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Efficacy and safety of extended-release guanfacine hydrochloride in children and adolescents with attention-deficit/hyperactivity disorder: A randomized, controlled, Phase III trial

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Abstract
Guanfacine extended-release (GXR), a selective α2A-adrenergic agonist, is a non-stimulant treatment for attention-deficit/hyperactivity disorder (ADHD). This study assessed the efficacy (symptoms and function) and safety of dose-optimized GXR compared with placebo in children and adolescents with ADHD. An atomoxetine (ATX) arm was included to provide reference data against placebo. Patients (6–17 years) were randomized at baseline to dose-optimized GXR (0.05–0.12 mg/kg/day – 6–12 years: 1–4 mg/day; 13–17 years: 1–7 mg/day), ATX (10–100 mg/day) or placebo for 4 or 7 weeks. The primary efficacy measure was change from baseline in ADHD Rating Scale version IV (ADHD-RS-IV). Key secondary measures were Clinical Global Impression-Improvement (CGI-I) and the Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P; learning and school, and family domains). Safety assessments included treatment-emergent

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adverse events (TEAEs), electrocardiograms and vital signs. A total of 272 (80.5%) patients from Europe, the USA and Canada completed the study. Significant differences were observed in least squares mean change from baseline in ADHD-RS-IV total score (placebo-adjusted differences) (GXR: [−8.9, $p<0.001$]; ATX: [−3.8, $p<0.05$]), the difference from placebo in the percentage of patients showing improvement (1 ['very much improved'] or 2 ['much improved']) for CGI-I (GXR: [23.7, $p<0.001$]; ATX: [12.1, $p<0.05$]), WFIRS-P learning and school domain (GXR: [−0.22, $p<0.01$]; ATX: [−0.16, $p<0.05$]) and WFIRS-P family domain (GXR: [−0.21, $p<0.01$]; ATX: [−0.09, $p=0.242$]). Most common TEAEs for GXR were somnolence, headache and fatigue; 70.1% of GXR subjects reported mild-to-moderate TEAEs. GXR was effective and well tolerated in children and adolescents with ADHD.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders of childhood. The worldwide prevalence in children ≤18 years has been estimated at 5.3% in a systematic review of 102 studies from all continents, with a majority from North America and Europe (Polanczyk et al., 2007).

Stimulant medications, such as methylphenidate and amphetamine-based medications, have been the mainstay of pharmacological management for behavioral problems in children since 1937 (Bradley, 1937). Despite their effectiveness in treating ADHD, potential issues may arise in some patients prescribed with stimulant medications, including side effects and/or inadequate response (Barkley et al., 1990; Childress and Sallee, 2014; Olfson, 2004). Caution in prescribing stimulants may be required as pre-existing conditions (such as psychosis, bipolar disorder, tics, aggressive behavior and certain cardiac abnormalities) may be exacerbated in some patients (Cortese et al., 2013; Graham et al., 2011; Wolraich et al., 2011).

Non-stimulant medications such as guanfacine (extended release; GXR) and atomoxetine (ATX) are considered as alternative options to stimulants for some patients with ADHD (Biederman et al., 2008a,b; Chappell et al., 1995; Hirota et al., 2014; Sallee et al., 2009b; Scahill et al., 2001; Silver, 1999; Spencer et al., 2009; Uhlen and Wikberg, 1991; Uhlen et al., 1995). ATX, a selective norepinephrine reuptake inhibitor, is approved for the treatment of ADHD in children, adolescents and adults in Europe, the USA and Canada (EMC, 2013). However, through its specific mechanism of action, it has shown several of the same side effects as stimulants, such as increased heart rate and blood pressure (Bushe and Savill, 2014), and up to 12 weeks of treatment can be necessary before a full response is demonstrated (Bangs et al., 2008; Bushe and Savill, 2014). Although the precise underlying physiological mechanisms of GXR are unknown, the beneficial behavioral effect of GXR on pre-frontal cortex cognitive functions has been well documented (Malhotra et al., 2006; Schulz et al., 2013; Singh-Curry et al., 2011; Wang et al., 2007). Efficacy and safety of GXR in patients with ADHD are well established (Biederman et al., 2008b; Connor et al., 2010; Kollins et al., 2011; Newcorn et al., 2013; Sallee et al., 2009b). Two US clinical trials have reported GXR monotherapy to be efficacious and well tolerated (majority of adverse events were mild to moderate) for the treatment of ADHD (Biederman et al., 2008b; Sallee et al., 2009b). GXR is currently approved in the USA as monotherapy or adjunctive treatment in children and adolescents (6–17 years) with ADHD and in Canada in children (6–12 years) with ADHD (Health Canada, 2014; Shire, 2014).

The present Phase III trial assessed the efficacy (symptoms and function) and safety of once-daily dose-optimized GXR compared with placebo in the treatment of children and adolescents aged 6–17 years with a diagnosis of ADHD as measured by the ADHD Rating Scale version IV (ADHD-RS-IV) in Europe, the USA and Canada. An ATX arm was included in the study to provide reference data against placebo.

2. Experimental procedures

A randomized, double-blind, multicenter, parallel-group, placebo-controlled, dose optimization, efficacy and safety study (ClinicalTrials.gov identifier: NCT01244490 and EudraCT: 2010-018579-12) was conducted in centers in Europe, the USA and Canada. The study was conducted in 58 centers across 11 European countries (Austria, France, Germany, Ireland, Italy, Poland, Romania, Spain, Sweden, the UK and Ukraine), the USA and Canada between January 2011 and May 2013. The study was performed in accordance with the current applicable regulations, the International Conference on Harmonisation of Good Clinical Practice, the principles of the Declaration of Helsinki and local ethical and legal requirements. The study protocol was approved by an independent ethics committee/institutional review board and regulatory agency in each center (as appropriate) before study initiation. Written, informed consent was obtained from each participant's parent or legal guardian, and assent was obtained from each participant, as applicable, before commencing study-related procedures.

2.1. Study population

Male and female children/adolescents (6–17 years old) with a diagnosis of ADHD of at least moderate severity, as defined by a baseline ADHD-RS-IV with a total score of 32 or higher and a minimum Clinical Global Impression-Severity (CGI-S) score of 4, were enrolled in the study. Those with age-appropriate intellectual functioning; blood pressure measurements within the 95th percentile for age, sex and height; and the ability to swallow tablets or capsules were included. Girls of childbearing potential had to have a negative urine pregnancy test at screening and baseline and to comply with any protocol contraceptive requirements. In addition, participants and their parent/legal guardian had to be willing, able

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and likely to fully comply with the study procedures and restrictions defined in the protocol. Subjects who took between 80% and 120% of their total medication were considered to be compliant with the study protocol. Exclusion criteria included: clinically significant illness, including a clinically significant abnormal screening visit; current, comorbid psychiatric diagnosis (except oppositional defiant disorder [ODD]); history/presence of cardiac abnormalities, cardiovascular or cerebrovascular disease, serious heart rhythm abnormalities, syncope, tachycardia, cardiac conduction problems, exercise-related cardiac events or clinically significant bradycardia; orthostatic hypotension and/or a known history of hypertension; seizures; and glaucoma. In addition, those with a family history of sudden cardiac death, ventricular arrhythmia or QT prolongation, a patient history of alcohol or substance abuse and those patients with serious tic disorder, including Tourette's syndrome, were excluded. In addition, enrollment was managed to ensure that approximately 25% of those enrolled were adolescents and at least 25% were female. Furthermore, at least 70% of those enrolled were to come from European centers and the remaining 30% from USA/Canada.

2.2. Study drug administration

The first 4 weeks (7 weeks if aged over 13 years) of the study was a double-blind dose-optimization period, which was followed by a 6-week double-blind maintenance period, a 2-week double-blind tapering period and a follow-up visit 1 week after the last dose (Figure 1). The total study treatment duration after the screening period was 10 weeks for children (6–12 years) and 13 weeks for adolescents (13–17 years), in order to allow all subjects to reach an optimal dose of between 0.05 mg/kg/day and 0.12 mg/kg/day GXR. Some incremental benefit may be observed at higher doses, but only if doses are well tolerated. A few patients may respond adequately at lower doses, but dose optimization is recommended in all cases. In this study, titration was at the discretion of the physician. Randomization occurred at baseline (day 0) and eligible participants were randomized, using a 1:1:1 ratio, to GXR, ATX or placebo (automatically, randomly assigned by the interactive voice response system). Allocation to treatment was stratified within age group (6–12 or 13–17 years) and country. Subjects were instructed to take their assigned medication once daily, at a similar time, each morning. They were also instructed to administer medication consistently with respect to the time of eating and type of food (avoiding a high-fat meal). Medication was dispensed at the baseline visit, at each dose optimization visit, each maintenance visit and the first tapering visit, for the subsequent dosing period.

GXR was administered as tablets (1, 2, 3 and 4 mg) and ATX as capsules (10, 18, 25, 40 and 60 mg) in a double-dummy design. For GXR, one GXR or matching placebo tablet (if optimized to 1–4 mg dose) or two tablets (if optimized to 5–7 mg) were taken. GXR dosing in children was initiated at 1 mg/day and increased by 1 mg increments after a minimum of 1 week to a maximum of 4 mg/day. GXR dosing in adolescents was initiated at 1 mg/day and increased by 1 mg increments after a minimum of 1 week to a maximum dose of 4, 5, 6 or 7 mg/day if between 34.0 and 41.4, 41.5 and 49.4, 49.5 and 58.4, and 58.5 and 91.0 kg, respectively. For ATX, either one ATX or matching placebo capsule (if optimized to up to 60 mg/day) or two capsules (if optimized to more than 60 mg) were taken. ATX dosing was initiated at 0.5 mg/kg/day in children and adolescents weighing less than 70 kg at baseline and increased to the target of approximately 1.2 mg/kg/day and, if well tolerated after a minimum of 1 week, to a maximum of 1.4 mg/kg/day. ATX dosing in children and adolescents weighing 70 kg or more at baseline (Visit 2) was initiated at 40 mg/day. This was increased to 80 mg/day and then, following 1 week at 80 mg/day, increased again to 100 mg/day, if required; this was the total permitted maximum daily dose. ATX was titrated as supported by the prescribing information/Summary of Product Characteristics European label. Patients on both ATX and GXR had the same length of time to optimize.

At least a 30% reduction in ADHD-RS-IV total score from baseline and a Clinical Global Impression-Improvement (CGI-I) rating of 1 ('very much improved') or 2 ('much improved'), in the absence of safety or tolerability issues, was considered to be an optimal response. Patients who did not achieve the above reduction, but still tolerated the treatment, could be titrated to a higher dose at the investigator's discretion. If a 30% or more reduction in ADHD-RS-IV total score from baseline was achieved, and the optimal dose was well tolerated and potential additional symptom reduction could be achieved, the dose could be increased to the next dosage strength. If necessary, the dose could be lowered once at, or prior to, Week 4 for children or Week 7 for adolescents. Following titration to optimal dose, daily morning doses were continued for an additional 6 weeks. Upon study completion or early termination, doses were tapered downward over a 2-week

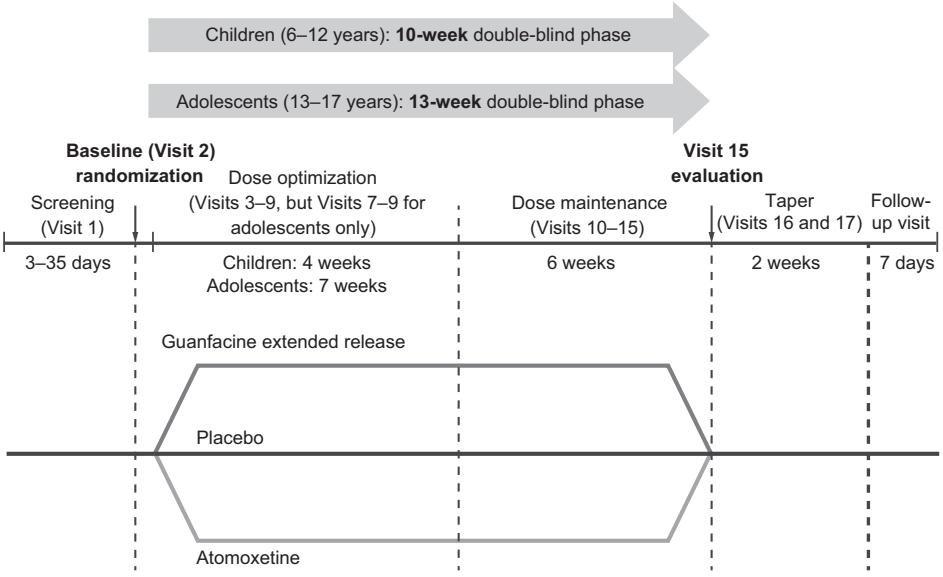

Figure 1 Study design.

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period. A follow-up safety visit took place 1 week after the last dose of investigational drug.

2.3. Assessments

The following measurements were made during visits throughout the study: investigator-rated ADHD-RS-IV (DuPaul et al., 1998), CGI-I scales (Guy, 1976), parental/proxy-rated Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P) (Weiss et al., 2007) and CGI-S (Guy, 1976) (reported in the Supplementary data) to evaluate the symptoms, disease severity, rate of improvement, function and health status of trial participants, respectively. All measures used last observation carried forward (LOCF) methodology. The LOCF technique was applied when data were missing from a particular visit, but existed before that visit. This technique creates efficacy records for missing visits by carrying data values from previous visits forward to the end. One exception was that observations from the baseline visit were never carried forward into the treatment phase visits.

2.4. Efficacy (symptoms and function)

The primary efficacy measure was the change from baseline in the investigator-rated ADHD-RS-IV score at Visit 15 (Week 10 for children and Week 13 for adolescents). The key secondary measures were the CGI-I rating scale (a binary variable; patients with 'very much' and 'much improved' ratings were combined into 1 category ['improved'] and the remaining ratings combined into a 'not improved' group) at Visit 15 and disease-specific function, which was assessed by change from baseline score of the WFIRS-P learning and school domain at Visit 15 and change from baseline score of the WFIRS-P family domain at Visit 15. The WFIRS-P is a parent-reported measure of ADHD-related functional impairment that is designed for both clinical and research use (CADDRA, 2011). The scale has demonstrated sensitivity (Maziade et al., 2009; Stein et al., 2011) and addresses the domains of daily functioning that are likely to be impaired in ADHD (Banaschewski et al., 2013; Eli Lilly and Co, 2007, 2008). It consists of 50 items rated on a 4-point Likert scale covering six domains: family, learning and school (learning and behavior), life skills, child's self-concept, social activities and risky activities. Total and domain scores are calculated as either sum or mean scores. The scale was completed by a parent/proxy. Other secondary measures included CGI-S at Visit 15 and WFIRS-P results for total and other domain scores. Details of prior medications, including behavioral therapy, were also collected at baseline. Concomitant behavioral therapy was permitted provided it had been in place for at least 1 month before the baseline visit, and was stable throughout the study period.

A comparison between GXR and the ATX reference arm was prespecified, and the comparison used the same methodology as the primary efficacy analyses. These analyses were not controlled for multiplicity.

Onset of efficacy (ADHD-RS-IV total score) was investigated as an ad-hoc analysis by looking at each of the visits in turn until the first LOCF statistical difference between GXR and placebo or ATX and placebo occurred.

2.5. Safety

Safety assessments included recording any treatment-emergent adverse events (TEAEs; coded using MedDRA® version 12.1 (MedDRA, 2009)), clinical laboratory results, physical examinations, vital signs and electrocardiograms (ECGs). In addition, brief psychiatric rating scale for children (BPRS-C) (Hughes et al., 2001; Overall and Pfefferbaum, 1982) and Columbia-suicide severity rating scale (C-SSRS) (Posner et al., 2007) assessments were performed to determine psychiatric symptomatology and if a suicide-related thought or behavior occurred.

2.6. Statistical analyses

All randomized participants who received at least one dose of investigational drug were included in the full analysis set (FAS). All participants who received at least one dose of investigational drug were also included in the safety population.

The primary efficacy variable was the change from baseline (Visit 2) for the ADHD-RS-IV total score at Visit 15. Approximately 111 randomized patients per group (GXR and placebo) were required to detect an effect size of at least 0.45 between GXR and placebo at a minimum 90% power. In addition, an ATX treatment group of 111 participants to provide reference data for an available non-stimulant therapy was included. Therefore, a total of 333 randomized participants was planned.

The primary efficacy analyses between GXR and placebo were conducted using an analysis of covariance (ANCOVA) model with the Type I error for rejecting the primary analyses null hypothesis set at 0.05 (2-sided). The least squares (LS) means and standard errors (SEs) for the treatment groups, the difference in LS means between the treatment groups with 95% confidence intervals (CIs) and the effect size were calculated as the absolute difference in LS means between the active treatment and placebo, divided by the root mean square error; the *p*-Value for difference between treatment groups was also derived. For the placebo-adjusted calculations, the LS mean and SE, effect size and *p*-Value were based on Type III sum of squares from an ANCOVA model for the change from baseline (Visit 2/Week 0), including treatment group, age group and country as fixed effects, and the baseline ADHD-RS-IV total score as a covariate.

CGI-I was analyzed using a Cochran–Mantel–Haenszel (CMH) test stratified by age group and country to examine treatment group effects at Visit 15.

CGI-S was summarized at all post-baseline visits and analyzed using a CMH test stratified by age group and country to examine treatment group effects at all visits in the maintenance period. The analyses were repeated with the responses dichotomized into two categories: 1 or 2 (normal/borderline mentally ill) and 3 or greater (mildly mentally ill or greater).

WFIRS-P key secondary measures, WFIRS-P global score and ADHD-RS-IV subscale scores were analyzed using a similar ANCOVA model as described above.

Safety outcomes were assessed for the safety population. The BPRS-C total and factor scores were summarized, and the change from baseline to Visit 15 and LOCF was calculated and summarized. A summary of results from the C-SSRS rating scale overall on-treatment, describing patients' responses at screening and all study visits, was collated. A 'yes' response was reported for the suicidal ideation category as either 'wish to be dead' or 'non-specific active suicidal thoughts' or to the suicidal behavior category as 'non-suicidal self-injurious behavior'.

3. Results

3.1. Patient disposition and baseline characteristics

Of 338 randomized patients, 272 (80.5%) completed the study to Visit 15 and 66 (19.5%) terminated prematurely (24/115 [20.9%], 23/112 [20.5%] and 19/111 [17.1%] from the GXR, ATX and placebo groups, respectively) (Figure 2). The most frequently reported reason for study discontinuation was lack of efficacy in 5/115 (4.3%), 5/112 (4.5%) and

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14/111 (12.6%) patients treated with GXR, ATX and placebo, respectively. One patient in the GXR group was lost to follow-up before receiving any treatment, so was excluded from the FAS and safety populations.

Baseline characteristics were similar across treatment groups (Table 1). The mean age (standard deviation [SD]) across treatment groups was 10.8 (2.8) years; children and adolescents comprised 71.8% and 28.2% of patients, respectively (FAS/safety population). The majority of patients had the combined subtype of ADHD (85.2%) with a mean ADHD-RS-IV total score of 43.3 at baseline and mean time since diagnosis of 2.2 years. The use of at least one prior stimulant medication was reported by approximately 50% of all patients (GXR: 54 [47.4%]; ATX: 57 [50.9%]; placebo: 56 [50.5%]), and the use of non-stimulant, non-antipsychotic, psychotropic medication was reported by 20.8% of patients (GXR: 30 [26.3%]; ATX: 22 [19.6%]; placebo: 18 [16.2%]). The distribution of randomized patients by country are shown in the Supplementary data.

3.2. Optimal dose

Following dose optimization (dispensed at Visit 10), the mean (SD) optimal doses were 3.6 (1.3) mg for GXR and 42.1 (20.1) mg for ATX. The mean weight-adjusted optimal doses were 0.09 (0.03) mg/kg for GXR and 1.03 (0.21) mg/kg for ATX. No protocol violations were reported; total mean compliance (SD) was 99.2% (2.9).

3.3. Efficacy

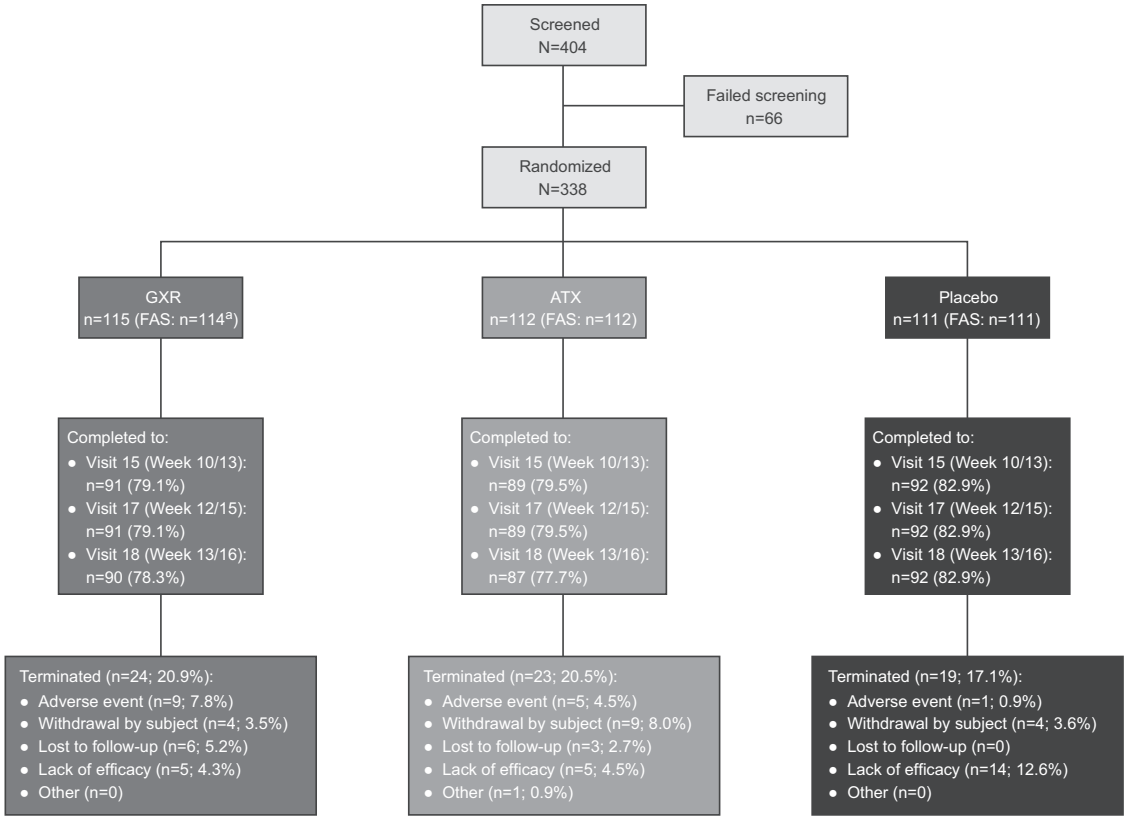
3.3.1. Primary endpoint

Mean ADHD-RS-IV total scores at baseline were similar across treatment groups (GXR: 43.1; ATX: 43.7; placebo: 43.2) (Table 2). The LS mean (SE) change in ADHD-RS-IV total score from baseline to Visit 15 (Week 10/13) was greater for GXR (−23.9 [1.2]) compared with placebo (−15.0 [1.2]) (Table 2). The placebo-adjusted difference in LS mean change from baseline in ADHD-RS-IV total score (95% confidence interval [CI], *p*-Value; effect size) for GXR was −8.9 (−11.9, −5.8, $p<0.001$; 0.76).

The LS mean (SE) change in ADHD-RS-IV total score from baseline to Visit 15 (Week 10/13) for ATX was −18.8 (1.2). The placebo-adjusted difference in LS mean change from baseline in ADHD-RS-IV total score (95% CI, *p*-Value; effect size) for ATX was −3.8 (−6.8, −0.7, $p=0.017$; 0.32).

3.3.2. Key secondary endpoints

The proportions (%) of patients showing an improvement (1 ['very much improved'] or 2 ['much improved']) in CGI-I at Visit 15 were 67.9% (76/114), 56.3% (63/112) and 44.1% (49/111) for GXR, ATX and placebo, respectively. Compared with placebo, the difference in the percentage of patients showing improvement in CGI-I rating (95% CI, *p*-Value) was 23.7 (11.1, 36.4, $p<0.001$) for GXR and 12.1 (−0.9, 25.1, $p=0.024$) for ATX (Figure 3).



[a]One patient was randomized to GXR but did not receive any treatment and was excluded from the FAS and the safety population.
ATX, atomoxetine; FAS, full analysis set; GXR, guanfacine extended release.

Figure 2 Patient disposition (all enrolled patients).

Table 1 Patient baseline characteristics and demographics data (safety population/full analysis set).

	GXR ($n=114$)	ATX ($n=112$)	Placebo ($n=111$)
Mean (SD) age, years	10.9 (2.77)	10.5 (2.81)	11.0 (2.76)
Age group, *n* (%)			
6–12 years	81 (71.1)	82 (73.2)	79 (71.2)
13–17 years	33 (28.9)	30 (26.8)	32 (28.8)
Male, *n* (%)	76 (66.7)	87 (77.7)	86 (77.5)
Mean (SD) BMI, kg/m^2	18.79 (3.02)	18.74 (2.95)	18.78 (2.76)
ADHD subtype, *n* (%)			
Predominantly inattentive	15 (13.2)	10 (8.9)	11 (9.9)
Predominantly hyperactive-impulsive	6 (5.3)	3 (2.7)	5 (4.5)
Combined subtype	93 (81.6)	99 (88.4)	95 (85.6)
Mean (SD) time since ADHD diagnosis, years	2.3 (2.67)	2.0 (2.27)	2.1 (2.57)
Mean (SD) baseline ADHD-RS-IV score	43.1 (5.47)	43.7 (5.86)	43.2 (5.60)
Baseline CGI-S, *n* (%)			
Moderately ill	21 (18.4)	23 (20.5)	33 (29.7)
Markedly ill	60 (52.6)	53 (47.3)	49 (44.1)
Severely ill	30 (26.3)	33 (29.5)	27 (24.3)
Among the most extremely ill subjects	3 (2.6)	3 (2.7)	2 (1.8)
Current psychiatric comorbidities, *n* (%)			
None	97 (85.1)	101 (90.2)	96 (86.5)
Diagnosis of ODD[a]	17 (14.9)	10 (8.9)	14 (12.6)
Other	1 (0.9)	1 (0.9)	1 (0.9)
Oppositional symptoms, *n* (%)[b]	60 (53.1)[c]	68 (61.8)[d]	60 (54.1)

ADHD, attention-deficit/hyperactivity disorder; ADHD-RS-IV; ADHD Rating Scale version IV; ATX, atomoxetine; BMI, body mass index; CGI-S, Clinical Global Impression-Severity; GXR, guanfacine extended release; ODD, oppositional defiant disorder; and SD, standard deviation.

[a]Diagnosis of ODD per psychiatric history case report form comes from the diagnosis of ODD in the current psychiatric comorbidities section.

[b]Defined as a Conners' Parent Rating Scales-Revised: Long oppositional subscale score at the baseline visit of ≥ 14 for males and ≥ 12 for females.

[c]$n=113$.

[d]$n=110$.

The placebo-adjusted difference in LS mean change from baseline in WFIRS-P learning and school domain at Visit 15 (95% CI, *p*-Value; effect size) for GXR was −0.22 (−0.36, −0.08, $p=0.003$; 0.42) and for WFIRS-P family domain at Visit 15 (95% CI, *p*-Value; effect size) was −0.21 (−0.36, −0.06, $p=0.006$; 0.38). The corresponding values for ATX were −0.16 (−0.31, −0.02, $p=0.026$; 0.32) and −0.09 (−0.24, −0.06, $p=0.242$; 0.16), respectively.

3.3.3. Other secondary endpoints

The placebo-adjusted difference in LS mean change from baseline in the ADHD-RS-IV hyperactivity/impulsivity score (95% CI, *p*-Value; effect size) for GXR was −4.8 (−6.4, −3.2, $p<0.001$; 0.79) and a similar change was seen for the inattention subscale score (−4.1 [−5.8, −2.5, $p<0.001$; 0.66]). The placebo-adjusted difference in LS mean change from baseline in the ADHD-RS-IV hyperactivity/impulsivity score (95% CI, *p*-Value; effect size) for ATX was −2.0 (−3.6, −0.4, $p=0.014$; 0.33) and for the inattention subscale score was −1.6 (−3.3, −0.0, $p=0.053$; 0.26).

The ADHD-RS-IV total scores summarized across weight-adjusted dose are presented in Table 2. The placebo-adjusted difference in LS mean change from baseline in WFIRS-P global score at Visit 15 (95% CI, *p*-Value; effect size) for GXR was −0.17 (−0.27, −0.06, $p<0.001$; 0.44) and for ATX was −0.10 (−0.21, −0.001, $p=0.048$; 0.28). WFIRS-P for global scores and all six domains are presented in Figure 4.

Compared with placebo, the difference in the percentage of patients with normal/borderline CGI-S at Visit 15 (95% CI, *p*-Value) for GXR was 12.3% (0.2, 24.3, $p=0.04$) and 0.7% (−10.8, 12.1, $p=0.69$) for ATX.

There was a significant difference between GXR and ATX when analyzing the difference in LS mean change from baseline in ADHD-RS-IV total score at Visit 15 (95% CI, *p*-Value; effect size); −5.1 (−8.2, −2.0, $p=0.001$; 0.440) favoring GXR (secondary analyses, not controlled for multiplicity).

3.3.4. Ad-hoc analyses

Assessing each visit in turn, onset of efficacy for GXR was seen at Visit 3 (Week 1) with a placebo-adjusted difference in LS mean (95% CI, *p*-Value; effect size) of −2.6 (−4.3, −0.9, $p=0.003$; 0.40). There was no significant placebo-adjusted difference in LS mean (95% CI, *p*-Value; effect size) for ATX until Visit 5 (Week 3): −2.7 (−5.0, −0.4, $p=0.024$; 0.31).

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Table 2 ADHD-RS-IV total scores (A) and ADHD-RS-IV total score by GXR weight-adjusted dose (B) (full analysis set).

A	GXR (n=114)	ATX (n=112)	Placebo (n=111)
Baseline mean (SD) score	43.1 (5.47)	43.7 (5.86)	43.2 (5.60)
Visit 15 LOCF mean (SD) score	19.2 (11.85)	25.0 (12.97)	28.1 (14.13)
Mean (SD) change from baseline to Visit 15 LOCF	−23.9 (12.41)	−18.6 (11.91)	−15.0 (13.07)
Comparison to placebo[a]			
LS mean	−23.9	−18.8	−15.0
Difference (95% CI) in LS means[b]	−8.9 (−11.9, −5.8)	−3.8 (−6.8, −0.7)	
Effect size	0.76	0.32	
p-Value	<0.001	0.017[c]	

B	GXR (0.01-0.04 mg/kg) n=13	GXR (0.05-0.08 mg/kg) n=40	GXR (0.09-0.12 mg/kg) n=47	GXR (0.13-0.16 mg/kg) n=12
Visit 15 LOCF mean (SD)[d] score	20.2 (14.49)	19.3 (12.35)	17.9 (9.76)	22.5 (15.08)
Mean (SD) change from baseline to Visit 15 LOCF	−23.1 (15.99)	−22.3 (12.03)	−26.2 (11.24)	−21.2 (13.90)

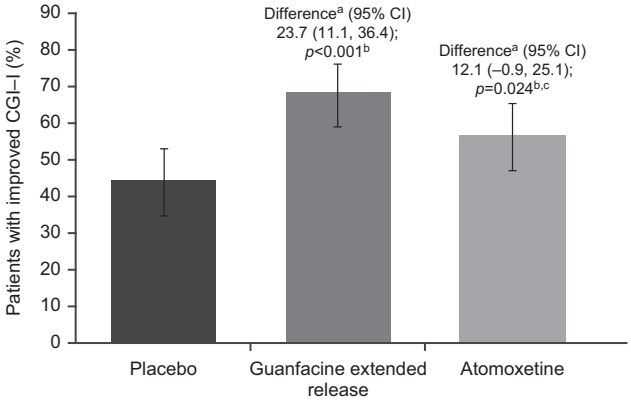
ADHD-RS-IV; Attention-Deficit/Hyperactivity Disorder Rating Scale version IV; ANCOVA, analysis of covariance; ATX, atomoxetine; CI, confidence interval; GXR, guanfacine extended release; LOCF, last observation carried forward; LS, least squares; and SD, standard deviation.

[a]LS mean and standard error, effect size and p-Value are based on Type III sum of squares from an ANCOVA model for the change from baseline, including treatment group, age group and country as fixed effects, and baseline value as a covariate.

[b]A negative difference in LS mean indicates a positive effect of the active treatment over placebo.

[c]Nominal p-Value not corrected for multiplicity.

[d]Subjects not assigned to a weight-adjusted dose at baseline but are included under all GXR treated.



[a]Difference in percentage of patients with improved CGI–I for active treatment compared with placebo.
[b]Based on Cochran–Mantel–Haenszel statistic comparing the respective treatment group with placebo, with country and age included as stratification factors.
[c]Nominal p-value uncorrected for multiplicity.
CGI–I, Clinical Global Impression–Improvement; CI, confidence interval.

Figure 3 Analyses of CGI-I (full analysis set).

3.4. Safety

3.4.1. Treatment-emergent adverse events

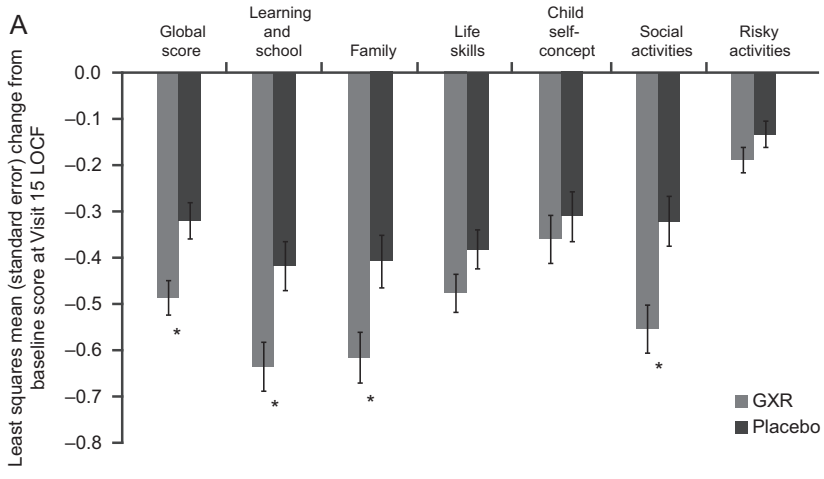
Eighty-eight (77.2%) patients in the GXR, 76 (67.9%) in the ATX and 73 (65.8%) in the placebo groups experienced TEAEs during the study (Table 3). The majority of subjects reported TEAEs of mild or moderate intensity: GXR 33.3% mild, 36.8% moderate, 7.0% severe; ATX 41.1% mild, 25.0% moderate, 1.8% severe; placebo 41.4% mild, 21.6% moderate, and 2.7% severe. No deaths occurred during the study. Some patients experienced TEAEs that led to discontinuation from the study (GXR: 9 [7.9%]; ATX: 5 [4.5%]; placebo: 1 [0.9%]). The most commonly reported TEAEs with GXR were somnolence, headache and fatigue, whereas with ATX they were decreases in appetite, nausea and fatigue (Table 3). The most common TEAEs with placebo were headache, fatigue and abdominal pain.

3.4.2. Serious adverse events

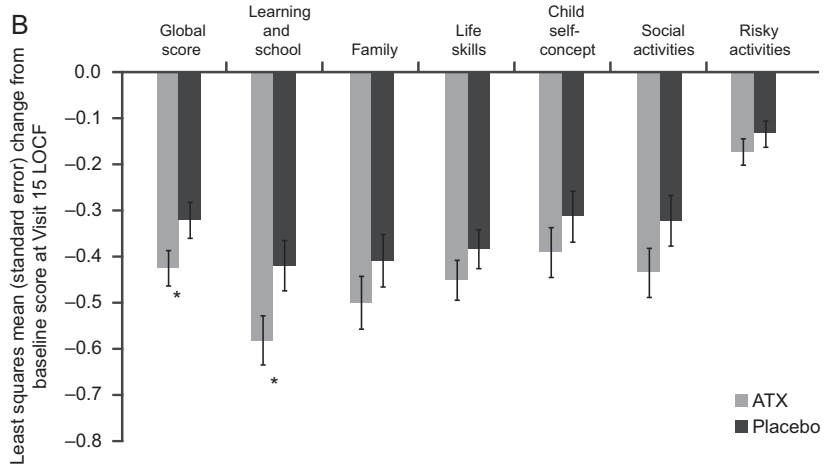
The occurrence of serious adverse events (SAEs) was low in all treatment groups. Overall, three (1.1%) were reported: one in the placebo group (syncope [considered treatment related]) and two in the GXR group (syncope [considered treatment related] and appendicitis [occurred prior to randomization and not treatment related]).

3.4.3. ECG and vital signs

There were generally no GXR-related, clinically meaningful changes in ECG and QTc-related parameters. However, mean changes from baseline were observed in pulse, systolic and diastolic blood pressures for GXR and ATX. For example, at Visit 15 (Week 10/13), patients receiving GXR demonstrated a mean decrease from baseline in supine pulse rate, supine systolic blood pressure and supine diastolic blood pressure (−3.3 beats per minute [bpm], −2.3 mmHg and −2.2 mmHg, respectively) compared with those receiving ATX (+2.7 bpm, +1.7 mmHg and +2.6 mmHg, respectively) and placebo (−0.2 bpm, +0.6 mmHg and +1.3 mmHg, respectively). The blood pressure and pulse observed in this study are consistent with the overall



	Global score	Learning and school	Family	Life skills	Child self-concept	Social activities	Risky activities
Difference[a] in least squares mean (95% CI)	−0.165 (−0.266, −0.064)	−0.217 (−0.358, −0.076)	−0.209 (−0.358, −0.059)	−0.094 (−0.204, 0.017)	−0.049 (−0.191, 0.094)	−0.233 (−0.374, −0.092)	−0.056 (−0.131, 0.018)
Effect size (95% CI)	0.44 (0.17, 0.71)	0.42 (0.15, 0.70)	0.38 (0.11, 0.64)	0.23 (−0.04, 0.50)	0.09 (−0.18, 0.37)	0.45 (0.18, 0.72)	0.21 (−0.07, 0.48)
p-value[b]	0.001	0.003	0.006	0.096	0.500	0.001	0.139



	Global score	Learning and school	Family	Life skills	Child self-concept	Social activities	Risky activities
Difference[a] in least squares mean (95% CI)	−0.104 (−0.207, −0.001)	−0.162 (−0.305, −0.019)	−0.090 (−0.241, 0.061)	−0.067 (−0.180, 0.046)	−0.078 (−0.222, 0.066)	−0.111 (−0.253, 0.031)	−0.039 (−0.115, 0.037)
Effect size (95% CI)	0.28 (0.00, 0.55)	0.32 (0.04, 0.60)	0.16 (−0.11, 0.43)	0.16 (−0.11, 0.43)	0.15 (−0.12, 0.42)	0.21 (−0.06, 0.49)	0.14 (−0.14, 0.42)
p-value[b]	0.048	0.026	0.242	0.242	0.288	0.124	0.315

[a]Calculated as treatment–placebo; a negative difference indicates a postive effect of active treatment over placebo.
[b]Uncorrected for multiplicity.
*$p<0.05$.
CI, confidence interval; GXR, guanfacine extended release; LOCF, last observation carried forward; WFIRS-P, Weiss Functional Impairment Rating Scale–Parent Report.

Figure 4 Change from baseline to Visit 15 in WFIRS-P domain and subdomain scores (full analysis set) for (A) guanfacine extended release versus placebo; and (B) atomoxetine versus placebo.

safety profile in previous studies of this class of agent. No patients withdrew from the study as a result of any ECG or blood pressure abnormality.

3.4.4. Other observations related to safety

The change from baseline in the BPRS-C total score at Week 10/13 (mean [SD]) was −8.3 (8.4), −6.5 (9.2) and −5.6 (8.8) for GXR, ATX and placebo, respectively. Overall for lifetime history, 10 patients had 1 or more 'yes' responses on the C-SSRS (GXR: 5; ATX: 3; placebo: 2) with 'yes' responses to the suicidal ideation category of the C-SSRS of 'wish to be dead' (GXR: 4; ATX: 3; placebo: 2) and 1 patient to 'non-specific active suicidal thoughts' (ATX: 1) or to the suicidal behavior category 'non-suicidal self-injurious behavior' (GXR: 1). Overall on-treatment, 10 patients had 1 or more 'yes' responses on the C-SSRS (GXR: 3; ATX: 5; placebo: 2). A 'yes' response was reported for the suicidal ideation category of the C-SSRS as either 'wish to be dead' (GXR: 2; ATX: 3; placebo: 1) or 'non-specific active suicidal thoughts' (GXR: 1;

Table 3 TEAEs[a] occurring in ≥5% of patients in any treatment group, by treatment group (safety population).

Preferred term	GXR ($n=114$)		ATX ($n=112$)		Placebo ($n=111$)	
	Patients, %[b]	Number of AEs	Patients, %[b]	Number of AEs	Patients, %[b]	Number of AEs
Any TEAE	88 (77.2)	509	76 (67.9)	424	73 (65.8)	322
Somnolence	50 (43.9)	94	20 (17.9)	32	16 (14.4)	18
Headache	30 (26.3)	51	22 (19.6)	36	27 (24.3)	46
Fatigue	29 (25.4)	45	24 (21.4)	32	20 (18.0)	22
Abdominal pain	19 (16.7)	29	19 (17.0)	31	20 (18.0)	32
Nausea	18 (15.8)	19	30 (26.8)	54	11 (9.9)	13
Decreased appetite	15 (13.2)	20	31 (27.7)	44	12 (10.8)	23
Dizziness	14 (12.3)	18	17 (15.2)	24	9 (8.1)	9
Insomnia	13 (11.4)	21	8 (7.1)	10	7 (6.3)	7
Increased appetite	12 (10.5)	15	4 (3.6)	4	9 (8.1)	11
Diarrhea	10 (8.8)	16	2 (1.8)	3	15 (13.5)	18
Anxiety	9 (7.9)	16	7 (6.3)	18	8 (7.2)	15
Upper abdominal pain	7 (6.1)	7	2 (1.8)	3	6 (5.4)	6
Pyrexia	7 (6.1)	9	3 (2.7)	4	4 (3.6)	4
Nasopharyngitis	6 (5.3)	7	3 (2.7)	3	6 (5.4)	7
Nervousness	6 (5.3)	7	6 (5.4)	6	6 (5.4)	7
Vomiting	6 (5.3)	8	18 (16.1)	29	8 (7.2)	9

AE, adverse event; ATX, atomoxetine; CI, confidence interval; GXR, guanfacine extended release; TEAE, treatment-emergent adverse event.

[a]TEAEs were defined as AEs that started or worsened during the period between the day of a subject's first dose of active treatment and the third day (inclusive) after treatment was stopped.

[b]The denominator for percentages was the number of subjects in the safety population of each treatment group.

ATX: 0; placebo: 2) or to the suicidal behavior category 'non-suicidal self-injurious behavior' (GXR: 1; ATX: 2; placebo: 0). There were no completed suicides reported. For treatment-emergent C-SSRS data, there were 7 patients who responded 'yes' to the suicidal ideation category (GXR: 2; ATX: 3; placebo: 2).

4. Discussion

GXR demonstrated robust efficacy in terms of improvement of ADHD core symptoms and global functioning in children and adolescents with ADHD in this placebo controlled, 10-13-week, Phase III study. There were clinically relevant and statistically significant differences seen in the primary outcome measure, change from baseline in ADHD-RS-IV total score with GXR. Furthermore, statistically significant differences were seen for the key secondary variable measures (CGI-I, WFIRS-P learning and school domains and WFIRS-P family domain) for GXR when compared with placebo. The reference arm, ATX, showed treatment effects consistent with those seen in other studies (Kratochvil et al., 2001; Michelson et al., 2002; Spencer et al., 2001, 2002).

The majority of participants who received GXR ($n=91$; 79%) completed the study. GXR was generally well tolerated, with most TEAEs mild or moderate in severity; the TEAEs that led to study discontinuation included somnolence, insomnia and fatigue. The three SAEs reported in the study were one case of appendicitis (prior to randomization) and two cases of syncope (one with placebo and one with GXR). Somnolence, headache and fatigue were more frequently reported in patients treated with GXR than in those who received ATX, whereas decreased appetite, nausea and vomiting were reported more frequently in the ATX group. The most common AEs reported here were consistent with the known safety profiles of GXR (Biederman et al., 2008a,b; Sallee et al., 2009a, 2009b; Spencer et al., 2009), ATX (Kratochvil et al., 2001; Michelson et al., 2002; Spencer et al., 2001, 2002) and in a recent meta-analysis of monotherapy/add-on to stimulant therapy in children/adolescents with ADHD (Hirota et al., 2014). Analyses showed slightly more pronounced mean changes from baseline in pulse, systolic and diastolic blood pressures for GXR and ATX than placebo; these changes were not unexpected for these two active treatments. There were no clinically meaningful changes on ECG and QTc related parameters, and BPRS-C and C-SSRS scores were similar at baseline and endpoint for all three treatment groups.

Importantly, while this study was not designed to provide a head-to-head comparison between GXR and ATX, secondary pre-specified analyses (not controlled for multiplicity) favored GXR versus ATX in ADHD-RS-IV score (−5.1 [−8.2, −2.0], $p=0.001$; 0.440), where the mean change from baseline was greater for GXR than ATX. This is consistent with other findings in the literature. In a matching-adjusted indirect comparison (MAIC) analysis of six studies (two GXR, four ATX), children and adolescents with ADHD who received GXR (0.09-0.12 mg/kg/day) were compared with those receiving ATX (1.2 mg/kg/day). In the base case analysis comprising three of the studies, GXR produced a significantly greater reduction in mean ADHD-RS-IV total and subscale

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scores from baseline to final on-treatment assessment than ATX (mean −7.0 [SE 2.2]; $p<0.01$) (Sikirica et al., 2013). A sensitivity analysis comprising all six studies gave similar results (mean −7.6 [SE 1.4]; $p<0.01$). Another MAIC study of GXR and ATX treatment in children and adolescents with ADHD and ODD also showed greater symptom reduction with GXR than with ATX (Signorovitch et al., 2012).

In this study, the onset of treatment action observed was more rapid with GXR than ATX. GXR achieved a statistical separation from placebo at Week 1 ($p=0.001$) versus Week 3 for ATX ($p=0.024$), as measured by the ADHD-RS-IV score. The 4–7-week dose-optimization period was designed for each medication based on the prescribing information/Summary of Product Characteristics for each product and allowed the investigator flexibility to titrate GXR and ATX to an optimal therapeutic level in the absence of safety/tolerability issues (EMC, 2013; NIH, 2014). Adverse events may have limited the ability to titrate ATX to the optimal dose rapidly, and may have contributed to the longer time to response relative to GXR. Importantly, the optimized doses reached in the trial were generally well balanced between the two treatments and by Week 7, the majority of patients in both the GXR (79%) and ATX (73%) groups were receiving the target daily dose referenced in their respective prescribing information/Summary of Product Characteristics. The additional 6-week maintenance treatment period in the trial also gave sufficient time for patients to achieve their fullest potential response at the optimized dose for both medications.

This randomized, double-blind, placebo-controlled study enrolled a large number of patients, a quarter of whom were female, at multiple centers across Europe, the USA and Canada. Individuals with comorbid conditions such as post-traumatic stress disorder, bipolar affective disorder and severe anxiety disorder were excluded from the study, but it is often the case in ADHD studies that patients with current uncontrolled psychiatric comoribidities are excluded from the trial populations (Kratochvil et al., 2002; Michelson et al., 2002; Spencer et al., 2002). As such, the trial population may not be a true reflection of patients with ADHD in the real-world setting, but the findings of the current study are consistent with findings from previous GXR trials (Biederman et al., 2008a,b; Sallee et al., 2009a,b). While the proportion of patients recording a formal diagnosis of comorbid ODD in the present trial is not as high as the 40–60% cited in the literature (Biederman and Faraone, 2005; Hazell, 2010; Olfson, 2004), the percentage of patients with a high burden of comorbid oppositional symptoms (more than 50% in all treatment groups, measured by the Conners' Parent Rating Scale) suggests that the data are generalizable to the wider population.

This Phase III study from centers in Europe, the USA and Canada evaluated the efficacy and safety of a once-daily optimized dose of GXR in children and adolescents with moderate-to-severe symptoms of ADHD and concluded that GXR was more effective than placebo in improving core symptoms and global functioning in patients with ADHD. Efficacy was also demonstrated for the reference arm of ATX compared with placebo. The pattern and incidence of TEAEs are consistent with known, published profiles of both GXR and ATX. This study demonstrates a positive risk-benefit profile in the treatment of children and adolescents with ADHD with GXR doses of up to 7 mg (0.05–0.12 mg/kg/day) and suggests that GXR will be a useful addition to the existing classes of medication effective in ADHD.

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Funding for this study was provided by Shire Development, LLC. Shire Development, LLC was involved in the study design, collection, analyses and interpretation of the data, and checking the information for scientific accuracy.

Contributors

The study sponsor was involved in the study design, collection, analyses and interpretation of data and checking of information for scientific accuracy.

Amaia Hervas was the Principal Co-ordinator of the study and the Principle Investigator in Spain. Michael Huss was the Principal Investigator at Germany/Mainz. Mats Johnson was the Principal Investigator at Gothenburg/Sweden. Fiona McNicholas was the Principal Investigator at the Irish site. Judy van Stralen was a Principal Investigator at a Canadian site. Sasha Sreckovic contributed to the analysis plan, conduct, analysis, safety, review and interpretation of data. Andrew Lyne and Ralph Bloomfield analyzed and interpreted the statistical data. Vanja Sikirica contributed to the design, analysis plan, analysis, review and interpretation of data. Brigitte Robertson contributed to the design, analysis plan, conduct, analysis, review and interpretation of data.

All authors contributed to and have approved the final manuscript. The content of this manuscript, the ultimate interpretation, and the decision to submit it for publication in *European Neuropsychopharmacology* was made by the authors independently.

Conflict of interest

AH has been on advisory boards for Janssen, Eli Lilly and Shire. MH is a member of advisory boards, advisor and recipient of honoraria as a speaker for Eli Lilly, Janssen Cilag, Medice, Novartis, and Shire, and has received consultation fees from Engelhard Arzneimittel and Steiner Arzneimittel. MJ has received funding for research support, advisory boards or speaker honoraria from Lilly, Shire, Vifor Pharma, Janssen, Otsuka, PCM Scientific and WM Lundgrens Research Fund. FM has acted as a speaker for Shire and Janssen Cilag and is on an advisory board for Shire. JvS has received research funding from Shire, and consultancy fees and fees for speaking at educational events from Shire, Bristol-Myers Squibb, Janssen and Purdue. SS, AL, RB, VS and BR are employees of Shire and own shares and stock options.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.euroneuro.2014.09.014.

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