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

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

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

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

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

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

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

METHOD

Participants

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

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

Study Design

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