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Authors:

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Journal:

2012

A Controlled Trial of Extended-Release Guanfacine and Psychostimulants for Attention-Deficit/Hyperactivity Disorder

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Objective: To examine efficacy, tolerability, and safety of guanfacine extended release (GXR; ≤4 mg/d) adjunctive to a long-acting psychostimulant for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents 6 to 17 years of age with suboptimal, but partial, response to psychostimulant alone. **Method:** In this multicenter, 9-week, double-blind, placebo-controlled, dose-optimization study, subjects (N = 461) continued their stable dose of psychostimulant given in the morning and were randomized to receive GXR in the morning (GXR AM), GXR in the evening (GXR PM), or placebo. Efficacy measures included ADHD Rating Scale IV (ADHD-RS-IV) and Clinical Global Impressions of Severity of Illness (CGI-S) and Improvement (CGI-I) scales. Safety measures included adverse events (AEs), vital signs, electrocardiograms, and laboratory evaluations. **Results:** At endpoint, GXR treatment groups showed significantly greater improvement from baseline ADHD-RS-IV total scores compared with placebo plus psychostimulant (GXR AM, $p = .002$; GXR PM, $p < .001$). Significant benefits of GXR treatment versus placebo plus psychostimulant were observed on the CGI-S (GXR AM, $p = .013$; GXR PM, $p < .001$) and CGI-I (GXR AM, $p = .024$; GXR PM, $p = .003$). At endpoint, small mean decreases in pulse, systolic, and diastolic blood pressure were observed in GXR treatment groups versus placebo plus psychostimulant. No new safety signals emerged following administration of GXR with psychostimulants versus psychostimulants alone. Most AEs were mild to moderate in severity. **Conclusions:** Morning or evening GXR administered adjunctively to a psychostimulant showed significantly greater improvement over placebo plus psychostimulant in ADHD symptoms and generated no new safety signals. J. Am. Acad. Child Adolesc. Psychiatry, 2012; 51(1):74–85. Clinical trial registration information—Efficacy and Safety of SPD503 in Combination With Psychostimulants; http://www.clinicaltrials.gov; NCT00734578. **Key Words:** Attention-deficit/hyperactivity disorder, α_2-adrenoceptor agonist

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurobehavioral disorders presenting for treatment in children.[1-3] ADHD is a heterogeneous disorder with multiple putative etiologies, and is a significant clinical and public health problem because of its associated comorbidity and disability in children and adolescents.[4,5] Both psychosocial and pharmacologic interventions have emerged as widely used treatments for children and adolescents with ADHD.[4,6]

Among pharmacologic treatments for pediatric ADHD, the psychostimulants atomoxetine, clonidine extended-release (CLON-XR), and guanfacine extended release (GXR) are approved by the Food and Drug Administration (FDA).[7-9] Psychostimulants are the most widely prescribed pharmacologic agents for the treatment of ADHD.[10] Their efficacy is supported by extensive research,[4,6,10,11] and they are considered to be among first-line treatments for ADHD.[6] However, some children have a suboptimal response to psychostimulant monotherapy,[12-14] and some may experience dose-limiting adverse effects.[15-17]

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The impairment associated with residual ADHD symptoms and the need to optimize treatment is becoming increasingly recognized.[18] A longitudinal study of children with ADHD found that subjects treated with medication alone or in combination with behavioral therapy had a higher success rate, characterized by a loss of symptoms, compared with subjects treated without medication.[15] Another longitudinal study found that youth with ADHD who did not achieve normalized function—defined relative to a control group without ADHD—manifested higher rates of academic, interpersonal, and family dysfunction.[18] Furthermore, a meta-analysis of medication trials found moderate to strong correlations between functional improvement and reductions in core symptoms of ADHD.[19] Despite psychostimulant treatment, a sizeable number of youth with ADHD continue to manifest symptoms of the disorder and will experience impairment as a result.[17] Given the importance of targeting treatment to improve symptoms with the goal of improving functioning, the adjunctive administration of a pharmacologic agent with a different mechanism of action for efficacy makes conceptual sense in addressing ADHD in some children and adolescents who do not optimally respond to psychostimulant monotherapy.

In clinical practice, the selective α_{2A}-adrenoceptor agonist guanfacine as well as the nonselective α_2-adrenoceptor agonist clonidine are commonly administered adjunctively to a psychostimulant for the treatment of ADHD.[20,21] Both GXR and CLON-XR are currently approved as monotherapy and as adjunctive therapy to psychostimulants for the treatment of ADHD.[8,9] Combining psychostimulants with α_2-adrenoceptor agonists may have additive beneficial effects in the treatment of ADHD and/or associated problems.[22] In addition, the potential for opposing influences on adverse effects such as blood pressure, pulse, and weight is also of interest.

Although α_2-adrenoceptor agonists are administered adjunctively to psychostimulants in clinical settings,[20,21] there have been limited published controlled trials of adjunctive therapy in ADHD; some of those studies have been in children with ADHD and comorbid tics or aggression and have used immediate release (IR) clonidine preparations.[23-25] Recently, a parallel-design multisite study reported greater reductions in ADHD symptoms with CLON-XR dosed twice a day added to a psychostimulant compared with placebo added to a psychostimulant.[26] Whereas older case reports raised significant safety concerns with clonidine administered adjunctively to methylphenidate,[20,27] no serious cardiovascular adverse outcomes were reported in these studies, although drowsiness, somnolence, and sedation were common adverse effects.[23,25,28] Compared with clonidine, data on the use of guanfacine administered adjunctively to psychostimulants have been limited.

An extended-release formulation of guanfacine (GXR) dosed once daily has been shown to be efficacious as monotherapy treatment of ADHD in children and adolescents aged 6 to 17 years in randomized, double-blind, placebo-controlled studies.[8,29,30] The adjunctive use of GXR with a psychostimulant was studied in an open-label, 9-week study of 75 children and adolescents with ADHD who had operationally defined suboptimal response to a psychostimulant and significant ($p < .0001$) improvements in ADHD symptoms were observed.[31] Of these subjects, 54 entered into a 2-year open-label safety extension study. There were no unique adverse events (AEs) compared with those reported historically with either treatment alone.[32]

The current study is the first randomized placebo-controlled trial designed to assess efficacy and safety of GXR as an adjunct to psychostimulants in children and adolescents diagnosed with ADHD who had a suboptimal response to a psychostimulant alone. Clinical trials of GXR reported to date used AM administration and, because many clinicians use evening administration of α_{2A}-agonists, examination of GXR dosed morning or evening was warranted. We hypothesized that either morning or evening administration of GXR adjunctively to a psychostimulant would be superior in the reduction of ADHD symptoms relative to placebo plus psychostimulant.

METHOD

Participants

Subjects were 6 to 17 years of age with a diagnosis of predominantly inattentive, hyperactive/impulsive, or combined subtype based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* diagnosis of ADHD with a suboptimal response to an extended-release oral preparation of methylphenidate or amphetamine. ADHD was as-

sessed using the Kiddie-Schedule for Affective Disorders—Present and Lifetime–Diagnostic Interview (K-SADS-PL) and the ADHD Rating Scale IV (ADHD-RS-IV).

Suboptimal response was defined as follows: ≥4 weeks of a stable dose of treatment with an extended-release psychostimulant with improvement but continued mild to moderate symptoms of ADHD; ADHD-RS-IV total score of ≥24 and a Clinical Global Impressions of Severity of Illness (CGI-S) indicative of at least mild impairment (≥3); and investigator assessment of inadequate response to current psychostimulant.

The following long-acting oral psychostimulants were allowed at the start of the study: mixed salts of a single-entity amphetamine product (Adderall XR, Shire US Inc., Wayne, PA), lisdexamfetamine dimesylate (Vyvanse, Shire US Inc., Wayne, PA) for subjects 6 to 12 years of age only, methylphenidate HCl (Concerta, McNeil Pediatrics, Titusville, NJ), or FDA-approved generic equivalents. During enrollment, the inclusion criteria were expanded to include three more psychostimulants: dexmethylphenidate HCl (Focalin XR, Novartis Pharmaceuticals, East Hanover, NJ), methylphenidate HCl extended release (Ritalin LA, Novartis Pharmaceuticals, East Hanover, NJ) for subjects 6 to 12 years of age only, methylphenidate HCl, USP (Metadate CD, UCB, Inc., Smyrna, GA) for subjects 6 to 15 years of age only, or FDA-approved generic equivalents.

Subjects were required to be receiving a stable once-daily dose of one of these medications in a manner consistent with the appropriate package insert for a minimum of the previous 4 weeks. A suboptimal response was to be documented at least 14 days before the baseline visit and confirmed at the baseline visit. Exclusion criteria included lack of response to current psychostimulant medication, the presence of cardiovascular abnormalities, body weight of <55 or >176 lb, or any current, controlled or uncontrolled, comorbid psychiatric diagnosis (except oppositional defiant disorder), including any severe comorbid Axis II disorders or severe Axis I disorders.

Institutional review board approval was obtained prior to study initiation. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice requirements. Parents or legal guardians provided informed consent, and subjects provided additional assent as required per local regulation.

Study Design

This was a 9-week, double-blind, placebo-controlled dose-optimization study conducted at 59 sites in the United States. Subjects were evaluated for eligibility at screening (visit 1). At baseline (visit 2), eligibility was confirmed, and subjects were randomized in a 1:1:1 ratio to receive one of the following in addition to their current stable morning dose of psychostimulant: GXR upon awakening and placebo at bedtime (GXR AM), placebo upon awakening and GXR at bedtime (GXR PM), or placebo upon awakening and at bedtime (placebo). Randomization was stratified by age group and stimulant type.

Visits were to be scheduled 7 (±2) days apart during the study. Subjects received GXR or placebo at the start of the 5-week dose-optimization period, were maintained at their optimal dose of GXR during the 3-week dose-maintenance period, and tapered off GXR or placebo over the last week of the study. Stimulant doses were to remain fixed throughout the study. GXR was initiated at 1 mg/d and increased no sooner than weekly in 1-mg/d increments to a maximum of 4 mg/d. Subjects' doses were optimized at the discretion of the investigator based on a significant reduction in ADHD symptoms and acceptable tolerability and safety. During the study, subjects could have a one-time 1-mg/d reduction in their dosing for tolerability reasons. Beginning at visit 10, the dose of GXR or placebo was tapered over 9 days following a schedule based on the subject's specific dose prior to visit 10.

Assessments

The primary efficacy measure was the 18-item ADHD-RS-IV based on the *DSM-IV-TR* diagnostic criteria. Each item is scored from 0 (behavior occurring never or rarely) to 3 (behavior occurring very often) yielding a total score with a range of 0 to 54 with higher scores representing more severe ADHD symptoms.[33] The ADHD-RS-IV was administered by clinicians at all study visits through dose tapering.

Secondary efficacy measures included the CGI-S and the CGI-Improvement (CGI-I) scales.[34] The clinician-rated CGI-S scale, a global rating of disease severity, was performed at baseline and at each visit through dose tapering. The CGI-S rates the severity of a subject's condition on a 7-point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill subjects). The CGI-I scale, a clinician-rated global rating of improvement relative to baseline as assessed by a seven-point scale ranging from 1 (very much improved) to 7 (very much worse), was also performed at all postbaseline visits through dose tapering.

Safety assessments included assessment of AEs, vital signs, findings from physical examinations, clinical laboratory evaluations, and electrocardiograms (ECGs). AEs and vital signs were assessed at screening, baseline, at each visit during the dose-optimization and dose-maintenance phases, at endpoint/early termination, at the end of dose tapering, and at final follow-up 7 to 9 days after the final dose of study drug. Treatment-emergent AEs (TEAEs) were defined as events that started or were exacerbated between the first dose of study medication and the third day after treatment cessation (inclusive).

Data Analysis

For this adjunctive therapy study, where subjects had already experienced a reduction in ADHD symptoms on a stimulant alone before entry, a four-point difference in ADHD-RS-IV total score between treatments was determined to be representative of clinically meaningful additional improvement. Assuming a standard deviation of 10 points, sample size was chosen to detect a difference between treatments of at least four points, equivalent to an effect size of 0.4, between either of the GXR plus psychostimulant groups and placebo plus psychostimulant for the primary efficacy measure (ADHD-RS-IV total score). To achieve this with approximately 90% power and using a two-sided test of significance at the 0.05 level, it was determined that at least 399 subjects would need to be assessed for the ADHD-RS-IV total score at endpoint. It was anticipated that 10% of randomized subjects would not provide a postrandomization primary efficacy measurement; therefore, at least 441 subjects needed to be randomized in a 1:1:1 (GXR AM:GXR PM:placebo) allocation ratio.

The primary efficacy analysis was performed on the change from baseline to endpoint in ADHD-RS-IV total score, using an analysis of covariance model. Endpoint was defined as the last on-therapy, postrandomization treatment week, before any dose taper, at which a valid ADHD-RS-IV total score was collected. Two primary treatment group comparisons were defined: GXR AM + psychostimulant versus placebo + psychostimulant; and GXR PM + psychostimulant versus placebo + psychostimulant.

Dunnett's adjustment for multiplicity was used to control the false-positive error rate for the primary efficacy variable at 0.05 (two-sided). The study was not designed or powered to make statistical comparisons between active treatment groups (i.e., GXR AM + psychostimulant versus GXR PM + psychostimulant).

The ADHD-RS-IV inattention and hyperactivity/impulsivity subscale scores were analyzed using an analysis of covariance model that included treatment group (the effect of interest), psychostimulant type (the blocking factor, amphetamine, or methylphenidate), and the corresponding baseline score (the covariate). CGI-S and CGI-I results were each analyzed using a Cochran–Mantel–Haenszel test stratified by psychostimulant type (amphetamine or methylphenidate) for each visit after baseline and for endpoint.

Efficacy and safety analyses were performed using the full analysis set (FAS) and safety population, respectively. Both study populations were defined to include all subjects who received at least one dose of study medication.

RESULTS

A total of 615 subjects were screened and 461 were randomized (Figure S1, available online). The safety and FAS populations included 455 subjects: 153 in the placebo + psychostimulant group, 150 in the GXR AM + psychostimulant group, and 152 in the GXR PM + psychostimulant group. Overall, 386 subjects completed the dose-maintenance period (visit 10) and 378 completed the study through the follow-up visit 12. Adherence rates for GXR, as measured by tablet counts, were 97.2% in the GXR AM + psychostimulant group and 98.5% in the GXR PM + psychostimulant group. Adherence rates for psychostimulants, as assessed by asking subjects if they had missed any doses, ranged from 95.3% to 97.4% across the study visits.

Demographic characteristics and current psychostimulant treatment were generally similar among treatment groups for the FAS/safety population (Table 1). The mean (SD) optimal dose of GXR was 3.2 (1.0) mg/d and were similar between the GXR AM + psychostimulant (3.3 [1.0] mg/d) and GXR PM + psychostimulant (3.2 [1.0] mg/d) groups. The overall mean (SD) weight-adjusted optimal dose was 0.088 (0.04) mg/kg and was also similar between groups. For most subjects receiving GXR (64.2%), the weight-adjusted optimal dose was between 0.05 mg/kg and 0.12 mg/kg. The percentages of subjects in each weight-adjusted optimal dose group are available online in Table S1, available online.

Efficacy Measures

Baseline mean ADHD-RS-IV total scores were similar among all treatment groups (Table 1). For both morning and evening administration of GXR, subjects receiving GXR plus a psychostimulant showed significantly greater improvement from baseline to endpoint, as measured by the ADHD-RS-IV total score, compared with subjects receiving placebo plus a psychostimulant (placebo-adjusted LS mean reductions: GXR AM, −4.5, 95% confidence interval [CI] −7.5, −1.4, $p = .002$; GXR PM, −5.3, 95% CI −8.3, −2.3, $p < .001$) (Figure 1). At endpoint, mean (SD) ADHD-RS-IV total scores were 21.7 (12.98), 17.3 (12.86), and 16.1 (11.84) for the placebo + psychostimulant, GXR AM + psychostimulant, and GXR PM + psychostimulant treatment groups, respectively. Effect sizes of GXR plus a psychostimulant versus placebo plus a psychostimulant were 0.377 for the GXR AM + psychostimulant group and 0.447 for the GXR PM + psychostimulant group.

TABLE 1 Demographics in the Full Analysis Set (FAS)/Safety Population (N = 455)

Characteristic	Placebo + Psychostimulant (n = 153)	GXR AM + Psychostimulant (n = 150)	GXR PM + Psychostimulant (n = 152)	FAS/Safety Population (N = 455)
Age, y, mean (SD)	10.8 (2.3)	11.0 (2.6)	10.6 (2.3)	10.8 (2.4)
6–12, n (%)	123 (80.4)	114 (76.0)	124 (81.6)	361 (79.3)
13–17, n (%)	30 (19.6)	36 (24.0)	28 (18.4)	94 (20.7)
Sex, n (%)				
Male	112 (73.2)	108 (72.0)	106 (69.7)	326 (71.6)
Female	41 (26.8)	42 (28.0)	46 (30.3)	129 (28.4)
Race, n (%)				
White	102 (66.7)	104 (69.3)	102 (67.1)	308 (67.7)
Black or African American	35 (22.9)	28 (18.7)	37 (24.3)	100 (22.0)
Native Hawaiian or other Pacific Islander	1 (0.7)	1 (0.7)	1 (0.7)	3 (0.7)
Asian	1 (0.7)	2 (1.3)	3 (2.0)	6 (1.3)
American Indian or Alaska Native	0	1 (0.7)	0	1 (0.2)
Other	14 (9.2)	14 (9.3)	9 (5.9)	37 (8.1)
Ethnicity, n (%)				
Hispanic or Latino	15 (9.8)	27 (18.0)	19 (12.5)	61 (13.4)
Not Hispanic or Latino	138 (90.2)	123 (82.0)	133 (87.5)	394 (86.6)
Weight, lb, mean (SD)	89.14 (27.9)	90.76 (29.7)	85.40 (26.5)	88.43 (28.1)
Baseline ADHD-RS-IV total score, mean (SD)	37.7 (7.75)	37.6 (8.13)	37.0 (7.65)	NA
Concomitant psychostimulant, n (%)				
MAS XR	27 (17.6)	26 (17.3)	28 (18.4)	81 (17.8)
OROS MPH	69 (45.1)	69 (46.0)	68 (44.7)	206 (45.3)
SODAS d-MPH	9 (5.9)	9 (6.0)	9 (5.9)	27 (5.9)
MPH CD	2 (1.3)	2 (1.3)	1 (0.7)	5 (1.1)
SODAS MPH	1 (0.7)	1 (0.7)	0	2 (0.4)
LDX	45 (29.4)	43 (28.7)	46 (30.3)	134 (29.5)

Note: This table is reproduced with permission from Shire Pharmaceuticals, October 21, 2011. ADHD-RS-IV = Attention-Deficit/Hyperactivity Disorder Rating Scale IV; FAS = full analysis set; GXR = guanfacine extended release; LDX = lisdexamfetamine dimesylate; MAS XR = mixed amphetamine salts extended release; MPH CD = methylphenidate controlled-delivery; OROS MPH = osmotic release oral system methylphenidate; SODAS d-MPH = spheroidal oral drug absorption system dexmethylphenidate; SODAS MPH = spheroidal oral drug absorption system methylphenidate.

The inattention subscale rating of the ADHD-RS-IV showed significantly greater improvements from baseline in subjects receiving GXR with a psychostimulant compared with subjects receiving placebo + psychostimulant (placebo-adjusted LS mean reductions: GXR AM, −2.4, 95% CI: −3.9, −0.9, $p = .002$; GXR PM, −3.1, 95% CI: −4.6, −1.5, $p < .001$) (Figure 2). Effect sizes for the inattention subscale of GXR plus a psychostimulant at endpoint were 0.359 in the GXR AM + psychostimulant group and 0.458 in the GXR PM + psychostimulant group.

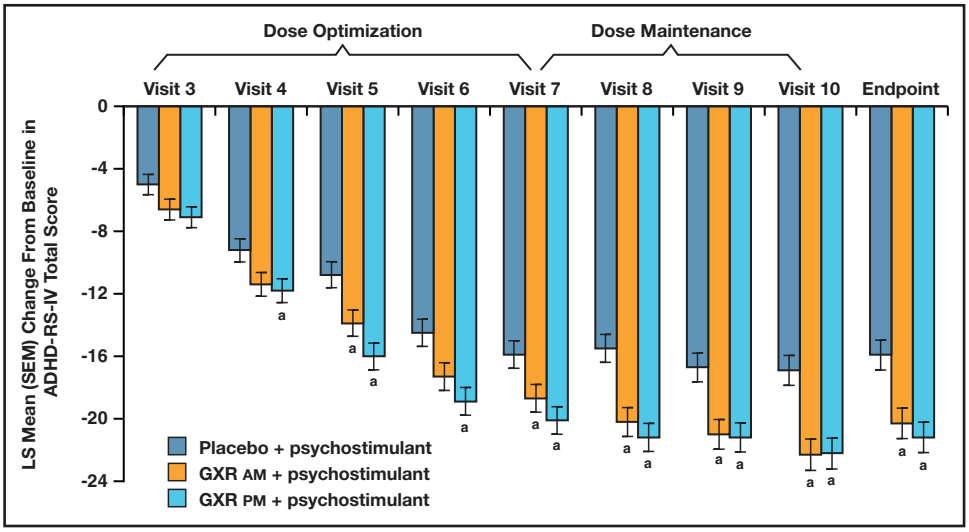
Similarly, the hyperactivity/impulsivity subscale rating of the ADHD-RS-IV at endpoint showed significantly greater improvements from baseline in subjects receiving GXR with a psychostimulant compared with those receiving placebo + psychostimulant (placebo-adjusted LS mean reductions: placebo group, −7.6; GXR AM, −2.1, 95% CI: −3.4, −0.7, $p = .002$ versus placebo; GXR PM, −2.3, 95% CI: −3.6, −0.9, $p < .001$ versus placebo) (Figure 3). Effect sizes for the hyperactivity/impulsivity subscale of GXR plus a psychostimulant at endpoint were 0.352 for the GXR AM + psychostimulant group and 0.387 for the GXR PM + psychostimulant group.

Secondary Efficacy Measures

Baseline CGI-S scores were similar across treatment groups. At endpoint, subjects in both the GXR AM and GXR PM groups were judged to be less severely ill, as measured by CGI-S scores, than subjects in the placebo group (GXR AM + stimulant group, $p = .013$; GXR PM + stimulant group, $p < .001$). CGI-S results at endpoint are summarized in Table S2, available online.

Similarly, significantly greater proportions of subjects in both the GXR morning- and evening-

FIGURE 1 Least squares (LS) mean (standard error of the mean [SEM]) change in Attention-Deficit/Hyperactivity Disorder Rating Scale IV (ADHD-RS-IV) total score from baseline by visit in the guanfacine extended release (GXR) AM + psychostimulant group and GXR PM + psychostimulant group (full analysis set). Note: In the GXR AM + psychostimulant group, significant improvements were observed at visit 5 (3 weeks on treatment) and from visit 7 (5 weeks on treatment) through endpoint. In the GXR PM + psychostimulant group, significant improvements were observed from visit 4 (2 weeks on treatment) through endpoint. Effect sizes at endpoint were 0.377 for the GXR AM + psychostimulant group and 0.447 for the GXR PM + psychostimulant group. This figure is reproduced with permission from Shire Pharmaceuticals, October 21, 2011. [a]$p < .05$ versus placebo, based on the Dunnett test.



dosing groups were judged as improved (including much or very much improved) at endpoint on the CGI-I, compared with the placebo group (placebo group, 57.9%; GXR AM + psychostimulant group, 70.5%, 95% CI: 1.8%, 23.3%, $p = .024$ versus placebo; GXR PM + psychostimulant group, 74.3%, 95% CI: 5.9%, 27.0%, $p = .003$ versus placebo).

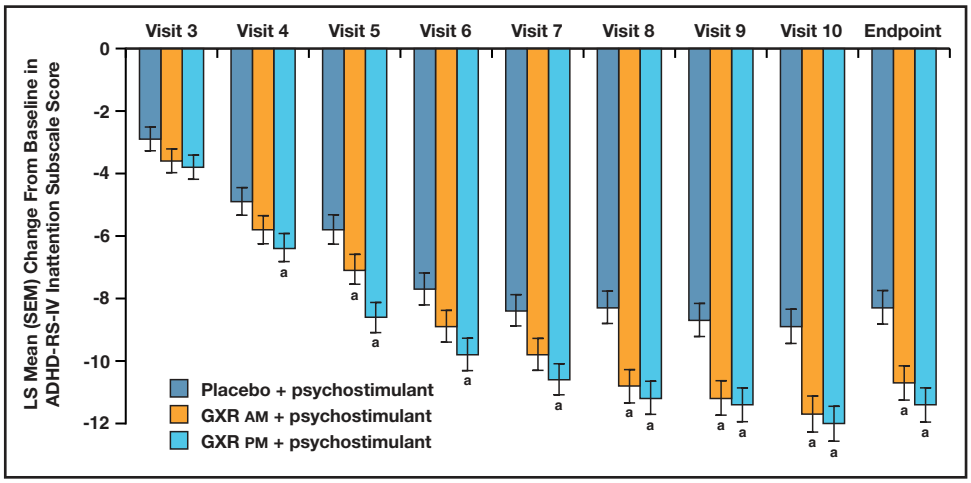
Safety Assessments

TEAEs are shown in Table 2. In this study, the overall rates of TEAEs were slightly elevated in the GXR AM (77.3%) and GXR PM (76.3%) + psychostimulant groups compared with the placebo + psychostimulant group (63.4%). Serious AEs occurred in three subjects (1%): all subjects were receiving GXR plus a psychostimulant, and all three events were deemed unrelated to study medication by investigators. One subject experienced syncope in the context of nausea, vomiting, and sinusitis; the subject completed the study. Another subject exhibited self-injurious behavior, aggression, homicidal ideation, and adjustment disorder with mixed disturbance of emotions and conduct. It was subsequently disclosed to the investigators that the subject had exhibited similar behaviors before the start of the study; the subject discontinued from the study. The third subject had poison ivy and discontinued from the study. One serious AE occurred in the 2-year-old brother of a subject, who accidentally ingested eight 1-mg tablets of GXR. He was taken to the emergency room, given activated charcoal, observed, and released. No symptoms were reported.

Most TEAEs were mild or moderate in severity. Severe TEAEs occurred in 0.7% (1/153) of the placebo + psychostimulant group, 2.0% (3/150) of the GXR AM + psychostimulant group, and 6.6% (10/152) of the GXR PM + psychostimulant group. The rate of discontinuation because of TEAEs was 0.7% (1/153) in the placebo + psychostimulant group, 2.7% (4/150) in the GXR AM + psychostimulant group, and 3.9% (6/152) in the GXR PM + psychostimulant group. No deaths occurred during the study. Aggression was the only TEAE leading to discontinuation that occurred in more than one subject; one subject in each of the three groups discontinued because of the TEAE of aggression.

The most common TEAEs were headache and somnolence in the two GXR groups and headache and upper respiratory tract infection

FIGURE 2 Least squares (LS) mean (standard error of the mean [SEM]) change in Attention-Deficit/Hyperactivity Disorder Rating Scale IV (ADHD-RS-IV) inattention subscale score from baseline by study visit (full analysis set). Note: In the guanfacine extended release (GXR) AM + psychostimulant group, significant improvements were observed at visit 5 (3 weeks on treatment) and from visit 8 (6 weeks on treatment) through endpoint. In the GXR PM + psychostimulant group, significant improvements were observed from visit 4 (2 weeks on treatment) through endpoint. Effect sizes at endpoint were 0.359 in the GXR AM + psychostimulant group and 0.458 in the GXR PM + psychostimulant group. This figure is reproduced with permission from Shire Pharmaceuticals, October 21, 2011. [a]$p < .05$ versus placebo + psychostimulant.



in the placebo + psychostimulant group (Table 2). The incidence of treatment-emergent somnolence, sedation, and hypersomnia (SSH) events combined was similar in the 2 GXR groups (18.0% in the GXR AM + psychostimulant group, and 18.4% in the GXR PM + psychostimulant group) and was 6.5% in the placebo + psychostimulant group. The bulk of the SSH events occurred in the initial 5 weeks of treatment (during the dose-optimization period), resolved before the dose-tapering period, and did not result in early discontinuation from the study. No new reports of SSH were reported at visits 9 or 10.

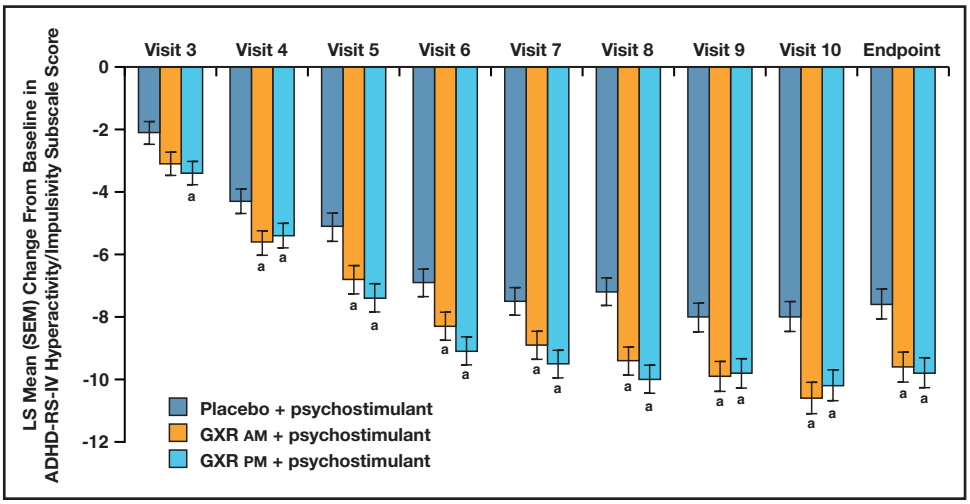
At endpoint, small mean (SD) decreases in supine pulse (GXR AM + psychostimulant, −5.8 [12.30]; GXR PM + psychostimulant, −5.4 [11.77] beats/min), systolic blood pressure (SBP) (GXR AM + psychostimulant, −1.5 [9.74]; GXR PM + psychostimulant, −2.9 [9.74] mm Hg), and diastolic blood pressure (DBP) (GXR AM + psychostimulant, −1.1 [7.47]; GXR PM + psychostimulant, −1.2 [8.52] mm Hg) were observed in subjects receiving GXR plus a psychostimulant compared with subjects receiving placebo plus a psychostimulant (2.1 [10.65] beats/min, −0.6 [8.38] mm Hg, and −0.0 [7.61] mm Hg, respectively). Outlier criteria were defined as a QTcF interval ≥480 milliseconds or a QTcB interval ≥500 milliseconds. No subjects in any treatment group met these criteria.

There were no clinically notable differences in physical examination findings between treatment groups. There were mean (SD) increases in weight from baseline at endpoint of 1.31 (2.93) lb in subjects receiving GXR + a psychostimulant and 0.90 lb (3.04) in subjects receiving placebo + psychostimulant. There were no clinically notable differences in hematology, chemistry, or urinalysis between treatment groups. No subject was discontinued early because of a treatment-emergent abnormal laboratory value.

DISCUSSION

The results of this study support the hypothesis that adjunctive administration of the selective α_{2A}-adrenoceptor agonist, GXR, to a psychostimulant in subjects with suboptimal response to psychostimulants reduces ADHD symptoms over placebo with a psychostimulant. Significant benefits of adjunctive administration were observed whether GXR was administered in the morning or evening. No new safety signals emerged after adjunctive administration of GXR with psychostimulants compared with psychostimulants alone. To our knowledge, the current study represents the largest double-

FIGURE 3 Least squares (LS) mean (standard error of the mean [SEM]) change in Attention-Deficit/Hyperactivity Disorder Rating Scale IV (ADHD-RS-IV) hyperactivity/impulsivity subscale score from baseline by study visit (full analysis set). Note: In the guanfacine extended release (GXR) AM + psychostimulant group, significant improvements were observed from visit 4 (2 weeks on treatment) through endpoint. In the GXR PM + psychostimulant group, significant improvements were observed from visit 3 (1 week on treatment) through endpoint. Effect sizes at endpoint were 0.352 for the GXR AM + psychostimulant group and 0.387 for the GXR PM + psychostimulant group. This figure is reproduced with permission from Shire Pharmaceuticals, October 21, 2011. [a]$p < .05$ versus placebo + psychostimulant.



blind, randomized, placebo-controlled study conducted to date examining adjunctive therapy for ADHD. The study results show that GXR was efficacious in augmenting treatment response in subjects with a suboptimal response to a psychostimulant alone.

Although this study was not designed to compare morning with evening dosing of GXR, upon visual inspection, similar responses were seen in the GXR AM + psychostimulant and GXR PM + psychostimulant groups, suggesting that both dosing regimens are efficacious, safe, and tolera-

TABLE 2 Treatment-Emergent Adverse Events (TEAEs) Occurring in ≥5% of Subjects in Any Treatment Group (Safety Population)

	Placebo + Psychostimulant (n = 153)	GXR AM + Psychostimulant (n = 150)	GXR PM + Psychostimulant (n = 152)
Any TEAE, n (%)	97 (63.4)	116 (77.3)	116 (76.3)
Headache	20 (13.1)	32 (21.3)	32 (21.1)
Somnolence	7 (4.6)	21 (14.0)	20 (13.2)
Upper respiratory tract infection	12 (7.8)	14 (9.3)	16 (10.5)
Fatigue	4 (2.6)	18 (12.0)	11 (7.2)
Insomnia	6 (3.9)	8 (5.3)	18 (11.8)
Upper abdominal pain	3 (2.0)	12 (8.0)	13 (8.6)
Dizziness	6 (3.9)	15 (10.0)	8 (5.3)
Decreased appetite	6 (3.9)	9 (6.0)	11 (7.2)
Cough	7 (4.6)	9 (6.0)	7 (4.6)
Irritability	11 (7.2)	6 (4.0)	9 (5.9)
Nausea	5 (3.3)	4 (2.7)	11 (7.2)
Pyrexia	6 (3.9)	6 (4.0)	8 (5.3)
Sedation	3 (2.0)	5 (3.3)	8 (5.3)
Pharyngolaryngeal pain	5 (3.3)	2 (1.3)	8 (5.3)

Note: This table is reproduced with permission from Shire Pharmaceuticals, October 21, 2011. GXR = guanfacine extended release.

ble. In fact, treatment effect sizes at endpoint compared with placebo + psychostimulant were 0.38 in the GXR AM + psychostimulant group and 0.45 in the GXR PM + psychostimulant group. Of note, because subjects in this adjunctive therapy study had already experienced reductions in ADHD symptoms with a psychostimulant alone, comparisons with treatment effects of monotherapy may not be appropriate. Effect sizes presented in this study do not represent the overall improvement with these treatment regimens; they account for additional benefits beyond those already provided by psychostimulant monotherapy.

In the present study, mean ADHD-RS-IV total scores at endpoint were <18, a score that is consistent with low overall ADHD symptoms, in both the morning and evening dosing groups.[16] Furthermore, a score of <18 suggests that a subject is minimally ill and may be below the *DSM-IV* diagnostic threshold for ADHD.[16]

The findings of this study are consistent with those of other studies, discussed previously evaluating adjunctive administration of α_2-adrenoceptor agonists with psychostimulants. In a 6-week randomized study of clonidine added to either methylphenidate or dexamphetamine, Hazell et al. found a significant reduction in Conners' Parent Rating Scale Conduct and Hyperactive Index scores with the addition of IR clonidine.[23] In a multisite randomized study in subjects with ADHD plus tic disorders, the authors concluded that a greater treatment effect was found with IR clonidine administered adjunctively to methylphenidate ($p < .0001$) than with either IR clonidine ($p = .02$) or methylphenidate ($p = .02$) alone.[25] Palumbo et al. also examined IR clonidine and methylphenidate, and reported benefits of adjunctive therapy relative to treatment with clonidine but not methylphenidate monotherapy.[24] Similarly, a recent controlled study of CLON-XR dosed twice a day in addition to a stable psychostimulant regimen was conducted in children with ADHD who had a lack of adequate response to the psychostimulant and demonstrated significantly greater reductions in ADHD-RS-IV total scores with CLON-XR added to a psychostimulant compared with placebo added to a psychostimulant (mean [SD] −15.7 [12.3] versus −11.5 [12.2], respectively, $p = .009$).[26]

The current data also corroborate the efficacy results of the GXR short-term open-label adjunctive study that found reductions in ADHD symptoms when GXR dosed once daily was added to psychostimulants in subjects with ADHD who had suboptimal control of ADHD symptoms on a psychostimulant alone.[31] In that study, the addition of morning-dosed GXR resulted in statistically significant improvements in ADHD-RS-IV total scores; the mean reduction in ADHD-RS-IV total scores from baseline to endpoint was 16.1 ($p < .0001$). Subjects continued in a 2-year open-label extension study, and no new safety signals were observed.[32]

Nonetheless, an important consideration with adjunctive pharmacologic therapy regimens is the potential for increased or novel TEAEs. In this study, the overall rates of TEAEs were greater in the GXR AM (77.3%) and GXR PM (76.3%) + psychostimulant groups compared with the placebo + psychostimulant group (63.4%). Most TEAEs associated with GXR administered adjunctively to a psychostimulant were mild or moderate in severity. Furthermore, although limited by our design and relatively short trial duration, no unique adverse effects were observed with adjunctive administration compared with those observed historically with psychostimulants alone or historically with GXR alone.[8,29,30,35] There were no serious AEs judged related to study medication by investigators. Similarly, while studying otherwise healthy subjects, our data are reassuring in that, similar to previous adjunctive α_2-adrenoceptor agonist and psychostimulant trials, there was an absence of serious adverse cardiovascular events or findings that emerged. Of interest, despite older case reports that raised safety concerns with IR clonidine administered adjunctively to methylphenidate,[20,27] no serious cardiovascular adverse outcomes have been reported in recent multisite studies of adjunctive administration of α_2-adrenoceptor agonists and psychostimulants in medically screened youth.[23,25,28] The four studies that evaluated clonidine IR (n = 325) or XR (n = 198) adjunctively administered with psychostimulants discussed previously and the present study evaluating GXR administered with psychostimulants (n = 455) total 978 subjects. No serious cardiovascular AEs were reported in these studies.[23,25,26,28] Drowsiness, somnolence, and sedation were typically noted.[23,25,26,28]

In this GXR adjunctive study, the incidence of treatment-emergent SSH events was 18.0% in the GXR AM + psychostimulant group, and 18.4% in the GXR PM + psychostimulant group. This was a lower incidence than that seen in

two short-term randomized GXR monotherapy studies in subjects aged 6 to 17 years, in which the reported incidences of treatment-emergent SSH events were 44.2% and 32.5% in subjects treated with GXR.[36,37]

Mean decreases in pulse, SBP, and DBP were observed at endpoint in subjects receiving GXR plus a psychostimulant. In subjects who received placebo plus a psychostimulant, a small mean (SD) increase in pulse was observed (2.1 [10.65] beats/min), whereas those who received GXR plus a psychostimulant demonstrated a decrease in mean (SD) pulse (GXR AM + psychostimulant, −5.8 [12.30]; GXR PM + psychostimulant, −5.4 [11.77] beats/min). In addition, subjects receiving GXR adjunctive to a psychostimulant manifested slightly more weight gain at endpoint than with a psychostimulant alone. These differences from baseline when subjects were receiving psychostimulant alone suggests a potential partial offsetting of some of the adverse effects associated with psychostimulants with GXR,[35,38-41] although use of GXR alone was not examined in the present study. Also, no study measurements were taken before the start of psychostimulant therapy; therefore, the impact of psychostimulant monotherapy on the growth or cardiovascular parameters of these subjects is unknown.

There are a number of methodologic limitations in the current study. The relatively short duration of the study limited the conclusions that can be drawn regarding the safety or efficacy of longer-term adjunctive therapy. The study was not designed to compare morning with evening dosing of GXR, which may be of clinical interest. Subjects were not assessed before beginning their psychostimulant regimen; therefore, the response attributable to the psychostimulant is unknown. However, subjects had to manifest some improvement in ADHD symptoms (in the judgment of the investigator) in response to psychostimulant monotherapy to be included in the study. The study design did not incorporate psychostimulant optimization during the conduct of the study and optimization was assumed to have occurred prior to study start. Psychostimulant doses were not changed beginning at least 4 weeks before the baseline visit and throughout the study. Therefore, any subjects who were not receiving a fully optimized dose of psychostimulant before study start may have continued to manifest suboptimal response to their psychostimulant during the study. However, the groups were randomized into the three treatment arms, and the possible lack of psychostimulant dose optimization should have affected each group equally. Similarly, adherence with psychostimulant therapy before the study start was not assessed, although adherence rates for psychostimulant therapy were high during this study. Therefore, participation in the study may have enhanced adherence to psychostimulants, resulting in an artificially enhanced placebo response in the psychostimulant plus placebo administration group. Finally, the inclusion and exclusion criteria produced a select group of medically and psychiatrically screened subjects that may not be comparable to the general clinical population.

This multisite, placebo-controlled study in children with ADHD suggests that the addition of GXR in either the morning or evening provides additional symptom reduction in subjects with suboptimal response to psychostimulant monotherapy. GXR administered adjunctively to psychostimulants was associated with predictable adverse effects of each class of medication alone. Specific outcomes and the duration of effect for each of the medications administered alone and adjunctively, as well as the effects of concurrent changes of psychostimulant and GXR, and the effects of optimized GXR followed by the addition of a psychostimulant could be explored in future studies. Effects of long-term dosing, and neuroimaging correlates for adjunctive therapy may also be beneficial. &

Accepted October 21, 2011.

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This study was supported by Shire Development Inc., Wayne, PA.

Clinical research was funded by the sponsor, Shire Development Inc. The primary manuscript was written by Dr. Wilens after discussion about the manuscript's content with the independent authors. Under the direction of the authors, Jennifer Steeber, PhD, an employee of SCI Scientific Communications and Information (SCI), provided additional writing assistance for this publication. Editorial assistance in formatting, proofreading, copy editing, and fact checking was also provided by SCI. Jonathan Rubin, M.D., M.B.A., Ryan Dammerman, M.D., Ph.D., Carla White, B.Sc., C.Stat., Edward Johnson, Michael Kahn, and Gina D'Angelo,

Pharm.D., M.B.A., from Shire Development Inc., also reviewed and edited the manuscript for scientific accuracy. Shire Development Inc. provided funding to OCHSC for support in writing and editing this manuscript. Although the sponsor was involved in the design, collection, analysis, interpretation, and fact checking of information, the content of this manuscript, the ultimate interpretation, and the decision to submit it for publication in *Journal of the American Academy of Child and Adolescent Psychiatry* were made by the authors independently.

Disclosure: Dr. Wilens receives or has received grant support from Abbott, Eli Lilly and Co., McNeil, Merck, the National Institutes of Health (NIH), National Institute on Drug Abuse (NIDA), and Shire. He has served as a speaker for Eli Lilly and Co., McNeil, Novartis, and Shire. He has served as a consultant for Abbott, AstraZeneca, Eli Lilly and Co., Euthymics, McNeil, Merck, NextWave, NIH, NIDA, Novartis, and Shire. Dr. Wilens receives royalties from Guilford Press. Dr. Bukstein receives or has received research support from McNeil and Shire. He has acted as a consultant, and/or served on a speakers' bureau for Cephalon, McNeil, Novartis, and Shire. He receives royalties from Routledge Press. Dr. Brams has served on the speakers' bureau and as a consultant for AstraZeneca, Eli Lilly and Co., Cephalon, McNeil, Novartis, Pfizer, Shire, Shionogi, Sunovion. He has received research support from AstraZeneca, Addremax, Bristol-Myers Squibb, Cephalon, GlaxoSmithKline, Janssen, Johnson and Johnson, Merck, Novartis, Ortho McNeil, Otsuka, Pfizer, Sepracor, Shionogi, Shire, and Sunovion. Dr. Cutler has received research grants from Abbott, Addrenex, AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, Cephalon, Eli Lilly and Co., GlaxoSmithKline, Janssen, Jazz Pharmaceuticals, Johnson and Johnson, McNeil Pharmaceuticals, Memory Pharmaceuticals, Merck, Novartis, Ortho-McNeil, Otsuka, Pfizer, Sanofi, Sepracor, Shionogi, Shire, Solvay, Supernus, and Targacept. He has served as a consultant for Abbott, Addrenex, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly and Co., GlaxoSmithKline, Janssen, Johnson and Johnson, Neuroscience Education Institute, Novartis, Ortho-McNeil, Otsuka, Pfizer, Sepracor, Shionogi, Shire, Supernus, and Targacept. He has served on the speakers' bureau for Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Co., GlaxoSmithKline, Janssen, Neuroscience Education Institute, Novartis, Ortho-McNeil, Pfizer, Sepracor, Shionogi, and Shire. He has received continuing medical education credits from an advisory board for Neuroscience Education Institute. Dr. Childress has served as a consultant for NextWave, Novartis, and Shire. She has served on the speakers' bureau for Bristol-Myers Squibb, GlaxoSmithKline, Shire, and Novartis. She receives research support from Abbott, Bristol-Myers Squibb, Eli Lilly and Co., Johnson and Johnson, NextWave, Novartis, Ortho-McNeill, Otsuka, Janssen Scientific Affairs, Rhodes, Sepracor, Shire, and Somerset. Dr. Rugino has served as a consultant for Lexicor, Bristol-Myers Squibb, and Shire. He has served on the speakers' bureau for Shire. Children's Specialized Hospital received research support from Bristol-Myers Squibb, Eli Lilly and Co., Forest Research Institute, Lexicor, Novartis, and Shire. Ms. Grannis holds stock and/or stock options in Shire. Mr. Lyne holds stock and/or stock options in Shire. Dr. Youcha holds stock and/or stock options in Shire.

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0890-8567/$36.00/©2012 American Academy of Child and Adolescent Psychiatry

DOI: 10.1016/j.jaac.2011.10.012

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FIGURE S1 Study flow diagram. Note: FAS = full analysis set; GXR = guanfacine extended release. This figure is reproduced with permission from Shire Pharmaceuticals, October 21, 2011. *Other reasons included subjects who declined to participate. The number of subjects who specifically declined participation was not captured. †One subject was randomized in error after being excluded from the study. The subject did not receive study medication.

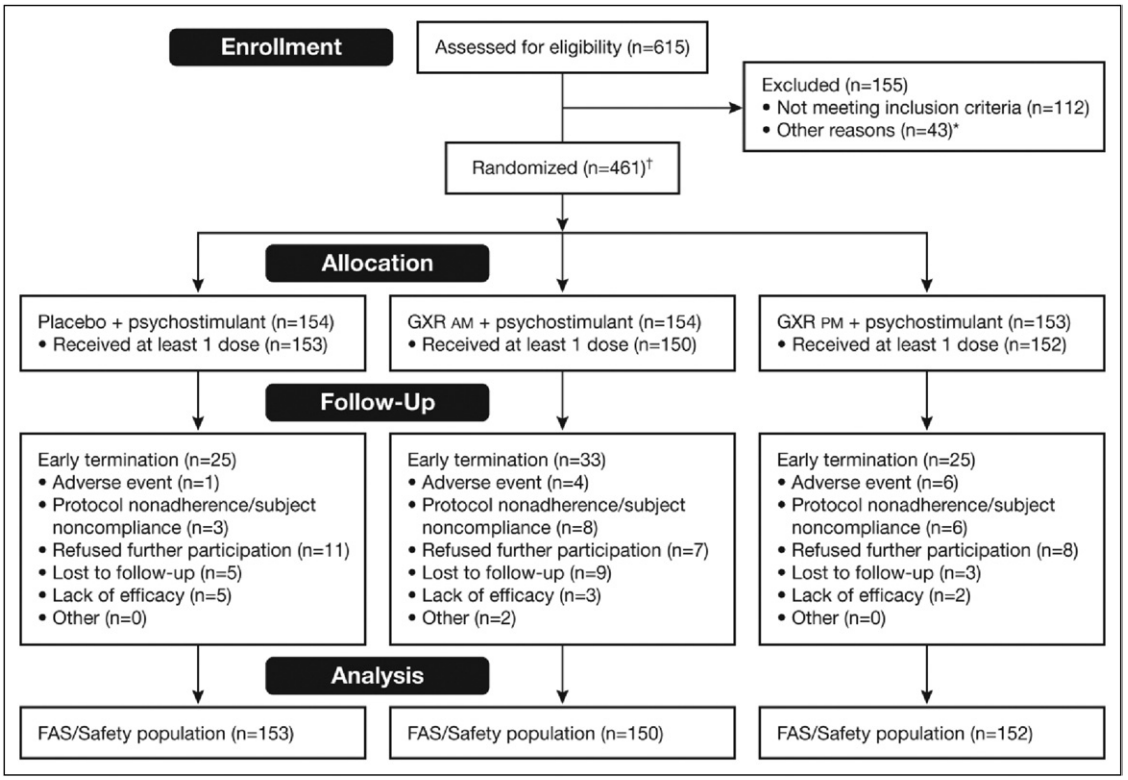

TABLE S1 Optimal Dose (Safety Population)

	GXR AM + Psychostimulant (n = 150)	GXR PM + Psychostimulant (n = 152)	All GXR + Psychostimulant (n = 302)
Optimal dose			
Mean (SD)	3.3 (1.0)	3.2 (1.0)	3.2 (1.0)
Subjects receiving, n (%)			
1 mg/d	8 (5.3)	8 (5.3)	16 (5.3)
2 mg/d	22 (14.7)	27 (17.8)	49 (16.2)
3 mg/d	26 (17.3)	35 (23.0)	61 (20.2)
4 mg/d	79 (52.7)	66 (43.4)	145 (48.0)
Weight-adjusted optimal dose, mg/kg			
Mean (SD)	0.088 (0.04)	0.089 (0.03)	0.088 (0.04)
Subjects receiving, n (%)			
0.01–0.04 mg/kg	21 (14.0)	14 (9.2)	35 (11.6)
0.05–0.08 mg/kg	46 (30.7)	51 (33.6)	97 (32.1)
0.09–0.12 mg/kg	49 (32.7)	48 (31.6)	97 (32.1)
0.13–0.16 mg/kg	19 (12.7)	23 (15.1)	42 (13.9)

Note: Column totals may not equal the numbers listed for each group as only subjects who reached the end of dose optimization were included in this analysis. This table is reproduced with permission from Shire Pharmaceuticals, October 21, 2011. GXR = guanfacine extended release.

TABLE S2 Summary of Clinical Global Impressions of Severity of Illness Scores at Endpoint (Full Analysis Set)

	GXR AM + Psychostimulant n = 150 n (%)	GXR PM + Psychostimulant n = 152 n (%)	Placebo + Psychostimulant n = 153 n (%)
Normal, not at all ill	34 (22.8)	37 (25.0)	23 (15.1)
Borderline mentally ill	29 (19.5)	39 (26.4)	27 (17.8)
Mildly ill	51 (34.2)	39 (26.4)	44 (28.9)
Moderately ill	24 (16.1)	24 (16.2)	41 (27.0)
Markedly ill	9 (6.0)	8 (5.4)	14 (9.2)
Severely ill	2 (1.3)	1 (0.7)	3 (2.0)
Among the most extremely ill subjects	0 (0.0)	0 (0.0)	0 (0.0)

Note: This table is reproduced with permission from Shire Pharmaceuticals, October 21, 2011. GXR = guanfacine extended release.