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Extended-release guanfacine hydrochloride in 6–17-year olds with ADHD: a randomised-withdrawal maintenance of efficacy study

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Background: Extended-release guanfacine hydrochloride (GXR), a selective α2A-adrenergic agonist, is a nonstimulant medication for attention-deficit/hyperactivity disorder (ADHD). This phase 3, double-blind, placebo-controlled, randomised-withdrawal study evaluated the long-term maintenance of GXR efficacy in children/adolescents with ADHD. **Methods:** Children/adolescents (6–17 years) with ADHD received open-label GXR (1–7 mg/day). After 13 weeks, responders were randomised to GXR or placebo in the 26-week, double-blind, randomised-withdrawal phase (RWP). The primary endpoint was the percentage of treatment failure (≥50% increase in ADHD Rating Scale version IV total score and ≥2-point increase in Clinical Global Impression-Severity compared with RWP baseline, at two consecutive visits). The key secondary endpoint was time to treatment failure (TTF). **Trial registration:** ClinicalTrials.gov identifier NCT01081145; EudraCT 2009-018161-12. **Results:** A total of 528 participants enrolled; 316 (59.8%) entered the RWP. Treatment failure occurred in 49.3% of the GXR and 64.9% of the placebo group ($p = 0.006$). TTF was significantly longer in GXR versus placebo ($p = 0.003$). GXR was well tolerated. **Conclusions:** Guanfacine hydrochloride demonstrated long-term maintenance of efficacy compared with placebo in children/adolescents with ADHD. Implications of the placebo substitution design and findings with different ADHD medications are discussed. **Keywords:** Long term; efficacy; randomised; withdrawal; attention-deficit/hyperactivity disorder; guanfacine.

Introduction

Nonstimulant medications, such as atomoxetine (ATX), clonidine and guanfacine are considered alternatives to psychostimulants for the treatment of attention-deficit/hyperactivity disorder (ADHD) (Childress & Sallee, 2014). The selective noradrenaline reuptake inhibitor ATX is an approved treatment for ADHD in Europe, Asia-Pacific and North America and has demonstrated maintenance of efficacy in children and adolescents using a relapse-prevention or randomised-withdrawal trial design (Buitelaar et al., 2007; Michelson et al., 2004). Clonidine is an α2-adrenergic agonist that enhances the effect of noradrenaline on α2-adrenergic receptors in the prefrontal cortex (Arnsten, Steere, & Hunt, 1996), and has a high affinity for all three subtypes of α2-adrenoceptors (Arnsten, Scahill, & Findling, 2007); a long-acting formulation is approved for children and adolescents in the United States and South Korea. Guanfacine is a selective α2A-adrenoceptor agonist (Arnsten et al., 2007). A long-acting formulation (guanfacine extended release; GXR) is approved for children and adolescents in the United States and Canada. It was recently approved in Europe in children and adolescents (6–17 years) for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. Short-term (8–9 week) placebo-controlled clinical trials in children and adolescents have shown an effect size of 0.43–0.86 on ADHD-Rating Scale version IV (ADHD-RS-IV) symptom scores (Biederman, Melmed, Patel, McBurnett, Konow, et al., 2008; Hervas et al., 2014; Sallee, McGough, et al. 2009).

The objective of this study was to evaluate long-term (26-week) maintenance of GXR efficacy in children and adolescents with ADHD in Europe and the United States who responded to short-term (13-week), open-label treatment. The randomised-withdrawal design represents the current state-of-the-art approach to evaluating efficacy over the long term (European Medicines Agency, 2010; Goodman, 2013), as it tests the need for continued treatment rather than simply assessing the continued benefit of open extension treatment. Owing to its more rigorous methodology, this design is now required by regulatory agencies in the United States and Europe to support a label claim of long-term efficacy.

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Methods

Study design

This phase 3, multicentre, double-blind, placebo-controlled, randomised-withdrawal study, which included 7 weeks of open-label dose optimisation, followed by 6 weeks of open-label maintenance of the optimised dose (ClinicalTrials.gov identifier: NCT01081145 and EudraCT: 2009-018161-12) was conducted in 67 centres across 8 European countries (Belgium, France, Germany, Italy, the Netherlands, Spain, Sweden and the United Kingdom), the United States and Canada between May 2010 and June 2013. The purpose of the open-label phase was to identify responders, who would then either continue with their optimised GXR dose or discontinue active treatment using random assignment, to assess maintenance of efficacy. Participants were enrolled from specialist outpatient clinics, or were otherwise identified by the clinical research programmes that participated in the trial. The study was performed in accordance with the International Conference on Harmonisation of Good Clinical Practice (GCP) regulations, 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 centre before study initiation. Each participant's parent or legal guardian provided written, informed consent and assent was obtained from each participant.

Study population

Male and female participants aged 6–17 years who satisfied the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) criteria for a primary diagnosis of ADHD, any subtype, based on a detailed psychiatric evaluation by a licenced clinician using the ADHD-RS-IV and the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version (K-SADS-PL) could be enrolled into the study. At baseline, participants had an ADHD-RS-IV total score of at least 32, and symptom severity was judged to be at least moderate, as defined by a minimum Clinical Global Impression-Severity (CGI-S) score of 4.

Participants with age-appropriate intellectual functioning, blood pressure measurements within the 95th percentile for age, sex and height, and the ability to swallow tablets were eligible to participate. Girls of childbearing potential underwent pregnancy tests at screening and baseline and had to comply with protocol contraceptive requirements. Participants and their parent/legal guardian had to be willing, able and likely to comply with study procedures and restrictions. Exclusion criteria (at Screening Visit 1 or enrolment at open-label baseline [if reassessed]) included:

1. clinically significant illness, including clinically significant abnormal laboratory values or conditions that might, in the opinion of the investigator, present an unacceptable risk to the participant or confound interpretation of the study results;
2. current, controlled (requiring a prohibited medication or behavioural modification programme) or uncontrolled comorbid psychiatric diagnoses (except oppositional defiant disorder [ODD]), including any severe comorbid Axis II disorders or severe Axis I disorders such as post-traumatic stress disorder, bipolar disorder, psychosis, pervasive developmental disorder, obsessive–compulsive disorder, substance abuse disorder, or other symptomatic manifestations or lifetime history of bipolar disorder, psychosis or conduct disorder that, in the opinion of the investigator, contraindicate GXR treatment or confound efficacy or safety assessments. These conditions were excluded to ensure that the effect of the medication on the condition of greatest interest (ADHD) was not confounded. As in most ADHD trials, ODD was permitted due to the large overlap of impulsive and oppositional symptoms in ADHD;
3. history/presence of cardiac abnormalities, cardiac conduction problems, serious heart rhythm abnormalities, clinically significant bradycardia, exercise-related cardiac events or syncope;
4. orthostatic hypotension or hypertension.

In addition, participants with seizures, glaucoma, a history of alcohol or substance abuse, and those with a serious tic disorder (including Tourette's syndrome) were excluded. Participants who were currently considered a suicide risk (investigator opinion), had previously made a suicide attempt or demonstrated prior or current active suicidal ideation were also excluded.

The Oppositional Subscale of the Conners' Parent rating Scale-Revised: Long Form (CPRS-R:L; Enrolment, Visit 2) was used to characterise oppositional symptoms in the baseline population.

Randomisation

Treatments were automatically assigned by an Interactive Voice Response System (IVRS). Randomisation was stratified by country (≥40% from European countries) and age group (6–12 and 13–17 years), with at least 25% per group being adolescents (aged 13–17 years).

Study drug administration

The study comprised six time periods: screening and washout; 7-week, open-label dose optimisation; 6-week, open-label maintenance of optimised dose; 26-week, double-blind, randomised-withdrawal of treatment; 2-week, post-treatment taper and 1-week safety follow-up (see Appendix S1, Figure S1). GXR (Shire US Manufacturing, Owings Mills, Maryland, US) was provided as an extended-release tablet (1, 2, 3 and 4 mg) to be taken once daily.

Open-label phase

Following screening, eligible participants received an intial dose of 1 mg GXR, once daily in the morning. During the first 7 weeks (open-label, optimisation period), the dose of GXR was titrated to a pre-specified response, defined as at least a 30% reduction from open-label baseline (Visit 2/Week 0) in the ADHD-RS-IV total score and a CGI-S score of 1 or 2 (i.e. normal or minimally ill, respectively) with tolerable side effects. The dose could be further increased if the clinician felt further improvement was possible and the medication was well tolerated. All participants initiated treatment at 1 mg/day and their dose was increased in 1 mg increments after a minimum of 1 week to a maximum of 4 mg/day in children (6–12 years) and 7 mg/day in adolescents (13–17 years). The higher dose levels allowed for adolescents ensured that the weight-adjusted target dose range of 0.05–0.12 mg/kg/day could be achieved through up-titration (e.g. 4 mg/day for 34.0–41.4 kg; 5 mg/day for 41.5–49.4 kg; 6 mg/day for 49.5–58.4 kg; 7 mg/day for 58.5–91.0 kg). Participants continued taking the same daily morning dose that was dispensed at Visit 9/Week 7 for the remainder of the open-label, dose-maintenance phase.

Randomised-withdrawal phase

Participants who met the response criteria in the open-label phase, defined as at least a 30% reduction in ADHD-RS-IV total score and a CGI-S score of 1 or 2 at both Weeks 12 and 13, were entered into the 26-week, double-blind, randomised-withdrawal

phase (RWP). At Visit 13/Week 13, responders were randomised 1:1 to receive either their optimised GXR dose or matching placebo. Participants who entered the RWP underwent a 2-week blinded taper during Weeks 14 and 15 according to a schedule that was based on their optimised GXR dose.

All participants who completed the study (or withdrew early) were tapered off the study drug at Visit 23 (RWP) or Visit 13 (open-label phase) and a safety follow-up visit occurred 7–9 days after the last dose of study drug. Drug dose was reduced in four steps over 2 weeks, with maximum decrements of 1 mg at each step, based on the participant's optimised dose. Further details are included in the Supporting Information (Appendix S2) and the taper schedule is shown in Table S1.

Efficacy determinations

The ADHD-RS-IV (DuPaul, Power, Anastopoulos, & Reid, 1998) was completed by a licenced clinician familiar with the scale who had been trained to a reliable standard, after interview with the parent. This scale was administered at each visit except the End of Taper and Follow-Up Visits (Visits 24 and 25). The CGI-S and CGI-Improvement (CGI-I) scales (Guy, 1976) were recorded at each visit (except baseline for CGI-I) during the open-label phase; the CGI-S was administered at each visit during the RWP.

Ratings of functional outcome were also obtained using the Weiss Functional Impairment Rating Scale-Parent report (WFIRS-P), a 50-item, parent-reported questionnaire of ADHD-related functional impairment (CADDRA, 2011a,b; Weiss et al., 2007) with demonstrated sensitivity (Maziade et al., 2009; Stein et al., 2011) in evaluating six domains of daily functioning (Family, Learning and School, Life Skills, Child's Self-Concept, Social Activities, and Risky Activities) likely to be impacted by ADHD. The Health Utility Index-Mark 2 and Mark 3 (HUI2/3) was also administered in this study, to measure the impact of treatment on the perception of health status. However, as the HUI2/3 data address a substantially different topic (utility values required for economic evaluation purposes), the results are not reported in this paper.

The primary endpoint was the percentage of treatment failures at the end of the RWP, defined as at least a 50% increase in ADHD-RS-IV total score and a 2 or more point increase in CGI-S score from the corresponding scores at randomisation (Visit 13) at two consecutive visits. Participants meeting these criteria were immediately withdrawn from the study. For the primary analysis, participants who withdrew for any reason during the RWP were considered to be treatment failures. Time to treatment failure (TTF), using the primary endpoint definition, was added via a protocol amendment in November 2012, prior to study conclusion and unblinding, and was considered the key secondary endpoint.

Safety

Safety assessments including treatment-emergent adverse events (TEAEs), medical and medication history, physical examinations, vital signs, laboratory evaluations and electrocardiograms were performed throughout the duration of the study. In addition, the Columbia-Suicide Severity Rating Scale (C-SSRS), a semistructured interview which captures the occurrence, severity and frequency of suicide-related thoughts and behaviours, was performed during the assessment period by a licenced clinician (at screening ['baseline' version] and at all other visits ['since last visit' version]) (Posner et al., 2010).

Statistical analyses

To detect a between-treatment group difference assuming treatment failure rates of 40% and 60% in the GXR and placebo groups, respectively, at 90% power and a two-sided significance level of 0.05 using a chi-square test, it was necessary to assess the primary efficacy measure among 280 participants (140 in each treatment group who had been responders in the open-label phase and entered the double-blind RWP). Assuming that approximately 55% of enrolled participants would be eligible for the double-blind RWP of this study, approximately 510 participants were planned to be enrolled into the 13-week, open-label phase.

The safety populations consisted of all participants who received at least one dose of GXR during the study. The open-label safety population was used to assess safety during the whole study and the open-label phase; the randomised safety population consisted only of those participants who entered the double-blind RWP and received at least one dose of study drug during the RWP.

The full analysis sets (FAS) for each phase were as described above, except both excluded participants from one site that was reported to have a serious breach of GCP.

Efficacy analyses/Treatment failure. Efficacy outcomes were assessed for the randomised FAS. Last observation carried forward (LOCF) was used to impute for missing data other than treatment failure during the RWP. The primary efficacy analysis examined the treatment failure rates during the double-blind RWP using a Cochran–Mantel–Haenszel test stratified by age group (6–12 and 13–17 years) and country. The null hypothesis stated that there was no difference in treatment failure rates between GXR and placebo, with a two-sided alternative of a nonzero difference between the groups. The primary treatment comparison was evaluated using a 2-sided significance level of 0.05. Treatment failure was assessed at each visit during the double-blind RWP. Participants who met the treatment failure criteria at one visit and then discontinued the study were summarised and analysed in a similar way to the primary endpoint (i.e. failure criteria met at two successive visits).

Time to treatment failure (measured in days from randomisation [Visit 13] to the assessment visit at which the criteria for treatment failure were met, or date of withdrawal) for the randomised FAS was analysed using a log-rank test stratified by age group and country. Kaplan–Meier estimates of treatment failure for each treatment group and median, upper and lower quartiles for the TTF and associated 95% confidence intervals (CIs) were calculated where possible.

Other secondary efficacy analyses included ADHD-RS-IV subscale scores and CGI-S scores during the double-blind RWP. The change from baseline (Visit 13) in ADHD-RS-IV total and hyperactivity–impulsivity and inattention subscale scores (using LOCF) was compared between the two treatment groups using an analysis of covariance (ANCOVA) model. CGI-S score was analysed using a Cochran–Mantel–Haenszel test stratified by age group and country. The change from baseline (Visit 13) WFIRS-P global score and the individual domain and subdomain scores were summarised by treatment group at Visits 20 and 23; ANCOVA for the randomised FAS was performed.

Clinical Global Impression-Improvement ratings during the open-label phase were dichotomised as 'improved' (CGI-I scores of 1 ['very much improved'] or 2 ['much improved']) and 'not improved' (CGI-I score of 3 or more).

Safety. Summary statistics for safety outcomes across both phases were assessed for the open-label safety population. The number and percentage of participants answering yes to one or more questions and who answered yes to each of the yes/no questions on the C-SSRS, were summarised at each visit, last on-treatment assessment, on-taper medication, post-treatment and overall-on-treatment.

Results

Participant disposition and baseline characteristics

Of 644 screened individuals, 528 participants were enrolled in the study and 526 received at least one dose of study medication (i.e. the open-label safety population). The mean (standard deviation) age was 10.7 (2.7) years; 75.3% were male (Table 1). Children and adolescents comprised 74.3% and 25.7% of participants, respectively (Table 1). While all subtypes of ADHD were allowed, the majority (83.5%) of enrolled participants had combined subtype; 13.1% of participants had the inattentive subtype. In addition, 25.7% had a diagnosis of ODD. Prior treatment was common; at least one prior psychoactive medication had been used by 70.9% of participants (Table 1). Of the 316 participants (59.8%) who entered the double-blind RWP, 157 were randomised to receive GXR and 159 received placebo (Fig. 1). After randomisation, the groups were well balanced (Table 1). The most frequently reported reasons for early termination in the open-label treatment phase were 'lack of efficacy' (10.6%), 'response criteria not met' (8.7%) and adverse events (AEs) (8.0%). For further discussion of the impact of response and relapse definitions on participant disposition, see Appendix S3.

Dosing

The mean (standard deviation) optimised GXR dose during the open-label phase was 3.5 (1.10) mg (children 3.2 [0.85] and adolescents 4.4 [1.28] mg). The mean (standard deviation) weight-adjusted optimal dose was 0.090 (0.0305) mg/kg (children 0.095 [0.0314] and adolescents 0.077 [0.0228] mg/kg) with most (80.9%) optimised at 0.05–0.12 mg/kg. During the double-blind RWP, the mean (standard deviation) optimal GXR dose was 3.5 (1.06) mg and the mean (standard deviation) weight-adjusted optimal dose was 0.089 (0.0300) mg/kg, with most (80.3%) optimised at 0.05–0.12 mg/kg.

Efficacy

Open-label phase. At completion of the open-label phase (Visit 13, LOCF), 68.6% of participants were considered to be responders to treatment; results were similar in children (68.4%) and adolescents (69.4%). Also at Visit 13 (LOCF), 76.1% of participants were reported as 'improved' on the CGI-I scale. There was a significant decrease in score (improvement) in all six domains of the WFIRS-P in the open-label phase; the mean (standard deviation) change from baseline at Visit 13 (LOCF) for the global score was −0.35 (0.414; $p < 0.001$; Table S2A).

Maintenance of efficacy (RWP). In the primary efficacy analysis, a significantly smaller proportion of participants failed treatment with GXR (49.3%) than with placebo (64.9%; difference −15.6, 95%CI; −26.6, −4.5, $p = 0.006$) (Fig. 2).

For the key secondary efficacy analysis, the median TTF was 56.0 days (95%CI: 44.0, 97.0) for the placebo group. The difference in TTF between the GXR and placebo groups was statistically significant ($p = 0.003$) (Fig. 3). The median TTF in the GXR group could not be calculated, as less than half the participants failed treatment.

The mean (standard deviation) ADHD-RS-IV total scores at RWP baseline were 12.3 (6.90) for the GXR group and 13.0 (7.62) for the placebo group. At the end of the RWP, the scores were 20.3 (13.10) and 27.0 (15.30), respectively. The change from baseline in least squares (LS) mean ADHD-RS-IV total score at RWP completion was 9.64 for GXR compared with 15.89 for placebo. The difference between GXR and placebo was −6.24 (95%CI: −9.01, −3.48, $p < 0.001$; effect size 0.51), indicating that the effect of treatment was better maintained with GXR than placebo. For the hyperactivity–impulsivity subscale, the change from baseline in LS mean ADHD-RS-IV total score at RWP completion was 4.43 for GXR and 8.10 for placebo; the difference between GXR and placebo was −3.66 (95% CI: −5.19, −2.14, $p < 0.001$; 0.55). For the inattention subscale, the change from baseline in LS mean was 5.22 for GXR and 7.78 for placebo; the difference between GXR and placebo was −2.56 (95%CI: −4.00, −1.12, $p < 0.001$; 0.40).

Based on the CGI-S, all participants entering the RWP were reported to be normal, not at all ill, or borderline mentally ill (CGI-S score of 1 or 2) at baseline of the RWP (Visit 13). At completion of the RWP, a larger proportion of participants in the GXR group ($n = 75$, 50%) was rated as normal or borderline mentally ill compared with placebo ($n = 49$, 32.5%) ($p = 0.001$). During the RWP, significant differences between the GXR and placebo groups were observed only in the WFIRS-P Learning and School domain and its two subdomains, Behaviour in School (at Visits 20 and 23; $p < 0.05$) and Academic Performance (Visits 20; $p < 0.05$), but not in either the Global score or in any other domains (Table S2B).

Safety

Details of AEs occurring during the open-label and maintenance of efficacy phases are summarised in Table S3.

AEs: open-label phase. During the open-label treatment phase, 42/526 (8.0%) participants recorded 50 TEAEs that led to discontinuation, five participants (1.0%) reported five treatment-related serious AEs (SAEs), three of which led to discontinuation (syncope, sinus bradycardia, somnolence) and no deaths were reported. One further SAE, aggression, was not considered related to treatment. The

Table 1 Baseline demographic and clinical characteristics of participants in open-label and randomised-withdrawal phases (safety populations)

	Open-label phase			Randomised-withdrawal phase		
	6–12 years (n = 391)	13–17 years (n = 135)	Total (N = 526)	Placebo (n = 158)	GXR (n = 157)	Total (N = 315)
Age, years: mean (*SD*)	9.4 (1.72)	14.4 (1.33)	10.7 (2.70)	11.0 (2.69)	10.7 (2.64)	10.8 (2.67)
Male, n (%)	293 (74.9)	103 (76.3)	396 (75.3)	116 (73.4)	118 (75.2)	234 (74.3)
Race, n (%)						
White	294 (78.0)[b]	109 (80.7)	403 (78.7)[c]	124 (80.5)[d]	120 (78.4)[e]	244 (79.5)[f]
All others	83 (22.0)[b]	26 (19.3)	109 (21.3)[c]	30 (19.5)[d]	33 (21.6)[e]	63 (20.5)[f]
Weight, kg: mean (*SD*)	35.43 (9.04)	58.60 (11.45)	41.38 (14.02)	43.17 (14.39)	41.52 (14.12)	42.35 (14.26)
ADHD-RS-IV total score at baseline[a]: mean (*SD*)	44.9 (5.98)	40.2 (5.96)	43.7 (6.31)	43.5 (6.27)	43.5 (6.33)	43.5 (6.29)
Time since ADHD diagnosis, years: mean (*SD*)	2.0 (2.18)[g]	4.2 (3.60)	2.6 (2.79)[h]	2.8 (2.97)[i]	2.5 (2.75)[j]	2.6 (2.86)[k]
Current diagnosis of ODD, n (%)	103 (26.3)	32 (23.7)	135 (25.7)	44 (27.8)	41 (26.1)	85 (27.0)
Significant oppositional symptoms, n (%)	229 (64.9)[l]	72 (58.1)[m]	301 (63.1)[n]	89 (61.0)[o]	94 (65.3)[p]	183 (63.1)[q]
ADHD subtype, n (%)						
Predominantly inattentive	34 (8.7)	35 (25.9)	69 (13.1)	18 (11.4)	20 (12.7)	38 (12.1)
Predominantly hyperactive-impulsive	17 (4.3)	1 (0.7)	18 (3.4)	8 (5.1)	4 (2.5)	12 (3.8)
Combined subtype	340 (87.0)	99 (73.3)	439 (83.5)	132 (83.5)	133 (84.7)	265 (84.1)
Prior psychoactive medication use in ≥5%, n (%)						
Any prior psychoactive medication	268 (68.5)	105 (77.8)	373 (70.9)	109 (69.0)	114 (72.6)	223 (70.8)
ATX[r]	66 (16.9)	40 (29.6)	106 (20.2)	34 (21.5)	27 (17.2)	61 (19.4)
Dexmethylphenidate HCl	30 (7.7)	10 (7.4)	40 (7.6)	10 (6.3)	11 (7.0)	21 (6.7)
Lisdexamphetamine mesilate	42 (10.7)	14 (10.4)	56 (10.6)	11 (7.0)	15 (9.6)	26 (8.3)
Melatonin	21 (5.4)	6 (4.4)	27 (5.1)	8 (5.1)	12 (7.6)	20 (6.3)
MPH[r]	231 (59.1)	83 (61.5)	314 (59.7)	91 (57.6)	90 (57.3)	181 (57.5)
Obetrol	50 (12.8)	26 (19.3)	76 (14.4)	18 (11.4)	21 (13.4)	39 (12.4)
Risperidone	23 (5.9)	4 (3.0)	27 (5.1)	9 (5.7)	6 (3.8)	15 (4.8)

ADHD, attention-deficit/hyperactivity disorder; ADHD-RS-IV; ADHD Rating Scale version IV; ATX, atomoxetine; GXR, guanfacine extended release; HCl, hydrochloride; MPH, methylphenidate; ODD, oppositional defiant disorder; *SD*, standard deviation.
[a]Baseline scores for both phases of the study are at study baseline (Week 0/Visit 2).
[b]n = 377.
[c]n = 512.
[d]n = 154.
[e]n = 153.
[f]n = 307.
[g]n = 389.
[h]n = 524.
[i]n = 157.
[j]n = 156.
[k]n = 313.
[l]n = 353.
[m]n = 124.
[n]n = 477.
[o]n = 146.
[p]n = 144.
[q]n = 290.
[r]ATX and ATX HCl are combined; MPH and MPH HCl are combined.

majority of TEAEs were mild to moderate with 31/526 (5.9%) participants reporting a total of 44 severe TEAEs. The only severe events reported by more than one participant were somnolence (1.0%), fatigue (1.0%), viral bronchitis (0.4%) and migraine (0.4%).

AEs: maintenance of efficacy phase (RWP). During the double-blind RWP, 89/157 (56.7%) participants receiving GXR and 76/158 (48.1%) participants receiving placebo reported TEAEs. TEAEs led to discontinuation in 3/157 (1.9%) in the GXR group (grand mal convulsion, sedation, somnolence) and 2/158 (1.3%) in the placebo group (one with irritability, the other with chest pain, dizziness, dyspnoea, nausea and tremor). Six participants (GXR, n = 2; placebo, n = 4) reported seven SAEs, one of which was judged to be related to treatment (GXR: grand mal convulsion). The majority of TEAEs were mild to moderate, with 5 (3.2%) GXR and 2 (1.3%) placebo participants reporting a severe TEAE.

The most frequently occurring TEAE over the entire study was somnolence, with 387 events in

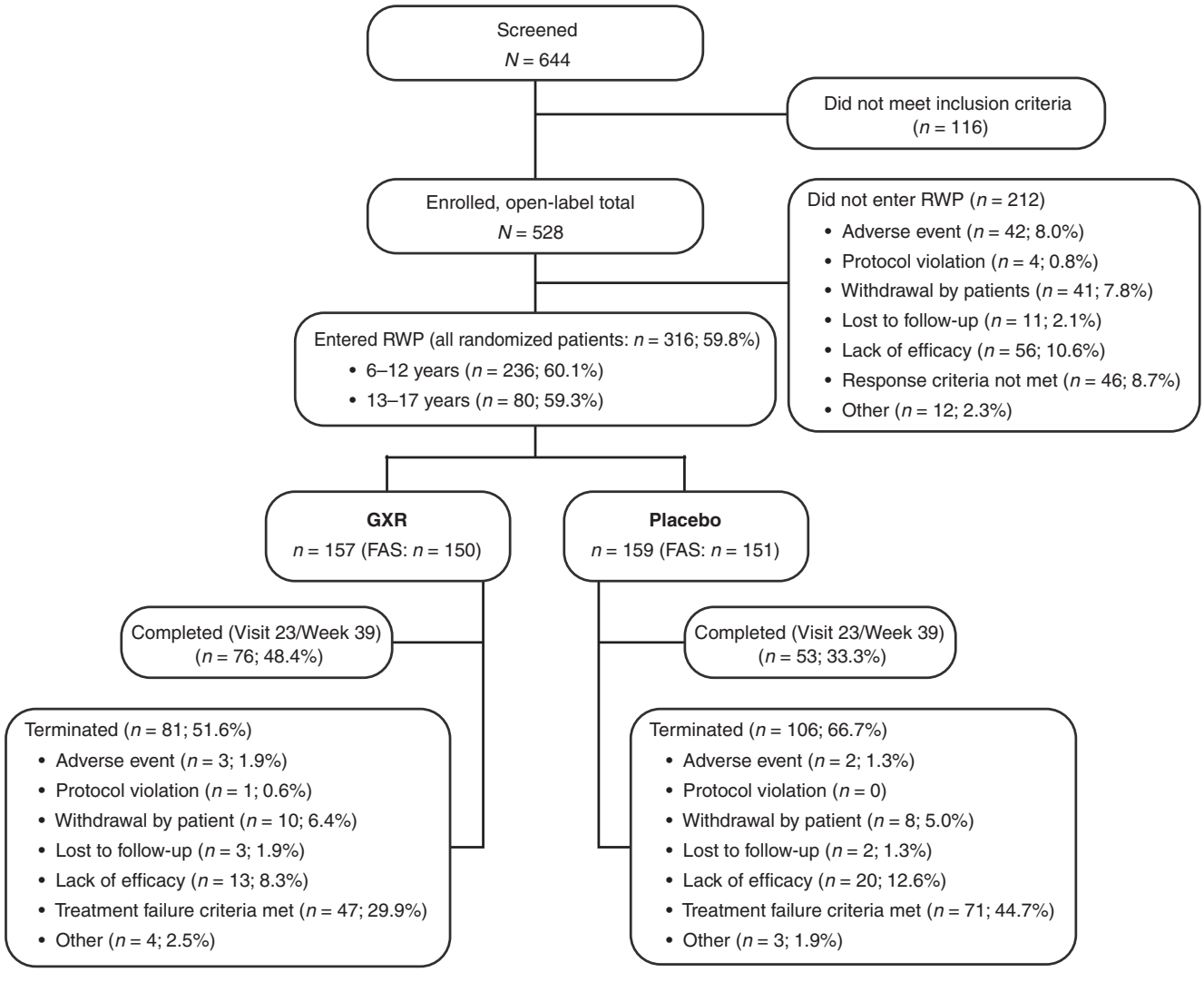

Figure 1 Participant disposition (all enrolled participants) in the phase 3, double-blind, placebo-controlled, randomised-withdrawal study evaluating the long-term maintenance of GXR efficacy in children/adolescents with ADHD. Enrolled is defined as all participants who were dispensed investigational product. Percentages are based on the number of enrolled participants or randomised participants in each treatment group. FAS, full analysis set; GXR, extended-release guanfacine hydrochloride; RWP, randomised-withdrawal phase

255 participants (48.5%) in the open-label phase and 27 events in 19 participants (12.1%) in the RWP phase, all in GXR recipients.

Columbia-Suicide Severity Rating Scale. During the open-label phase, 526 participants underwent one or more C-SSRS assessments (391 participants aged 6–12 years and 135 participants aged 13–17 years) and during the RWP, 315 participants underwent one or more C-SSRS assessments (157 participants in the GXR group and 158 participants in the placebo group). No safety signals or differences between treatment groups were evident.

Vital signs. Overall, changes in vital signs were consistent with the known effects of GXR treatment, and were without clinical relevance. A small decrease in blood pressure was observed during GXR treatment, and modest increases in mean blood pressure values from baseline were observed at the follow-up visit (at least 5 days after the last dose of investigational product) (Table S4). During the RWP, elevations in systolic and diastolic blood pressure and heart rate above original baseline were generally observed in the placebo group following the discontinuation of GXR; these increases were usually modest and asymptomatic, typically became less pronounced over time, and tended to return towards baseline in the majority of participants; however, increases did persist in some participants at follow-up.

Discussion

Children and adolescents, aged 6–17 years with a diagnosis of ADHD and no comorbidity other than ODD (27% of participants in the RWP) demonstrated maintenance of treatment efficacy of GXR compared

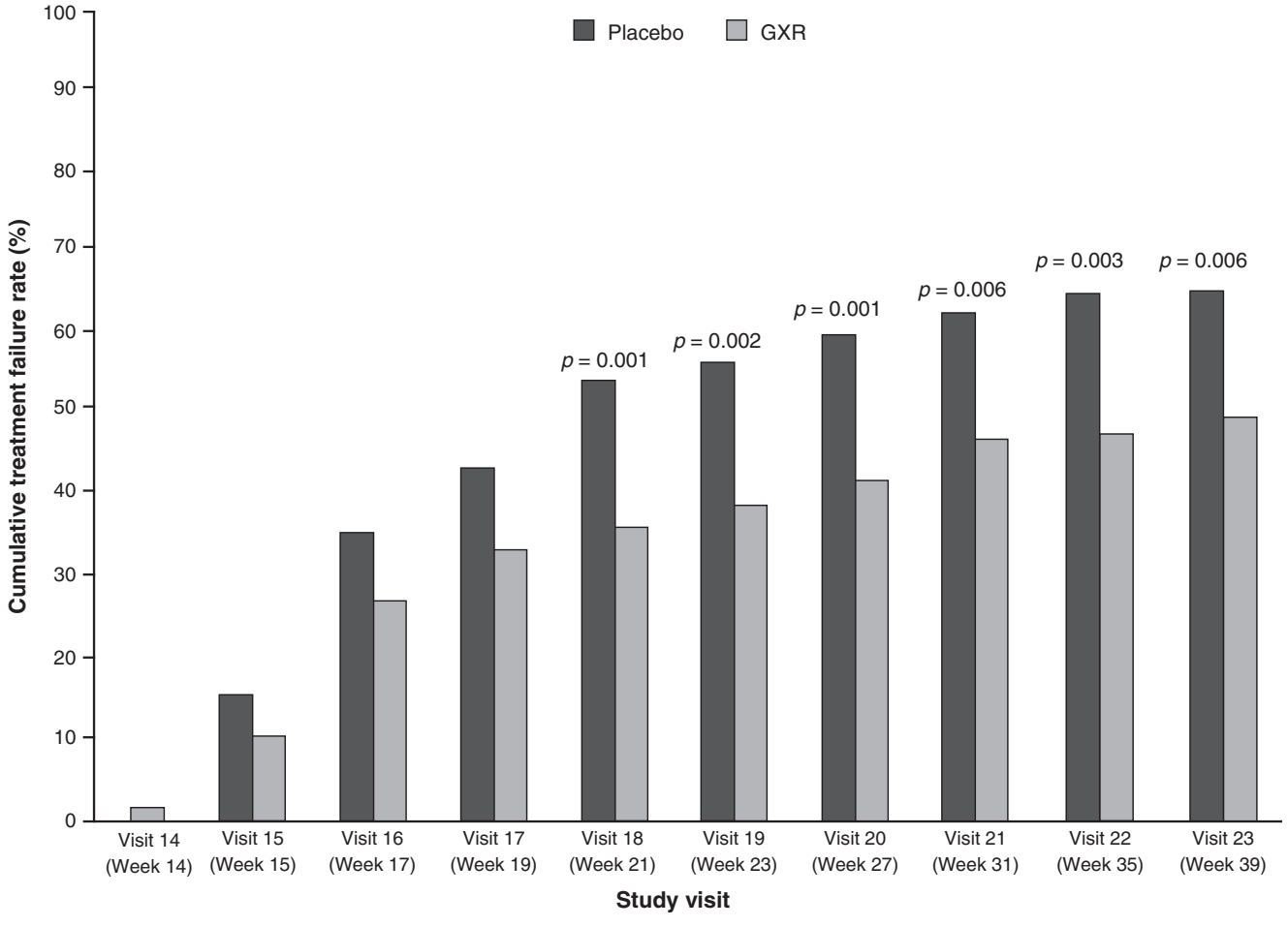

Figure 2 Cumulative treatment failure rate over time (randomised full analysis set). *p*-value is based on Cochran–Mantel–Haenszel statistic comparing the treatment groups with age group and country as stratification factors. GXR, extended-release guanfacine hydrochloride

with placebo as evidenced by fewer cumulative treatment failures (49.3% vs. 64.9%, respectively) over a 26-week treatment period. There was also a significant difference in TTF between GXR and placebo ($p = 0.003$). Long-term maintenance of GXR efficacy compared with placebo was additionally demonstrated for symptom measures (ADHD-RS-IV) and clinicians' assessments of ADHD severity (CGI-S).

The short-term efficacy of GXR monotherapy has previously been established in clinical trials (Biederman, Melmed, Patel, McBurnett, Konow, et al., 2008; Sallee, McGough, et al. 2009). Given the chronic nature of ADHD and its long-term impact, for example on educational outcomes (Washbrook, Propper, & Sayal, 2013), it is important to establish the long-term effects of treatment. The initial open-label treatment period in this study identified GXR responders, and by the end of this phase, 68.6% of participants met response criteria of at least a 30% reduction in ADHD-RS-IV score and a CGI-S score of 1 or 2. On completion of the RWP in this study, those participants who continued to receive GXR exhibited significantly less worsening from RWP baseline in LS mean ADHD-RS-IV total score ($p < 0.001$; effect size 0.51) than those participants who were switched to placebo.

Maintenance of efficacy during the RWP was less consistently demonstrated on the ratings of functional outcome. While there was separation between the GXR and placebo groups on the Learning and School subdomains of the WFIRS-P, the Global score was not significantly different between the GXR and placebo groups ($p = 0.07$). It is perhaps not surprising that this measure was less sensitive than the ADHD-RS-IV for detecting change from active drug to placebo, as it includes data from functional behaviours which are inconsistently present in children/adolescents with ADHD, such as Risky Behaviour. This is aligned with the findings that placebo-adjusted effect sizes for GXR on the WFIRS-P are consistently smaller in functional domains (Hervas et al., 2014), and that some domains of the WFIRS-P correlate less strongly with the symptoms and severity of ADHD than others (Gajria et al., 2015). Given the trend level of the findings on the Global scale, care should be exercised in interpreting the data in this study.

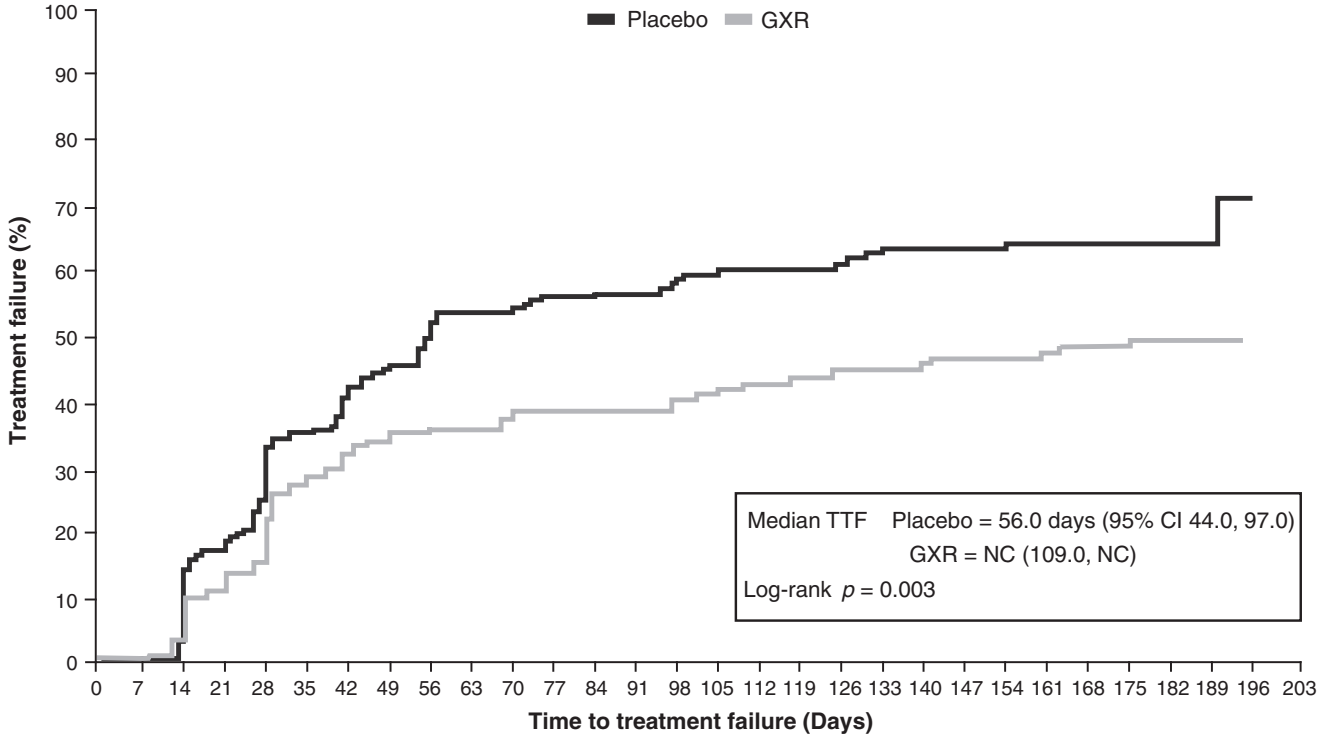

Figure 3 Time to treatment failure (TTF) – primary definition (randomised full analysis set). Plot has been curtailed at 196 days (2 weeks after end of study) when <5% of participants remained on study. Contact was temporarily lost with two participants in the GXR group, so treatment discontinuation was not noted until their first tapering visit, giving an artificially prolonged TTF. These participants were therefore excluded. The *p*-value is from a log-rank test stratified by age group and country, and excluding the two participants noted above. CI, confidence interval; GXR, extended-release guanfacine hydrochloride; NC, noncalculable

Guanfacine extended release was well tolerated, with TEAEs and mean changes from baseline in pulse, systolic and diastolic blood pressures consistent with this class of medications in the literature (Biederman, Melmed, Patel, McBurnett, Donahue, et al., 2008; Biederman, Melmed, Patel, McBurnett, Konow, et al., 2008; Sallee, McGough, et al. 2009; Sallee, Lyne, Wigal, and McGough, 2009; Spencer, Greenbaum, Ginsberg, & Murphy, 2009). There were no clinically meaningful trends in clinical laboratory results, height or weight, no safety signals or differences between GXR and placebo emerged from the C-SSRS (i.e. suicidal ideation and suicidal behaviours) and no deaths occurred during the study. The most frequently reported TEAEs in the GXR group during the double-blind RWP, occurring more than 5% in frequency and higher than placebo, were headache, somnolence, pyrexia and fatigue. There was one report of a grand mal seizure, which was deemed related to drug by the site investigator. However, given that the incidence of epileptic events is reported to be elevated in children and adolescents with ADHD (Chou et al., 2013), and the lack of a mechanism to explain this event, it remains uncertain whether the seizure observed in this participant was causally related to GXR.

The randomised-withdrawal (or placebo substitution) design used in this study has been recommended by regulatory agencies as the standard for documenting maintenance of efficacy. Randomised-withdrawal studies have previously been used to examine medium- to long-term efficacy of several other ADHD medications, specifically ATX (Buitelaar et al., 2007; Michelson et al., 2004), methylphenidate (Arnold et al., 2004; Biederman et al., 2010) and lisdexamfetamine dimesylate (Brams et al., 2012; Coghill et al., 2014). However, care should be taken when examining findings for different drug treatments across the various randomised-withdrawal studies due to inherent differences in design and participating populations. For example, the ATX study that is most similar to the current one (Michelson et al., 2004) has key differences in the study population (age range, distribution of ADHD subtype, participating countries) and study design (dosing schedules, inclusion criteria and primary/secondary endpoints, weekly vs. biweekly time between measurements). In addition, participants and investigators in the ATX study were not aware when randomisation occurred, only that it would occur within a given time interval. In contrast, in this study, both the investigators and participants had knowledge of when randomisation to maintenance GXR or placebo occurred. Thus expectations regarding maintenance of efficacy may have differed in these studies. Another difference between the two studies that could have affected relapse rates in the RWP is whether the initial trial used to determine responder status was placebo-controlled or open-label. Response is generally greater in open-label trials than controlled trials, which would yield a

greater number of participants to enter the RWP. However, this could inadvertently increase the number of participants who report continued response when switched from drug to placebo, as nonspecific factors related to response were not controlled in the initial period. These examples illustrate how subtle differences in trial design can affect relapse rates in apparently similar maintenance of efficacy studies.

The randomised-withdrawal studies conducted to date in children and adolescents all show that ADHD symptoms relapse on medication withdrawal, with relapse rates of 0–40% or even 50% on active medication, and 12–75% on placebo (Arnold et al., 2004; Biederman et al., 2010; Brams et al., 2012; Buitelaar et al., 2007; Coghill et al., 2014; Michelson et al., 2004). However, there are notable differences in findings across the studies and drug classes. For example, in randomised-withdrawal studies with stimulants, a large percentage (62–75%) of participants relapse on switching to placebo (Arnold et al., 2004; Brams et al., 2012; Coghill et al., 2014) and loss of efficacy is generally seen early (17 days) (Coghill et al., 2014). In contrast, in RWP studies of nonstimulants, the proportion of participants who maintain response on switching to placebo is reported to be as high as 50% (Upadhyaya et al., 2013) or even 62% (Michelson et al., 2004). Intriguing questions remain in attempting to understand and ascribe meaning to these findings. First, why is there such a difference in loss of response between stimulants and nonstimulants (i.e. a large majority of subjects switched from stimulant to placebo relapse, while this is seen in a smaller percentage with nonstimulants)? Could this be due to participants having a greater subjective awareness of when they are on or off active treatment, which is less apparent with nonstimulants than stimulants? If so, this could be due to either different levels of initial response (i.e. if the response to active medication is greater, perhaps differences on switching to placebo would be more noticeable), or the experience of side effects with active medication versus placebo. And most importantly, why is it that a large percentage of participants (about 35%) treated with nonstimulants for an extended period maintain their response when switched to placebo? One possible explanation is that the specific effects of a medication only account for a certain proportion of explained variance in the improvement seen when drug treatment is undertaken, and successful treatment may alter many contextual factors (e.g. positive attributions at home and school, changes in parent–child interactions, or study habits), which are maintained even when placebo is introduced. Finally, and most provocatively, some have speculated that failure to relapse after switching to placebo could reflect long-term changes in brain function that are maintained even after medication is stopped (Buitelaar et al., 2007). Although this has generally not been found to be the case with stimulants (Arnold et al., 2004; Biederman et al., 2010; Brams et al., 2012; Coghill et al., 2014), preliminary in vivo animal studies have shown that ATX could produce long-term changes in N-methyl-D-aspartate receptors and norepinephrine transporters that may support maintenance of response when medication is withdrawn (Udvardi et al., 2013). It has been proposed that GXR may also have long-term effects through a different mechanism; in vitro studies suggest that guanfacine influences the length and density of dendritic spines (Hu, Vidovic, Chen, Lu, & Song, 2008; Song, Abou-Zeid, & Fang, 2004), which may contribute to long-term benefit. The present findings are consistent with such an interpretation, though they do not address potential mechanisms associated with long-term improvement, and certainly do not prove that GXR produces long-term changes that maintain improvement after the drug is discontinued.

The findings of this study should be viewed within the context of several methodological limitations and considerations. As participants with uncontrolled, comorbid psychiatric diagnoses other than ODD or active cardiovascular conditions were excluded from this study, the generalisability of these findings to 'real-world' ADHD populations should be made with caution, and warrants further study. Maintenance of response can be measured only in 'responders', therefore, the response criteria selected at the outset of this trial may have affected how easy it was to meet relapse criteria, and thus the overall interpretation of the results. The limited occurrence of AEs may also be minimised in a group of 'responders', and certainly when compared with a nonresponding population; as per protocol, only those participants who responded well and tolerated GXR went on to enter the RWP.

Conclusions

The findings of this randomised-withdrawal study are consistent with the continued maintenance of treatment for symptomatic reduction in children/adolescents (6–17 years) with ADHD who respond to initial, acute open-label treatment with GXR (doses up to 7 mg/day [0.05–0.12 mg/kg/day]). Furthermore, GXR was generally well tolerated, with TEAEs as expected for this class of medications. The stringent randomised-withdrawal trial design used here has also been used to evaluate maintenance of efficacy of other recently developed medications for ADHD (Arnold et al., 2004; Buitelaar et al., 2007; Coghill et al., 2014; Michelson et al., 2004) and the degree of separation from placebo reported here appears to be comparable with other nonstimulants (Buitelaar et al., 2007; Michelson et al., 2004). More research on long-term efficacy of GXR and other existing ADHD medications is required to better understand why a relatively large number of children/adolescents treated with nonstimulants do not relapse when the active medication is discontinued.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Figure S1 study design.
Appendix S2. GXR dose tapering at RWP entry or end of study.
Table S1. Taper schedule.
Appendix S3. Response and relapse definitions.
Appendix S4. WFIRS-P changes during the OL and RWP.
Table S2A and S2B. Summary of WFIRS-P Global, Domain, and Subdomain Scores.
Appendix S5. TEAEs.
Table S3. Summary of frequently occurring TEAEs.
Table S4. Summary of mean changes in blood pressure from baseline to follow-up visit in the open-label safety population.

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Key points

- GXR is a nonstimulant treatment for ADHD approved for children and adolescents in the United States and Canada. It was recently approved in Europe in children for whom stimulants are not suitable, not tolerated or have been shown to be ineffective.
- Clinical trials have previously established the short-term efficacy of GXR monotherapy.
- In this phase 3 randomised-withdrawal study of children and adolescents with ADHD in 8 European countries, the United States and Canada, long-term maintenance of GXR efficacy was demonstrated versus placebo.

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