mean change from baseline demonstrated statistically significant ($p < 0.001$) improvement in CPRS-R scores at each postdose assessment. As shown in Fig. 6, mean improvement from baseline to end point was statistically significant ($p < 0.001$) at each postdose time point in the full analysis set, the GXR monotherapy subgroup, and the combination therapy subgroup.

The overall baseline mean (SD) CGI-S score was 4.6 (0.8). Investigator-rated CGI-I scores at end point showed that

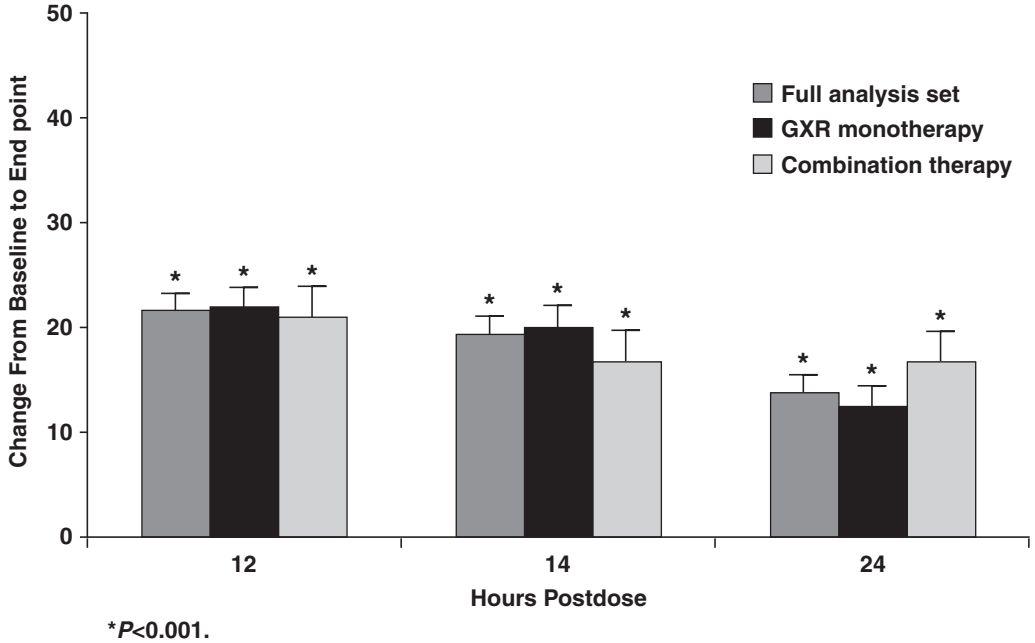

FIG. 6. CPRS-R total score change postdose * (full analysis set). Statistically significant ($p < 0.001$) mean improvement was achieved at 12, 14, and 24 hours postdose in the full analysis set, the GXR monotherapy subgroup, and the combination therapy subgroup, indicating a 24-hour duration of efficacy at these doses. GXR = guanfacine extended release; CPRS-R = Conners' Parent Rating Scale–Revised short form.

investigators rated the majority of subjects very much improved (29.3%) or much improved (28.8%). Using notes regarding their child's behavior from the last weekend day prior to visit 0 (the baseline visit for the open-label extension study), parent-rated scores at end point for the PGA were in close agreement with the investigator-rated CGI-I. For the PGA, 126 of 211 (59.7%) of subjects were rated as very much or much improved at end point.

Mean changes in CHQ-PF50 Physical Summary Scores from baseline to end point were not statistically significant. On the other hand, CHQ-PF50 Psychosocial Summary Scores demonstrated statistically significant improvement from baseline to end point for the overall full analysis set (9.2 [SD 11.9], $p < 0.001$).

Discussion

Guanfacine is an α_{2A}-adrenoreceptor agonist that is believed to improve cognition via selective action in the prefrontal cortex (Arnsten et al. 1988; Uhlén et al. 1991). Short-acting immediate-release formulations of guanfacine have been used to treat symptoms of ADHD (Scahill et al. 2001). More recently, GXR has been evaluated as monotherapy for ADHD in short-term, double-blind, controlled clinical trials (Biederman et al. 2008; Sallee et al. 2008). In each of these studies, GXR has demonstrated significant improvement in primary and secondary efficacy outcomes (Biederman et al. 2008; Sallee et al. 2008). The treatment effect sizes in the short-term controlled trial that served as one of the antecedent studies for the present study ranged from 0.41 for the 0.01- to 0.04-mg/kg weight-adjusted actual dose group to 0.89 for the 0.13- to 0.16-mg/kg group (Sallee et al. 2008).

This 2-year open-label study assessed the long-term safety and efficacy of GXR, and the overall results are consistent with findings from the short-term, blinded studies. The majority of TEAEs were mild to moderate in severity, including the majority of events that led to discontinuation. Regarding the overall dropout rate of approximately 77%, it is important to note that only 12% of subjects discontinued due to TEAEs and 10% due to lack of efficacy. Hypotension was an uncommon TEAE and was reported by only 5% of patients during the 2-year study. Syncope was not reported in either of the antecedent studies but was reported by 5 patients (1.9%) in the current study (Biederman et al. 2008; Sallee et al. 2008). Although judged as possibly or probably related to study medication, these episodes of syncope were associated with confounding circumstances, such as hot weather, dehydration, and prolonged standing. In one case, the subject reported a history of "black-out spells" and lightheadedness prior to use of study drug. Mean weight gain from baseline of the antecedent study to end point was 15.4 pounds, which is expected for this study population of growing children and adolescents, followed for up to 24 months, and the mean increase in height over the course of the study was 2.7 inches.

Most somnolence, sedation, or fatigue events were mild or moderate, occurred in the first few weeks of treatment, did not lead to premature discontinuation, and resolved during the study. The median onset was within the first 3 weeks, with a median duration lasting 44 days. However, the duration of the event was determined by the total number of days between the first and last reports of the event, and therefore may include days during which the event did not occur. Of the 31 subjects who discontinued the study because of a TEAE, 10 were associated with a somnolence, sedation, or fatigue event. Although this study was not designed to compare monotherapy with combination therapy, the rate of somnolence, sedation, or fatigue events was numerically lower in the psychostimulant co-therapy group, whereas irritability and decreased appetite occurred more frequently in the psychostimulant co-therapy group. There were no obvious trends in vital sign changes, with modest overall changes in pulse rate and blood pressure measures and no serious ECG abnormalities reported, although 15 subjects exhibited bradycardia (heart rate $\leq$50 bpm).

As an open-label extension study, this study was not designed to detect differences between GXR monotherapy and psychostimulant co-therapy. Keeping this caveat in mind, the incidences of TEAEs in the monotherapy group and combination therapy group were reasonably similar. As described previously and shown in Table 2, the lists of the most frequently occurring TEAEs were similar between the overall group and the monotherapy group. On the basis of the low rate of discontinuations due to TEAEs and the low incidence of severe or serious AEs, combination therapy with stimulants and GXR appeared generally to be safe.

Efficacy measures were secondary outcomes due to the design of this open-label study. Efficacy outcome measures included clinician and parent ratings. The main efficacy measure was the mean change in ADHD-RS-IV total score from baseline of the antecedent study to end point of the open-label extension study. Baseline symptom scores and clinician ratings indicated subjects enrolled in the study had moderate to severe ADHD. Statistically and clinically significant improvements were noted in ADHD-RS-IV total scores overall for each GXR dose group, whether or not GXR was given alone or in combination with psychostimulants. The mean ADHD-RS-IV score at end point was 18.1 for the overall group, 19.4 in the monotherapy group, and 13.2 in subjects co-administered psychostimulants, bringing the mean score of subjects in the combination therapy group below the criterion that has been suggested as indicating remission (ADHD-RS-IV score <18), and the mean score in the monotherapy group close to remission as well (McIntyre et al. 2006; Steele et al. 2006).

The effects of GXR therapy were early and long lasting. ADHD-RS-IV score improvements were noted at the first postbaseline evaluation point and were sustained throughout the study through end point. The results from CPRS-R scores at multiple times throughout the day demonstrated that GXR treatment is durable, in most cases lasting up to 24 hours past the previous dose. Symptom improvement was evaluated consistently based on clinician- and parent-rated scales. More than half of the subjects were rated as very much or much improved at end point by clinician ratings using the CGI-I scale. Similar results were obtained by parent ratings using the PGA scale. CHQ-PF50 scores demonstrated significant improvement in psychosocial functioning during the study.

Interpretation of these findings must consider the open-label and uncontrolled nature of the study design. While long-term data are essential to understanding the effect of a medication, long-term placebo-controlled studies are often not possible from an ethical perspective. In addition, a substantial percentage of subjects (27.9%) withdrew consent over the course of the 2-year study, such that it is unknown if they

withdrew due to a perceived lack of efficacy or due to other considerations, given the length of the study. Nonetheless, it is encouraging that the findings of this study are consistent with shorter-term controlled studies demonstrating the safety and efficacy of GXR.

Although the study was not designed to make direct comparisons between GXR monotherapy and combination therapy with psychostimulants, a few reasoned thoughts on the outcomes can be made. The vast majority of the study subjects received GXR as monotherapy; as such, overall results reported for the entire study population are indicative of the safety and efficacy of GXR monotherapy for the treatment of ADHD. Indeed, most comparisons of data between the overall group and the GXR monotherapy subgroup show a high level of similarity. Overall, these data support that GXR monotherapy is safe and effective for treating ADHD. In the population of subjects receiving GXR with psychostimulant co-therapy, statistically and clinically significant efficacy was observed and no exceptional safety issues were noted over the course of this 2-year study.

The results from the current study demonstrate the long-term safety and efficacy of GXR used to treat symptoms of ADHD in children and adolescents over the course of 24 months. Additional, more rigorously controlled evaluations comparing GXR monotherapy and co-administration with stimulants may be warranted.

Disclosures

Dr. Sallee is a grant awardee of Shire Development Inc. and Bristol-Myers Squibb Company, and is a consultant for Otsuka America Pharmaceutical, Inc., Merck, P2D Inc., and Shire Development Inc. He serves on the speakers bureau of Takeda Pharmaceuticals North America, Inc., Jazz Pharmaceuticals, and Pfizer Inc. He is on the board of directors for P2D, Inc., and is founder and principal in Satiety Solutions, LLC. Mr. Lyne is a full-time employee of Shire Pharmaceutical Development Ltd, Basingstoke, UK. Dr. Wigal has or has had financial relationships with Celltech Pharmaceuticals Inc/UCB, Cephalon Inc., Eli Lilly and Company, McNeil Pharmaceutical, Novartis Pharmaceuticals Corporation, and Shire Development Inc. Dr. McGough has received research support and has served as consultant for Shire Development Inc., Janssen Pharmaceutical, Eli Lilly and Company, and Novartis Pharmaceuticals Corporation.

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Long-Term Safety and Efficacy of Guanfacine Extended Release in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder

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Abstract

Objective: Short-term, controlled studies of extended-release guanfacine (GXR), a selective α_{2A}-adrenoreceptor agonist, demonstrate efficacy in treating attention-deficit/hyperactivity disorder (ADHD) symptoms as monotherapy. This 2-year open-label study was conducted to further assess the long-term safety and efficacy of GXR.
Methods: Study participants, aged 6–17 years with ADHD, had previously been exposed to GXR therapy alone or in combination with psychostimulants in one of two antecedent trials. In this study, doses were titrated to 1, 2, 3, or 4 mg/day of GXR alone or in combination with a psychostimulant. Safety and efficacy data collected at clinic visits over 24 months provided further evidence of the overall safety and efficacy of GXR for treating ADHD.
Results: The majority of adverse events (AEs) were mild to moderate, and few patients discontinued the study because of an AE. Efficacy measures demonstrated significant improvement beginning in the first month and lasting through the end of the 24-month treatment period. Throughout the entire 2-year study, 202 subjects (77.1%) discontinued and 60 (22.9%) completed the study.
Conclusions: Overall, these data support that GXR monotherapy is generally safe and effective for treating ADHD.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is characterized in children by developmentally inappropriate behaviors, including inattention, hyperactivity, and impulsivity. These behaviors may manifest as impairment in school performance, intellectual functioning, and social skills, among others (Brown et al. 2001; Biederman and Faraone 2005). In addition, an ADHD diagnosis can predict clinically meaningful risks for co-morbidity with other psychiatric disorders and for substance abuse, which can further complicate effective treatment (Brown et al. 2001; Olfson 2004; Biederman and Faraone 2005).

Stimulants, including methylphenidate and amphetamines, have been the primary treatment for ADHD for many decades (Olfson 2004; Biederman and Faraone 2005). However, there remains a need for effective nonstimulant treatment options for patients who may need a combined approach to treatment, who either have a suboptimal response to or cannot tolerate stimulant medications, or who prefer a nonstimulant. Although substantial research supports the efficacy and overall safety of stimulants in treating the symptoms of ADHD, approximately 30% of patients experience inadequate symptom relief and/or the development of treatment-limiting side effects (Scahill et al. 2001; Biederman et al. 2008). Nonstimulant medications can be used in place of stimulants in patients who do not adequately respond to or cannot tolerate stimulants, or when either the patient or the parent prefers alternatives to stimulant treatment (Olfson 2004; Biederman and Faraone 2005). Alternatively, nonstimulant medications may be combined with stimulants when response is suboptimal, or as a means to achieve and balance adequate symptom response and the emergence of dose-limiting side effects, or to treat co-morbid disorders (Biederman and Faraone 2005; Adler et al. 2006; Pliszka et al. 2006). Current clinical guidelines recommend monotherapy with stimulants or atomoxetine as first-line pharmacologic treatments for ADHD (Pliszka et al. 2006; American Academy of Child and Adolescent Psychiatry 2007). However, despite limited data from controlled trials and the lack of approval by

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the U.S. Food and Drug Administration (FDA), combination pharmacotherapy is fairly common in clinical practice in this population (Adler et al. 2006).

In the past, case-level data have raised safety concerns regarding certain combinations, for instance, the combination of clonidine and methylphenidate (Popper 1995; Swanson et al. 1995), although a later assessment of those cases concluded that they do not provide substantial support of an adverse interaction between the two drugs (Fenichel 1995). A more recent study also found no evidence of differences between the effects of clonidine and methylphenidate when given together compared with either agent given alone on electrocardiogram (ECG) measures or overall rates of AEs (Daviss et al. 2008).

Guanfacine is a selective α_{2A}-adrenoreceptor agonist that is believed to improve cognition via action in the prefrontal cortex (Arnsten et al. 1988; Uhlén et al. 1991; Arnsten et al. 1996). Recent data have shown that stimulation of the α_{2A}-adrenoreceptor, in the prefrontal cortex, as occurs with guanfacine, results in a strengthening of cortical networks (Wang et al. 2007). Clonidine, another α_2-adrenoreceptor agonist, has been shown to be effective in reducing symptoms of ADHD when measured by some scales (e.g., the Conners' Abbreviated Symptom Questionnaire for Parents, the Children's Global Assessment Scale) but not by others (e.g., the Conners' Teachers' Abbreviated Symptom Questionnaire) (Connor et al. 1999; Connor et al. 2000; Hazell et al. 2003; Palumbo et al. 2008). Studies have shown that guanfacine, in comparison with clonidine, is less likely to produce sedation or hypotension, possibly due to a greater selectivity for the α_{2A}-adrenoreceptor subtype (Arnsten et al. 1988; Uhlén et al. 1991; Newcorn et al. 1998).

Immediate-release guanfacine was shown in small studies to be effective in reducing ADHD symptoms (Chappell et al. 1995; Hunt et al. 1995; Scahill et al. 2001). An extended-release formulation of guanfacine (GXR) (SPD503, Shire Development Inc., Wayne, PA) is in development, with the goal of significantly reducing peak-to-trough fluctuations, thus potentially improving the safety profile while maintaining therapeutic drug levels. Furthermore, the extended-release formulation permits once-daily dosing. Randomized, double-blind, placebo-controlled short-term studies have demonstrated the efficacy of GXR monotherapy for treating symptoms of ADHD (Biederman et al. 2008; Sallee et al. 2008).

The goal of this study was to further evaluate the long-term safety and efficacy of GXR as monotherapy or in combination with psychostimulants in children and adolescents aged 6–17 years with ADHD.

Methods

Study design and eligibility

This multicenter, open-label study (SPD503-305) was conducted in 48 U.S. centers from June, 2004, to December, 2006, and was designed to assess the safety of GXR treatment for up to 24 months in children and adolescents aged 6–17 years with ADHD. All subjects signed informed consent/assent after a full explanation of study requirements following procedures approved by each participating site's respective Institutional Review Board. Subjects enrolled in this study were previously exposed to GXR in either of 2 antecedent trials (SPD503-205 or SPD503-304), as shown in Fig. 1. Clinical study SPD503-205 (study 1) was a phase 2 open-label, uncontrolled 9-week study to assess the safety of co-administration of GXR with psychostimulants to children and adolescents with ADHD (Clinical Trial NCT00151996) (Spencer et al. 2008). SPD503-304 (study 2) was a phase 3 multicenter, double-blind, dose-ranging, forced-dose titration, 16-week pivotal trial to assess the efficacy and safety of GXR versus placebo for treatment of ADHD in children and adolescents (Clinical Trial NCT00150618) (Sallee et al. 2008).

Subjects were eligible for the present study if they satisfied all entry criteria and completed all visits up through visit 9 in either of the antecedent trials, or had withdrawn from study 2 due to lack of efficacy after visit 4. Furthermore, subjects could not be experiencing any adverse events (AEs) that would preclude further exposure to GXR. Subjects from study 1 had to weigh >65 pounds; subjects from study 2 had to weigh >55 pounds. Nonpregnant subjects of child-bearing potential agreed to comply with applicable contraceptive measures. Written, informed consent was obtained from all subjects' parents or legally authorized representatives. Documentation of the subject's assent was also attained, indicating that the subject was aware of the investigational nature of the study and the required procedures and restrictions. Exclusion criteria included uncontrolled co-morbid psychiatric diagnosis (except oppositional defiant disorder) with significant symptoms, a body mass index of $\geq$35, a specific cardiac condition or family history deemed unsafe for continuation in the study, orthostatic hypotension or hypertension measurements outside the 95th percentile for age, weight, and gender, or other clinically significant laboratory abnormalities. Further exclusion criteria included concurrent use of medications that would affect blood pressure or heart rate, or a positive urine drug test with the exception of psychostimulant drug for those subjects from study 1 who chose to continue receiving their psychostimulant in the current study.

Dosing

Subjects received GXR once daily at a dosage of 1, 2, 3, or 4 mg. All subjects were tapered off study medication from the antecedent trial, began the present study at a titration dose of 1 mg/day, and were titrated to their optimal dose by 1 mg/day increments at weekly intervals during the first 4 weeks of the study. Optimal dose was defined as a clinically significant reduction in ADHD symptoms with minimal side effects. As a general rule, subjects were considered optimized if, after having at least a 30% reduction from baseline in ADHD Rating Scale Version IV (ADHD-RS-IV) total symptom scores, they were considered to have reached their optimum dose in the opinion of the clinician. Subjects who had not achieved at least a 30% reduction in ADHD-RS-IV total symptom scores were escalated to a higher dose level if judged appropriate by the investigator based on clinical experience.

Subjects were maintained at their optimal dose throughout the remainder of the study (until month 24) when GXR was tapered off by 1-mg/day decrements at weekly intervals. Subjects who previously participated in study 1 could receive GXR as monotherapy or co-administered with their same psychostimulant medication (amphetamine or methylpheni-

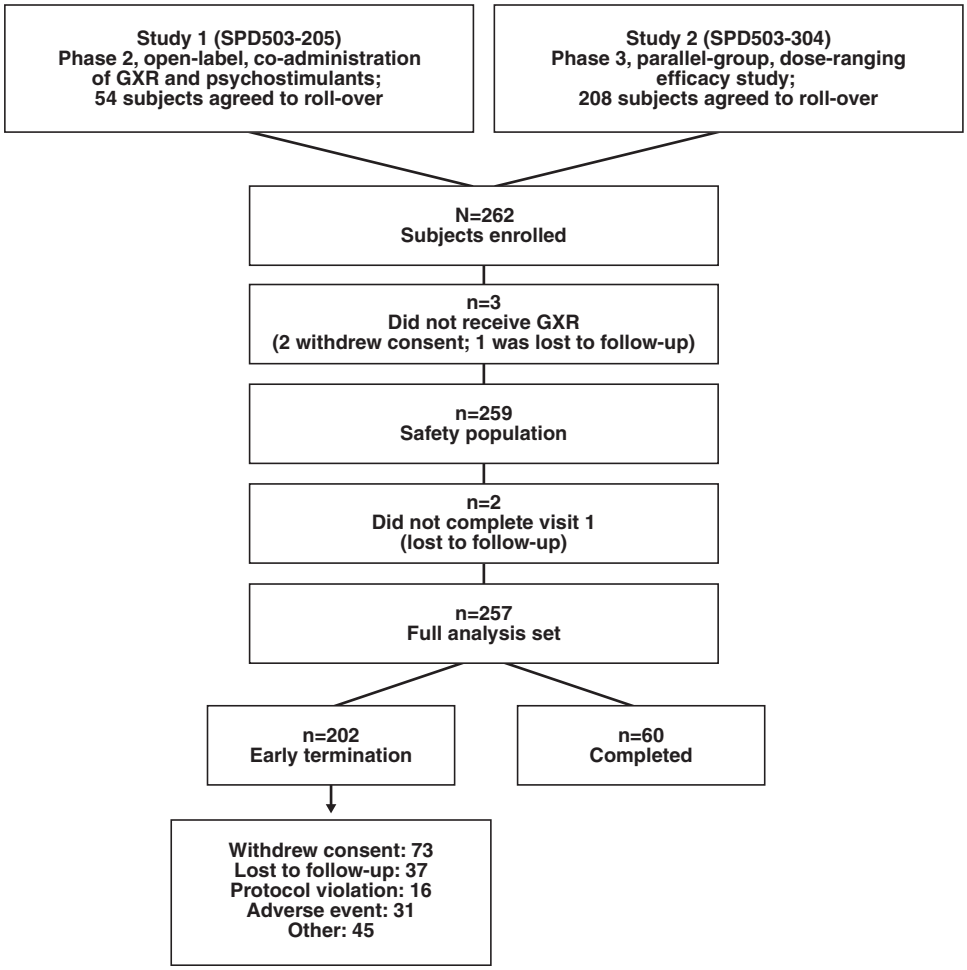

FIG. 1. Subject disposition. GXR = guanfacine extended release.

date). Investigators could adjust the dosage of GXR or psychostimulant for efficacy throughout the 24-month open-label investigation.

Study populations and evaluations

There were 32 planned clinic visits and a follow-up phone contact over the 25-month duration of the study. At visit 0, inclusion and exclusion criteria were reviewed to ensure that all subjects continued to meet eligibility criteria. Safety analysis was performed on the safety population, which was composed of all enrolled subjects ($N = 262$) except 3 subjects, who did not receive study medication ($n = 259$); of those 3 subjects, 2 withdrew consent and 1 was lost to follow up. Additional analyses of safety data were performed separately on the monotherapy subgroup ($n = 206$) and the psychostimulant co-administration subgroup ($n = 53$); however, this study was neither designed nor powered to evaluate differences between the subgroups, and these subgroups were not randomized but rather reflect enrollments from two different antecedent studies. The main efficacy analysis was conducted on the full analysis set, which included all subjects with an efficacy assessment from baseline in the antecedent study and at least one primary efficacy measurement recorded after the baseline of the current study ($n = 257$).

Safety

Safety was assessed via AE reports, vital signs, height and weight measurements, laboratory tests, physical examinations, ECGs, concomitant medications, the Pediatric Daytime Sleepiness Scale (PDSS), and evaluation of early discontinuation data. Descriptive statistics were used for the PDSS and clinical laboratory tests. Qualitative analysis for abnormalities of laboratory tests was performed using the shift-table method, which analyzed the shift from baseline values of the antecedent studies to end-of-treatment values in the number and percentage of subjects with normal and abnormal findings.

Diastolic blood pressure (DBP) and systolic blood pressure (SBP), pulse, and results from physical examinations were summarized descriptively. Vital sign outlier limits included pulse measurements of $\leq$50 or $\geq$100 beats per minute (bpm), postural orthostatic DBP decrease $\geq$15 mmHg or SBP decrease of $\geq$30 mmHg, seated SBP of $<$90 or $>$120 mmHg for 6 to 12 year olds and $<$100 or $>$140 mmHg for 13 to 17 year olds, or a seated DBP of $<$50 or $>$80 mmHg for 6 to 12 year olds and $<$60 or $>$90 mmHg for 13 to 17 year olds. ECGs were conducted at the baseline of the antecedent study, the baseline of the open-label extension study, and visits 6, 9, 12, 15, 21, and at follow up (visit 31). ECG outlier criteria were defined as follows: heart rate $\leq$50 bpm or $\geq$100 bpm, PR interval

≥200 msec, QT interval ≥480 msec, QRS interval ≥120 msec, QTcF ≥500 msec, QTcB ≥500 msec, and QTcF and QTcB change from baseline of the antecedent study of ≥30 msec to <60 msec or ≥60 msec. PDSS data were collected at every visit except for visits 31 and 32. For the safety analyses presented here, comparisons were made using baseline values from the antecedent studies.

Efficacy

The main efficacy measure was the ADHD-RS-IV total score collected at each monthly visit and the main efficacy outcome was the ADHD-RS-IV total score change from the baseline of the antecedent study at end point. The ADHD-RS-IV was developed to measure the behavior of children with ADHD and consists of 18 items, each scored from 0 (no symptoms) to 3 (severe symptoms). The total score ranges from 0 to 54. End point was defined as the last nonmissing valid assessment after baseline of the open-label extension study while the subject was on study drug. The analysis of the end point is thus numerically equivalent to the analysis of the last observation carried forward. The ADHD-RS-IV actual score and change from the baseline of the antecedent study in the full analysis set were evaluated overall, by therapy group (i.e., monotherapy and psychostimulant coadministration), by age group (6–12 and 13–17 years of age), and by actual dose and weight-adjusted actual dose prior to dose tapering at the end of the study.

Secondary efficacy measures included the investigator-rated Clinical Global Impressions of Improvement (CGI-I), the Parent Global Assessment (PGA) scale, the Child Health Questionnaire–Parent Form 50 (CHQ-PF50), and the Conners' Parent Rating Scale–Revised (CPRS-R) short form. The CGI scale is a global evaluation of baseline symptom severity and improvement over time. At baseline, the investigator used the CGI–Severity (CGI-S) to rate severity of symptoms on a 7-point scale ranging from 1 (no symptoms) to 7 (very severe symptoms). At each visit thereafter, the investigator used the CGI-I to rate the improvement relative to baseline on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). The PGA is a variant of the CGI scales of severity and improvement. For the PGA, the parent/caregiver rated their child's behavior at baseline of the antecedent study and assessed changes in behavior and symptoms relative to these baseline ratings. The CHQ-PF50 is designed to measure physical and psychosocial well being in children aged ≥5 years. Two summary scores were obtained using 14 Core Health Concepts, one score for physical well being and the other for psychosocial well being. GXR duration of effect was monitored via the CPRS-R short form, which assesses a cross section of ADHD-related symptoms and problem behaviors. The CPRS-R was completed by parents and contained four subscales (i.e., oppositional, cognitive problems, hyperactivity, ADHD index). The CPRS-R evaluations were designed to permit an analysis of the duration of effect of GXR throughout the day by assessing scores at 12, 14, and 24 hours postdose. Parents answered 27 questions regarding their child's behavior immediately preceding the assessment times. Analyses of efficacy measures were made relative to baseline of the antecedent study.

Compliance with the study drug was determined by tablet counts. Subjects were requested to return unused study drug at each visit, and those who had taken 80–120% of their prescribed amount were considered compliant. Statistical analysis was performed using SAS® version 9.1. Because this was an open-label extension study, a power analysis was not performed.

Results

Subject disposition and demographics

As shown in Fig. 1, a total of 262 eligible subjects from the antecedent studies enrolled in the current study: 54 from study 1 (psychostimulant co-administration) and 208 from study 2 (GXR monotherapy). The full analysis comprised 257 subjects who received the drug and had at least one

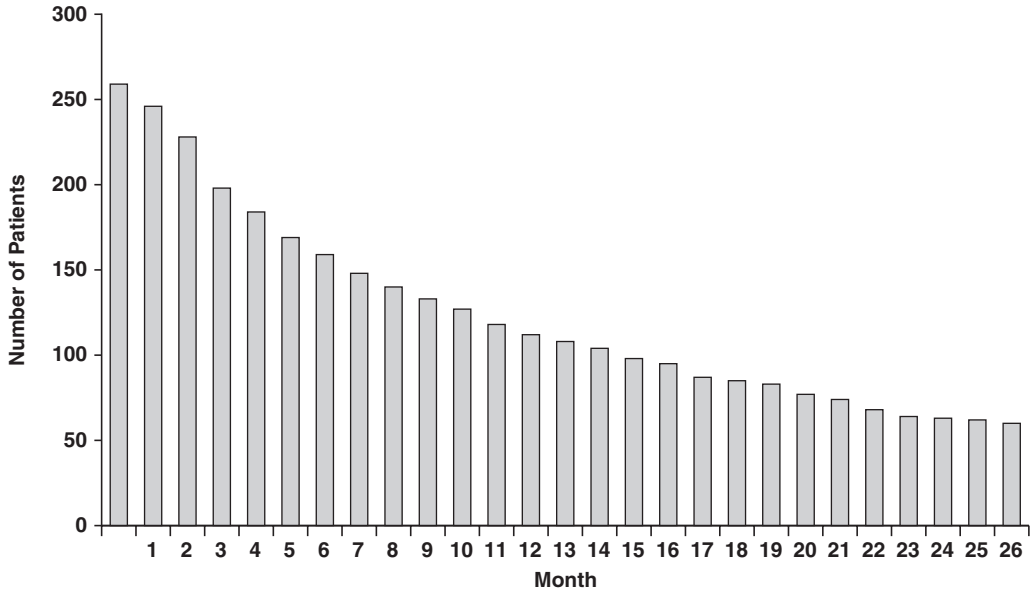

FIG. 2. Number of patients remaining in study by month.

primary efficacy measurement after the baseline of the open-label extension study. Throughout the entire 2-year study, 202 subjects (77.1%) discontinued and 60 (22.9%) completed the study (Fig. 2). The most common reason for early discontinuation was withdrawal of consent ($n = 73$, 27.9%). Over the 24-month treatment period, only 27 subjects (10.3%) terminated early due to lack of efficacy.

Early discontinuation occurred in 171 of 208 (82.2%) subjects in the monotherapy subgroup and 31 of 54 subjects (57.4%) receiving a co-administered psychostimulant. Withdrawal of consent was the most frequent reason for discontinuation in both subgroups. Other reasons for early termination in at least 10% of subjects in the monotherapy subgroup were lost to follow up (13.5%; 28 of 208 subjects), AE (13.5%; 28 of 208 subjects), or lack of efficacy (12.5%; 26 of 208 subjects). In the combination therapy subgroup, 16.7% of subjects (9 of 54) were lost to follow up, 5.6% of subjects (3 of 54) discontinued due to AEs, and 1.9% of subjects (1 of 54) discontinued due to lack of efficacy.

Subject demographics are shown in Table 1. The majority of subjects had the ADHD combined subtype (73.0%). Overall mean (standard deviation [SD]) years since diagnosis was 2.5 (2.9), although the mean time since diagnosis was 4.0 years (2.6 years) in the group of 53 subjects who received co-administered psychostimulants. The mean (SD) ADHD-RS-IV total symptom score at baseline of the antecedent study was 38.3 (10.1). Overall, mean symptom scores were similar across the 1, 2, 3, and 4 mg/day GXR dose groups. However, although significance testing was not performed, the mean total symptom score at baseline was numerically higher in the GXR monotherapy subgroup (40.6, SD 8.5) compared with the psychostimulant co-therapy subgroup (29.3, SD 10.9).

Table 1. Subject Demographics

Characteristics	*Overall* (n = *259*)	*Monotherapy* (n = *206*)	*Co-administered psychostimulants* (n = *53*)
Age (years)			
Mean (SD)	10.7 (2.6)	10.6 (2.7)	11.2 (1.8)
Median	10.0	10.0	11.0
Min, max	6, 17	6, 17	7, 15
Age category, *n* (%)			
6–12 years	191 (73.7)	151 (73.3)	40 (75.5)
≥13 years	68 (26.3)	55 (26.7)	13 (24.5)
Gender, *n* (%)			
Male	188 (72.6)	148 (71.8)	40 (75.5)
Female	71 (27.4)	58 (28.2)	13 (24.5)
Ethnic origin, *n* (%)			
White	180 (69.5)	142 (68.9)	38 (71.7)
Black	39 (15.1)	30 (14.6)	9 (17.0)
Hispanic	25 (9.7)	20 (9.7)	5 (9.4)
Asian or Pacific Islander	8 (3.1)	7 (3.4)	1 (1.9)
Other	7 (2.7)	7 (3.4)	0
Weight (pounds)			
Mean (SD)	96.6 (33.2)	95.4 (34.0)	101.2 (29.8)
Median	90.0	88.0	95.0
Min, max	55, 237	55, 237	61, 180
Height (inches)			
Mean (SD)	57.5 (5.7)	57.1 (5.9)	59.2 (4.4)
Median	58.0	57.40	60.0
Min, max	40.7, 71.3	40.7, 71.3	52, 70.3
ADHD subtype, *n* (%)			
Inattentive	62 (23.9)	51 (24.8)	11 (20.8)
Hyperactive	8 (3.1)	5 (2.4)	3 (5.7)
Combined	189 (73.0)	150 (72.8)	39 (73.6)
Years since ADHD diagnosis			
Mean (SD)	2.5 (2.9)	2.2 (2.8)	4.0 (2.6)
Median	1.6	0.8	4.0
Min, max	0, 12.2	0, 12.2	0, 10.1
Mean (SD total symptom score at baseline)	38.3 (10.1)	40.6 (8.5)	29.3 (10.9)

SD = Standard deviation; ADHD = attention-deficit/hyperactivity disorder.

Safety: Adverse events

Treatment-emergent AEs (TEAEs) were reported by 87.3% of subjects overall. TEAEs were reported in 87.4% of subjects in the monotherapy subgroup and 86.8% of subjects in the combination therapy subgroup. Over the long-term treatment period, discontinuations due to TEAEs occurred in 12.0% of subjects (31 of 259 subjects) in the overall safety population, 13.6% (28 of 206) subjects in the monotherapy subgroup, and 5.7% (3 of 53) subjects in the combined therapy subgroup. The majority of AEs leading to discontinuations were mild to moderate in intensity.

According to investigators, 73.4% of overall TEAEs were considered possibly or probably related to study medication. The incidence of possibly/probably related TEAEs was 77.2% in the monotherapy subgroup and 58.5% in the combined therapy subgroup. Twenty-two treatment-emergent serious AEs occurred in 16 (6.2%) subjects in the safety population. As discussed in further detail below, 5 of these subjects reported syncope. The next most common treatment-emergent serious AEs were head injury, loss of consciousness, and suicidal ideation, all of which were reported by 2 subjects each. Twenty-one of the 22 serious AEs resolved and one remains unknown because the patient was lost to follow up. Thirteen of the serious AEs were judged not related to study medication by investigators. Severe TEAEs were reported in 21 of 259 (8.1%) subjects overall, 9.2% of subjects in the monotherapy subgroup, and 3.8% of subjects in the combination therapy subgroup.

The most commonly reported TEAEs are shown in Table 2. Although not among the most common TEAEs, hypotension was reported in 13 subjects (5.0%), decreased DBP was found in 9 subjects (3.5%), decreased blood pressure in 7 subjects (2.7%), and decreased SBP in 6 subjects (2.3%) of the safety population. Three of the subjects who had decreased SBP also had decreased DBP. The most common TEAEs were similar in the GXR monotherapy subgroup relative to the overall group (Table 2). Decreased appetite (13.2%), irritability (13.2%), and pharyngitis (11.3%) were among the most common TEAEs that differed in the subgroup co-administered psychostimulants relative to monotherapy or the overall safety population (Table 2).

Safety:Syncope

Five subjects (all from the monotherapy subgroup) reported syncope. All syncopal events were deemed serious adverse events (SAEs) and were considered by the investigators possibly or probably related to study medication. All of the episodes were brief and resolved. Confounding factors may have been associated with at least some episodes of syncope. In one case, a female subject reported a history of "black-out spells" and lightheadedness prior to use of study drug. At the time of the syncopal event, she had not yet eaten breakfast or taken her daily dose of GXR. At the time of this event, the subject also had a mild fever and moderate dehydration. She had also experienced vomiting, diarrhea, and gastroenteritis the day before the event. In another instance, the syncopal event occurred while the subject was at church. Subsequently, there were additional reports of other people fainting at the church, possibly related to the heat. Another subject felt dizzy and fainted while playing soccer on a 90-degree day. The syncopal episode resolved the same day without medical treatment. The fourth subject who experienced syncope had taken her daily dose of GXR 10 minutes after awakening and on an empty stomach. The subject fainted a few minutes later during an argument with her father. The syncope resolved the same day without treatment. In the remaining case of syncope, the subject fainted after standing for an extended length of time. The investigator judged that the event was related to both dehydration and prolonged standing.

Safety: Somnolence, sedation, or fatigue events

The incidence of somnolence, sedation, or fatigue events is summarized in Fig. 3. The majority of somnolence, sedation, or fatigue events were moderate or mild in severity and resolved by end of treatment. The median day of onset for a somnolence, sedation, or fatigue event was within the first 3 weeks of treatment (17 days). Figure 4 depicts the overall incidence and severity of somnolence, sedation, or fatigue events over the course of the study. The frequency of som-

Table 2. Most Common Treatment Emergent Adverse Events Occurring in ≥10% of the Safety Population of Each Therapy Subgroup

Adverse event	*Safety population,* N = *259,* n *(%)*	*Monotherapy,* n = *206,* n *(%)*	*Psychostimulant co-therapy,* n = *53,* n *(%)*
Somnolence	79 (30.5)	78 (37.9)	—
Headache	63 (24.3)	51 (24.8)	12 (22.6)
Upper respiratory tract infection	46 (17.8)	33 (16.0)	13 (24.5)
Nasopharyngitis	37 (14.3)	29 (14.1)	8 (15.1)
Fatigue	36 (13.9)	31 (15.0)	—
Upper abdominal pain	33 (12.7)	25 (12.1)	8 (15.1)
Sedation	29 (11.2)	26 (12.6)	—
Pharyngitis	—	—	6 (11.3)
Decreased appetite	—	—	7 (13.2)
Irritability	—	—	7 (13.2)

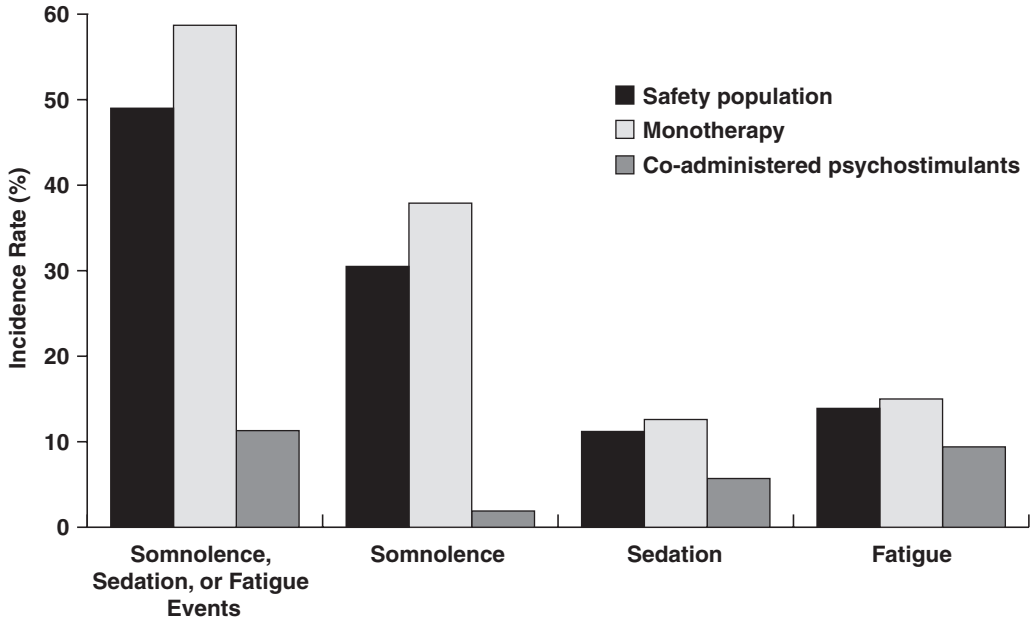

FIG. 3. Incidence of treatment-emergent somnolence, sedation, or fatigue events (safety population). Somnolence, sedation, or fatigue events were reported by 49% (127 of 259) of subjects in the safety population, 58.7% of subjects (121 of 206) administered monotherapy and 11.3% of subjects (6 of 53) administered guanfacine extended release with a psychostimulant.

nolence, sedation, or fatigue events steadily declined during the first 6 months of treatment from 37.8% to 15.8% and remained below 15.8% for the remainder of the study with the exceptions of visits 13 (15.9%) and 14 (17.1%).

Safety:Vital signs

There were small changes from baseline to end point in pulse, DBP, and SBP. Over the long-term treatment period, there were no overt trends in vital sign measurements over time or across actual doses at time of assessments. The mean (SD) change in pulse at the end of treatment in the safety population was −0.1 (14.7) bpm and the range of mean changes in the all active treatment group (excluding end point) varied from −3.5 bpm to −0.2 bpm. In the monotherapy subgroup there was a −0.8 (14.7) bpm mean decrease in pulse rate, whereas in the combination therapy subgroup there was a 2.6 (14.4) bpm mean increase.

Overall, there was a mean (SD) increase in SBP of 1.2 (12.4) mmHg at end of treatment, with a range of means in the all active treatment group (excluding end point) of −3.8 mmHg to +4.7 mmHg. At the end of treatment, there was a mean (SD) increase in DBP of 0.9 (10.0) mmHg (range −2.7 to +2.5 mmHg in the all-active group). Mean (SD) changes from baseline of the antecedent study to end point in SBP and DBP were 6.6 (11.3) mmHg and 4.6 (9.9) mmHg.

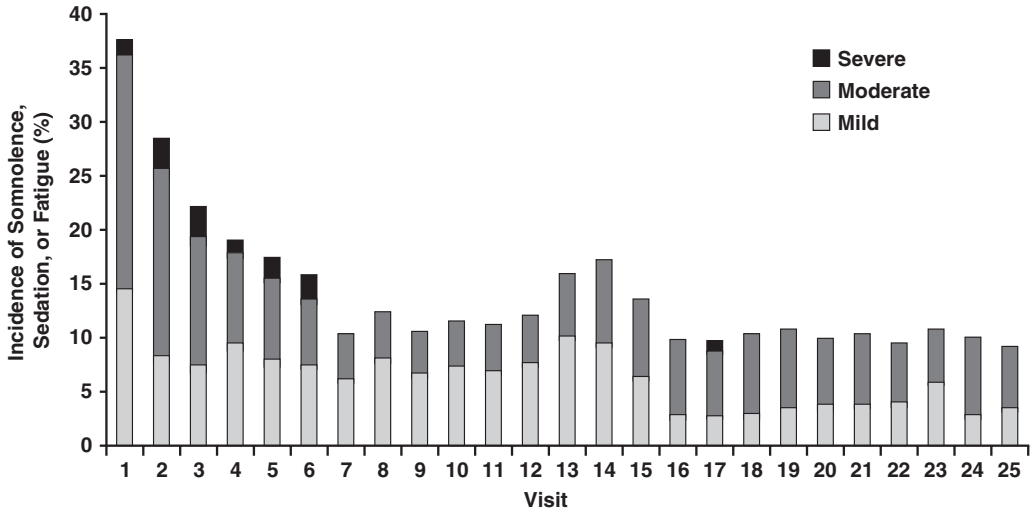

FIG. 4. Incidence of somnolence, sedation, or fatigue by visit (safety population). The frequency of sedative events steadily declined during the first 6 months of treatment and remained near that level throughout most of the study. Visit 25 includes all data after visit 24.

Reports of vital sign outliers from the safety population demonstrated that most pulse outliers were due to pulse increases, and most blood pressure outliers were due to decreases in blood pressure. Pulse rates of <50 bpm were reported in 15 subjects (5.9%) in contrast with 77 subjects (30.1%) of the safety population who demonstrated pulse rates of >100 bpm. SBP measures of <90 mmHg were reported in 46.8% of subjects aged 6–12 years and <100 mmHg in 61.8% of older subjects, aged 13–17 years. In contrast, elevated SBP (>120 mmHg) was reported in 23.9% of the younger subjects and 13.2% of adolescents (>140 mmHg). DBP outliers followed a similar pattern. Decreased DBP (<50 mmHg) was observed in 27.7% of children and in 67.6% of adolescents (<60 mmHg). Conversely, increased DBP of >80 mmHg or >90 mmHg was reported in 16% of 6- to 12-year-old subjects and 5.9% of 13- to 17-year-old subjects, respectively.

Mean weight gain from baseline of the antecedent study to end point was 15.4 pounds.

Only 2.3% (6 of 259 subjects) of subjects experienced increases in weight deemed possibly related or related to study medication. Mean height increase from baseline of the antecedent study to end point was 2.7 inches.

Safety: ECG

No ECG abnormality was considered by investigators as a serious AE. Twenty eight subjects had new, abnormal ECGs at end point; only 2 were considered clinically significant by the investigators. In the first subject, advanced atrioventricular block was initially reported as a serious AE and subsequently changed to a nonserious conduction disorder not otherwise specified (NOS) after further tests and evaluation. The subject's pulse rate and QRS intervals never met outlier criteria during the study, and QTcF intervals never exceeded 366 msec. This subject had shown intraventricular delay on ECGs at baseline of the antecedent study and at baseline of the open-label extension study. This is the only subject to have discontinued the study due to an ECG abnormality. The second subject with a clinically significant ECG displayed sinus bradycardia in month 3. The subject's baseline heart rate was 63 bpm but repeat measures in month 3 showed a heart rate of 45 and 46 bpm, and an end-of-study rate of 76 bpm. The subject did not report any other symptoms at the time of the event.

Further analysis of ECG outlier criteria demonstrated that throughout the duration of the study, no subject had a QRS interval ≥120 msec, a QT interval ≥480 msec, a QTcB or QTcF interval ≥500 msec, or a QTcB or QTcF increase from baseline of ≥60 msec. Thirty subjects had a QTcF change from baseline measure between ≥30 and <60 msec, and the same QTcB change from baseline criterion was met by 21 subjects. A heart rate ≤50 bpm was observed in 15 subjects and an increased heart rate of ≥100 bpm was recorded in 9 subjects.

Efficacy: Main efficacy measure; ADHD-RS-IV scores

Overall mean (SD) ADHD-RS-IV total score at baseline of the antecedent study was 38.3 (10.1). There were no notable differences in baseline (SD) ADHD-RS-IV total scores between dose groups (1 mg, 38.6 [7.3]; 2 mg, 35.8 [10.7]; 3 mg, 38.4 [11.1]; and 4 mg, 39.5 [9.1]). At baseline, the mean (SD) ADHD-RS-IV total score was 29.3 (10.9) for the population of subjects co-administered psychostimulants and 40.6 (8.5) for the monotherapy subgroup.

The mean (SD) ADHD-RS-IV score at end point across all active GXR dose groups was 18.1 (12.4), representing a reduction of more than 50% from the mean baseline score. Mean (SD) changes in ADHD-RS-IV total score from baseline to end point showed statistically significant improvement: overall, −20.1 (13.5) ($p < 0.001$), and for all GXR dose groups, −23.8 (12.3), −22.5 (12.3), −20.0 (14.0), and −18.4 (13.7) for the 1-, 2-, 3-, and 4-mg dose groups, respectively ($p < 0.001$ for each). GXR monotherapy yielded a significant reduction in ADHD-RS-IV mean score (overall group final mean [SD] score was 19.4 [12.9], mean score reduction was −21.2 [13.9], $p < 0.001$), and significant (SD) score reductions were demonstrated in each monotherapy dose group: 1 mg = −24.3 (12.8), 2 mg = −24.3 (11.5), 3 mg = −22.1 (14.2), and 4 mg = −18.0 (14.6); $p < 0.001$ for all. Similarly, in the smaller group of subjects who received psychostimulant co-therapy, the overall ADHD-RS-IV mean [SD] total score also showed a significant reduction from baseline to end point (overall group final mean score was 13.2 [8.5], mean score reduction was −16.1 [11.0], $p < 0.001$). Statistically significant [SD] improvements were seen in the co-therapy subgroups receiving 2, 3, and 4 mg of GXR (−14.4 [12.7], $p = 0.006$; −12.5 [10.2], $p < 0.001$; −19.7 [10.2], $p < 0.001$, respectively). There was a −21.5 (SD 13.4) point mean score reduction observed in the 1 mg GXR combination therapy subgroup; however, statistical significance was not attained, most likely due to the small sample size ($n = 2$) of this group.

GXR therapy elicited early improvement based on a mean (SD) ADHD-RS-IV total score reduction of −15.8 (11.0) achieved for the overall full analysis set at the first assessment after baseline of the open-label extension study (visit 1, week 1) and for each GXR dose group; (1 mg = −19.3 [9.6], 2 mg = −17.2 [10.2], 3 mg = −16.5 [12.1], 4 mg = −13.9 [10.2]). Efficacy was sustained throughout the 24-month study as determined by ADHD-RS-IV scores at each monthly evaluation up to and including end point.

Similar results were obtained when data from the full analysis set were analyzed based on weight-adjusted actual doses. Mean (SD) changes in ADHD-RS-IV total score from baseline to visit 1 were −12.2 (11.8), −16.5 (12.7), and −21.4 (12.4) for the 0.01- to 0.04-mg/kg, 0.05- to 0.08-mg/kg, and 0.09- to 0.12-mg/kg dose groups, respectively. The earliest time point that included subjects in the 0.13- to 0.17-mg/kg dose group was not until the month 1 visit, at which point this dose group demonstrated a −27.7 (9.4) mean (SD) reduction in ADHD-RS-IV total score. At end point, mean ADHD-RS-IV total scores were significantly ($p < 0.001$) reduced from baseline in each weight-adjusted dose group. Mean (SD) changes were −18.9 (12.1) for the 0.01-to 0.04-mg/kg group, −19.8 (14.7) for the 0.05- to 0.08-mg/kg group, −25.5 (14.3) for the 0.09- to 0.12-mg/kg group, and −20.8 (15.5) for the 0.13- to 0.17-mg/kg group. Results from this analysis are shown in Fig. 5.

Efficacy: Additional outcomes (CPRS-R, CGI-I, PGA, and CHQ-PF50)

CPRS-R mean changes from baseline to end point were statistically significant in the overall treatment group (−18.2; $p<0.001$). Similar results were obtained when analyzing the

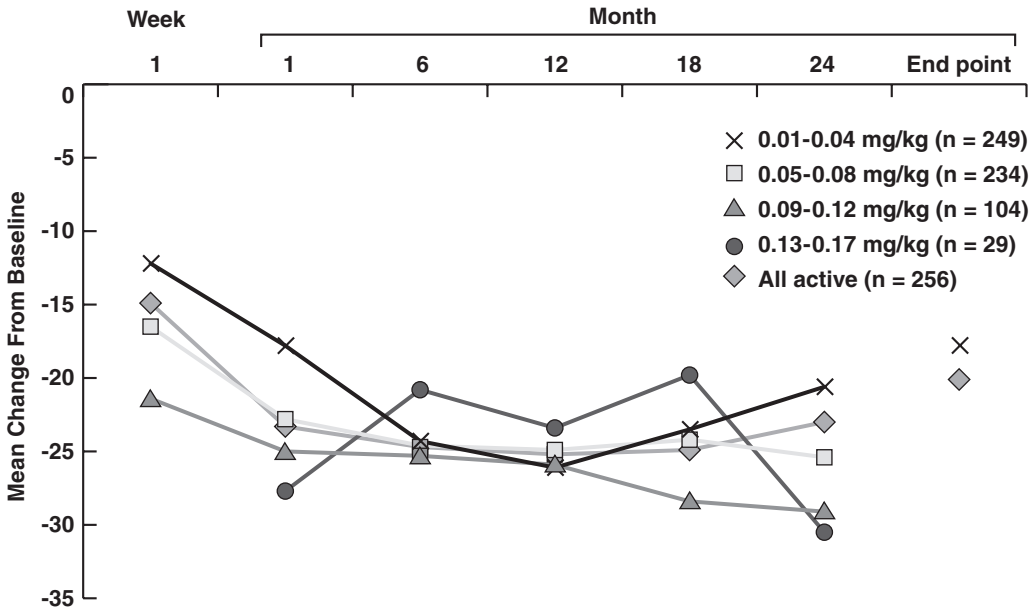

FIG. 5. ADHD-RS-IV total score by weight-adjusted actual dose (full analysis set). The earliest time point that included subjects in the 0.13- to 0.17-mg/kg dose group was the month 1 visit. At end point, mean ADHD-RS-IV total scores were significantly ($p < 0.001$) reduced from baseline in each weight-adjusted dose group. End point is the last valid ADHD-RS-IV total score obtained postbaseline and on treatment. ADHD-RS-IV = Attention-Deficit/Hyperactivity Disorder Rating Scale Version IV.

monotherapy and combination therapy subgroups separately. The overall mean change from baseline demonstrated statistically significant ($p < 0.001$) improvement in CPRS-R scores at each postdose assessment. As shown in Fig. 6, mean improvement from baseline to end point was statistically significant ($p < 0.001$) at each postdose time point in the full analysis set, the GXR monotherapy subgroup, and the combination therapy subgroup.

The overall baseline mean (SD) CGI-S score was 4.6 (0.8). Investigator-rated CGI-I scores at end point showed that

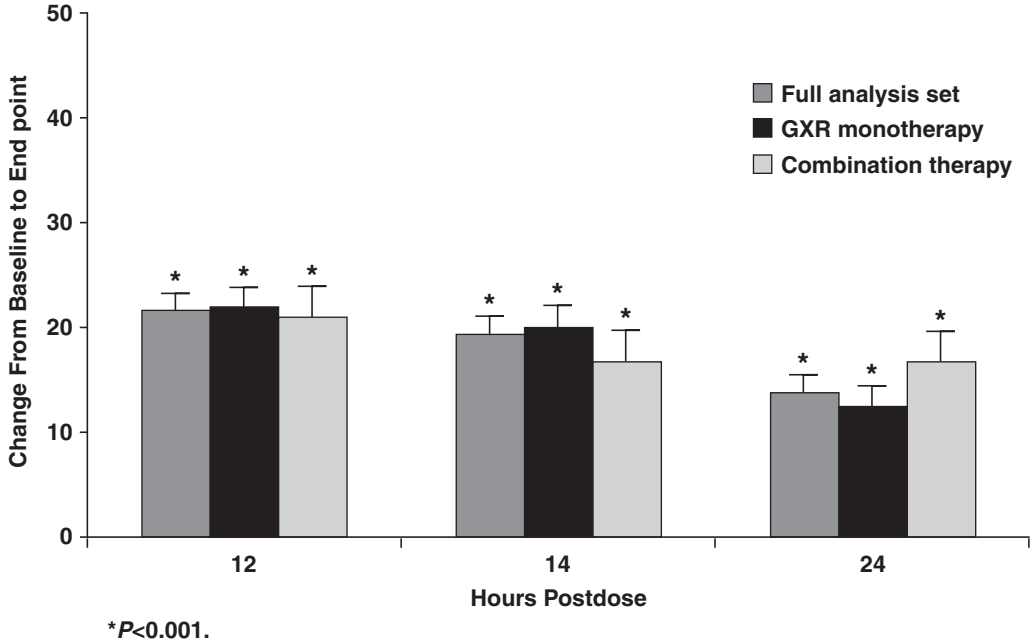

FIG. 6. CPRS-R total score change postdose * (full analysis set). Statistically significant ($p < 0.001$) mean improvement was achieved at 12, 14, and 24 hours postdose in the full analysis set, the GXR monotherapy subgroup, and the combination therapy subgroup, indicating a 24-hour duration of efficacy at these doses. GXR = guanfacine extended release; CPRS-R = Conners' Parent Rating Scale–Revised short form.

investigators rated the majority of subjects very much improved (29.3%) or much improved (28.8%). Using notes regarding their child's behavior from the last weekend day prior to visit 0 (the baseline visit for the open-label extension study), parent-rated scores at end point for the PGA were in close agreement with the investigator-rated CGI-I. For the PGA, 126 of 211 (59.7%) of subjects were rated as very much or much improved at end point.

Mean changes in CHQ-PF50 Physical Summary Scores from baseline to end point were not statistically significant. On the other hand, CHQ-PF50 Psychosocial Summary Scores demonstrated statistically significant improvement from baseline to end point for the overall full analysis set (9.2 [SD 11.9], $p < 0.001$).

Discussion

Guanfacine is an α_{2A}-adrenoreceptor agonist that is believed to improve cognition via selective action in the prefrontal cortex (Arnsten et al. 1988; Uhlén et al. 1991). Short-acting immediate-release formulations of guanfacine have been used to treat symptoms of ADHD (Scahill et al. 2001). More recently, GXR has been evaluated as monotherapy for ADHD in short-term, double-blind, controlled clinical trials (Biederman et al. 2008; Sallee et al. 2008). In each of these studies, GXR has demonstrated significant improvement in primary and secondary efficacy outcomes (Biederman et al. 2008; Sallee et al. 2008). The treatment effect sizes in the short-term controlled trial that served as one of the antecedent studies for the present study ranged from 0.41 for the 0.01- to 0.04-mg/kg weight-adjusted actual dose group to 0.89 for the 0.13- to 0.16-mg/kg group (Sallee et al. 2008).

This 2-year open-label study assessed the long-term safety and efficacy of GXR, and the overall results are consistent with findings from the short-term, blinded studies. The majority of TEAEs were mild to moderate in severity, including the majority of events that led to discontinuation. Regarding the overall dropout rate of approximately 77%, it is important to note that only 12% of subjects discontinued due to TEAEs and 10% due to lack of efficacy. Hypotension was an uncommon TEAE and was reported by only 5% of patients during the 2-year study. Syncope was not reported in either of the antecedent studies but was reported by 5 patients (1.9%) in the current study (Biederman et al. 2008; Sallee et al. 2008). Although judged as possibly or probably related to study medication, these episodes of syncope were associated with confounding circumstances, such as hot weather, dehydration, and prolonged standing. In one case, the subject reported a history of "black-out spells" and lightheadedness prior to use of study drug. Mean weight gain from baseline of the antecedent study to end point was 15.4 pounds, which is expected for this study population of growing children and adolescents, followed for up to 24 months, and the mean increase in height over the course of the study was 2.7 inches.

Most somnolence, sedation, or fatigue events were mild or moderate, occurred in the first few weeks of treatment, did not lead to premature discontinuation, and resolved during the study. The median onset was within the first 3 weeks, with a median duration lasting 44 days. However, the duration of the event was determined by the total number of days between the first and last reports of the event, and therefore may include days during which the event did not occur. Of the 31 subjects who discontinued the study because of a TEAE, 10 were associated with a somnolence, sedation, or fatigue event. Although this study was not designed to compare monotherapy with combination therapy, the rate of somnolence, sedation, or fatigue events was numerically lower in the psychostimulant co-therapy group, whereas irritability and decreased appetite occurred more frequently in the psychostimulant co-therapy group. There were no obvious trends in vital sign changes, with modest overall changes in pulse rate and blood pressure measures and no serious ECG abnormalities reported, although 15 subjects exhibited bradycardia (heart rate $\leq$50 bpm).

As an open-label extension study, this study was not designed to detect differences between GXR monotherapy and psychostimulant co-therapy. Keeping this caveat in mind, the incidences of TEAEs in the monotherapy group and combination therapy group were reasonably similar. As described previously and shown in Table 2, the lists of the most frequently occurring TEAEs were similar between the overall group and the monotherapy group. On the basis of the low rate of discontinuations due to TEAEs and the low incidence of severe or serious AEs, combination therapy with stimulants and GXR appeared generally to be safe.

Efficacy measures were secondary outcomes due to the design of this open-label study. Efficacy outcome measures included clinician and parent ratings. The main efficacy measure was the mean change in ADHD-RS-IV total score from baseline of the antecedent study to end point of the open-label extension study. Baseline symptom scores and clinician ratings indicated subjects enrolled in the study had moderate to severe ADHD. Statistically and clinically significant improvements were noted in ADHD-RS-IV total scores overall for each GXR dose group, whether or not GXR was given alone or in combination with psychostimulants. The mean ADHD-RS-IV score at end point was 18.1 for the overall group, 19.4 in the monotherapy group, and 13.2 in subjects co-administered psychostimulants, bringing the mean score of subjects in the combination therapy group below the criterion that has been suggested as indicating remission (ADHD-RS-IV score <18), and the mean score in the monotherapy group close to remission as well (McIntyre et al. 2006; Steele et al. 2006).

The effects of GXR therapy were early and long lasting. ADHD-RS-IV score improvements were noted at the first postbaseline evaluation point and were sustained throughout the study through end point. The results from CPRS-R scores at multiple times throughout the day demonstrated that GXR treatment is durable, in most cases lasting up to 24 hours past the previous dose. Symptom improvement was evaluated consistently based on clinician- and parent-rated scales. More than half of the subjects were rated as very much or much improved at end point by clinician ratings using the CGI-I scale. Similar results were obtained by parent ratings using the PGA scale. CHQ-PF50 scores demonstrated significant improvement in psychosocial functioning during the study.

Interpretation of these findings must consider the open-label and uncontrolled nature of the study design. While long-term data are essential to understanding the effect of a medication, long-term placebo-controlled studies are often not possible from an ethical perspective. In addition, a substantial percentage of subjects (27.9%) withdrew consent over the course of the 2-year study, such that it is unknown if they

withdrew due to a perceived lack of efficacy or due to other considerations, given the length of the study. Nonetheless, it is encouraging that the findings of this study are consistent with shorter-term controlled studies demonstrating the safety and efficacy of GXR.

Although the study was not designed to make direct comparisons between GXR monotherapy and combination therapy with psychostimulants, a few reasoned thoughts on the outcomes can be made. The vast majority of the study subjects received GXR as monotherapy; as such, overall results reported for the entire study population are indicative of the safety and efficacy of GXR monotherapy for the treatment of ADHD. Indeed, most comparisons of data between the overall group and the GXR monotherapy subgroup show a high level of similarity. Overall, these data support that GXR monotherapy is safe and effective for treating ADHD. In the population of subjects receiving GXR with psychostimulant co-therapy, statistically and clinically significant efficacy was observed and no exceptional safety issues were noted over the course of this 2-year study.

The results from the current study demonstrate the long-term safety and efficacy of GXR used to treat symptoms of ADHD in children and adolescents over the course of 24 months. Additional, more rigorously controlled evaluations comparing GXR monotherapy and co-administration with stimulants may be warranted.

Disclosures

Dr. Sallee is a grant awardee of Shire Development Inc. and Bristol-Myers Squibb Company, and is a consultant for Otsuka America Pharmaceutical, Inc., Merck, P2D Inc., and Shire Development Inc. He serves on the speakers bureau of Takeda Pharmaceuticals North America, Inc., Jazz Pharmaceuticals, and Pfizer Inc. He is on the board of directors for P2D, Inc., and is founder and principal in Satiety Solutions, LLC. Mr. Lyne is a full-time employee of Shire Pharmaceutical Development Ltd, Basingstoke, UK. Dr. Wigal has or has had financial relationships with Celltech Pharmaceuticals Inc/UCB, Cephalon Inc., Eli Lilly and Company, McNeil Pharmaceutical, Novartis Pharmaceuticals Corporation, and Shire Development Inc. Dr. McGough has received research support and has served as consultant for Shire Development Inc., Janssen Pharmaceutical, Eli Lilly and Company, and Novartis Pharmaceuticals Corporation.

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