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

Jeffrey H. Newcorn,1 Valerie Harpin,2 Michael Huss,3 Andrew Lyne,4† Vanja Sikirica,5† Mats Johnson,6 Josep Antoni Ramos-Quiroga,7,8 Judy van Stralen,9 Benoit Dutray,10 Sasha Sreocovic,11† Ralph Bloomfield,4† and Brigitte Robertson5†

1Icahn School of Medicine at Mount Sinai, New York, NY, USA; 2Ryegate Children’s Centre, Sheffield NHS Foundation Trust, Sheffield, UK; 3Johannes Gutenberg-University Mainz, Mainz, Germany; 4Shire, Basingstoke, UK; 5Shire, Wayne, PA, USA; 6Gillberg Neuropsychiatry Centre, University of Gothenburg, Gothenburg, Sweden; 7Department of Psychiatry, CIBERSAM, Hospital Universitari Vall d’Hebron, Barcelona; 8Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain; 9Center for Pediatric Excellence, Ottawa, ON, Canada; 10Icahn School of Medicine at Mount Sinai, New York, NY, USA; 11Icahn School of Medicine at Mount Sinai, New York, NY, USA.

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 a 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-adrenergic receptor 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.

© 2016 The Authors. Journal of Child Psychology and Psychiatry published by John Wiley & Sons Ltd on behalf of Association for Child and Adolescent Mental Health.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

[The legal statement for this article was changed on 25 February 2020 after original online publication]
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 (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 enrollment 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 initial 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...
Maintenance of guanfacine efficacy in ADHD treatment

Efficacy determinations
The ADHD-RI-V (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-l) during the open-label phase; the CGI-S was administered at each visit during the RWP.

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).

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.
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) 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
The 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, dysphagia, 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

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

|                      | 6–12 years (n = 391) | 13–17 years (n = 135) | Total (N = 526) |
|----------------------|----------------------|------------------------|-----------------|
| **Age, years:**      |                      |                        |                 |
|                      | mean (SD)            | mean (SD)              | mean (SD)       |
|                      | 9.4 (1.72)           | 14.4 (1.33)            | 10.7 (2.70)     |
| **Male,** n (%)      | 293 (74.9)           | 103 (76.3)             | 396 (75.3)      |
|                      | 11.0 (2.69)          | 10.7 (2.64)            | 10.8 (2.67)     |
| **Race,** n (%)      | 116 (73.4)           | 118 (75.2)             | 234 (74.3)      |
| White                | 294 (78.0)           | 109 (80.7)             | 403 (78.7)      |
|                      | 124 (80.5)           | 120 (78.4)             | 244 (79.5)      |
| All others           | 83 (22.0)            | 26 (19.3)              | 109 (21.3)      |
|                      | 30 (19.5)            | 33 (21.6)              | 63 (20.5)       |
| **Weight, kg:**      |                      |                        |                 |
|                      | mean (SD)            | mean (SD)              | mean (SD)       |
|                      | 35.43 (9.04)         | 58.60 (11.45)          | 41.38 (14.02)   |
| ADHD-RS-IV total score at baseline:** 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) | 4.2 (3.60) | 2.6 (2.79) |
|                      | 2.8 (2.97)           | 2.5 (2.75)             | 2.6 (2.86)      |
| **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) | 72 (58.1) | 301 (63.1) |
| Predominantly inattentive | 34 (8.7) | 35 (25.9) | 69 (13.1) |
| Predominantly hyperactive-impulsive | 17 (4.3) | 1 (0.7) | 18 (3.4) |
| Combined subtype     | 340 (87.0)           | 99 (73.3)              | 439 (83.5)      |
| **Prior psychoactive medication use in ≥5%, n (%)** | 268 (68.5) | 105 (77.8) | 373 (70.9) |
| ATX **                   | 66 (16.9)           | 40 (29.6)              | 106 (20.2)      |
| Dexamfetamine HCl      | 30 (7.7)            | 10 (7.4)               | 40 (7.6)        |
| Lisdexamfetamine mesilate | 42 (10.7)         | 14 (10.4)              | 56 (10.6)       |
| Melatonin             | 21 (5.4)            | 6 (4.4)                | 27 (5.1)        |
| MPH **                   | 231 (59.1)          | 83 (61.5)              | 314 (59.7)      |
| Obetrol               | 50 (12.8)           | 26 (19.3)              | 76 (14.4)       |
| Risperidone           | 23 (5.9)            | 4 (3.0)                | 27 (5.1)        |

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.

**n** = 377.

**n** = 313.

**n** = 353.

**n** = 124.

**n** = 477.

**n** = 144.

**n** = 290.

**n** = 313.

**n** = 353.

**n** = 124.

**n** = 477.

**n** = 144.

**n** = 290.

© 2016 The Authors. Journal of Child Psychology and Psychiatry published by John Wiley & Sons Ltd on behalf of Association for Child and Adolescent Mental Health.
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
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 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
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

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

© 2016 The Authors. Journal of Child Psychology and Psychiatry published by John Wiley & Sons Ltd on behalf of Association for Child and Adolescent Mental Health.
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.

Acknowledgements
The study was sponsored by Shire Development, LLC. Professional medical writing assistance for this manuscript was received from Debby Moss, and Jackie Marchington, employees of Caudex, Oxford, UK (funded by Shire International GmbH) working at all times under the direction of the authors. Editorial assistance in formatting, proofreading, copy-editing, fact checking, and coordination and comments collation was also provided by Caudex. Antonia Panayi of Shire, Switzerland also reviewed the manuscript for scientific accuracy. Jeffrey H. Newcorn (J.H.N.) had full access to the study data and acts as guarantor for the work.
J.H.N. has been an advisor/consultant to Alcobra, Biobehavioral Diagnostics, Enzymotec, Gencosciences, Ironshore, lupin, Neos, neurovance, nfl, Rhodes and Shire, and a member of the DSMB for Sunovion. He has received research funding from Enzymotec and Shire. V.H. has received unrestricted research grants from Shire, Lilly and Flynn Pharma; she has also received honoraria for giving educational presentations from Shire, Lilly and Janssen and attended advisory boards run by Shire. M.H. reports personal fees and nonfinancial support from Shire, grants, personal fees and nonfinancial support from Medice, personal fees and nonfinancial support from Novartis, Eli Lilly, Engheid Araneimittel and Actelion, outside the submitted work; in addition, he also has two patents issued. M.J. has received unrestricted research grants from Shire and Vifor Pharma; he has been engaged as a speaker and/or consultant by Lilly, Shire, and Vifor Pharma, and by PCM scientific in the development of educational materials. J.A.R.Q. was on the speakers bureaux and/or acted as consultant for Eli Lilly, Janssen-Cilag, Novartis, Shire, Lundbeck, Ferrer and Rubió in the last 3 years; he has also received travel support for taking part in psychiatric meetings from Janssen-Cilag, Rubió, Shire and Eli Lilly; the ADHD Programme he chaired received unrestricted educational and research support from the following companies in the last 3 years: Eli Lilly, Janssen-Cilag, Shire, Rovi and Rubió. J.V.S. has received research grants from Shire and has been a principal investigator in trials sponsored by Shire and Purdue Pharma; she has participated in advisory boards for Shire and Janssen-Cilag and has received educational grants from Shire, Purdue Pharma, Janssen-Cilag and Bristol-Myers Squibb; she has also received speaking honoraria from Shire, Purdue Pharma and Janssen-Cilag, and consultancy fees from Shire and Janssen-Cilag. B.D. has participated in clinical trials as a principal investigator sponsored by Shire Development LLC and as a co-investigator in trials sponsored by Eli Lilly; he has participated in meetings sponsored by Shire Development LLC. At the time of the study, A.L., V.S., S.S., R.B. and B.R. were employees of Shire, and owned stock/options in Shire.

Correspondence
Jeffrey H. Newcorn, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA; Email: jeffrey.newcorn@mssm.edu

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.

References
Arnold, L.E., Lindsay, R.L., Conners, C.K., Wigal, S.B., Levine, A.J., Johnson, D.E., ... & Zeldis, J.B. (2004). A double-blind, placebo-controlled withdrawal trial of dexmethylphenidate hydrochloride in children with attention deficit hyperactivity disorder. Journal of Child and Adolescent Psychopharmacology, 14, 542–554.

© 2016 The Authors. Journal of Child Psychology and Psychiatry published by John Wiley & Sons Ltd on behalf of Association for Child and Adolescent Mental Health.
for attention-deficit hyperactivity disorder. *Archives of General Psychiatry*, 53, 448–455.

Biederman, J., Melmed, R.D., Patel, A., McBurnett, K., Donahue, J., & Lyne, A. (2008). Long-term, open-label extension study of guanfacine extended release in children and adolescents with ADHD. *CNS Spectrums*, 13, 1047–1055.

Biederman, J., Melmed, R.D., Patel, A., McBurnett, K., Konow, J., Lyne, A., & Scherer, N. (2008). A randomized, double-blind, placebo-controlled study of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. *Pediatrics*, 121, e73–e84.

Biederman, J., Mick, E., Surman, C., Doyle, R., Hammerness, P., Kotarski, M., & Spencer, T. (2010). A randomized, 3-phase, 34-week, double-blind, long-term efficacy study of osmotic-release oral system-methylphenidate in adults with attention-deficit/hyperactivity disorder. *Journal of Clinical Psychopharmacology*, 30, 549–553.

Brans, M., Weisler, R., Findling, R.L., Gasior, M., Hamdani, M., Ferreira-Cornwell, M.C., & Squires, L. (2012). Maintenance of efficacy of liosexamftamine dimeylate in adults with attention-deficit/hyperactivity disorder: Randomized withdrawal design. *Journal of Clinical Psychiatry*, 73, 977–983.

Buitelaar, J.K., Michelson, D., Danckaerts, M., Gillberg, C., Spence, T.J., Zuddas, A., ... & Biederman, J. (2007). A randomized, double-blind study of continuation treatment for attention-deficit/hyperactivity disorder after 1 year. *Biological Psychiatry*, 61, 694–699.

CADDRA (2011a). Weiss Functional Impairment Rating Scale (WFIRS) Instructions. Available at: http://www.caddra.ca/cms4/pdfs/CADDRA2011WFIRSInstructions.pdf. Accessed: 12 February 2015.

CADDRA (2011b). Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P). Available at: http://www.caddra.ca/cms4/pdfs/caddraGuidelines2011WFIRS-P.pdf. Accessed: 12 February 2015.

Childress, A.C., & Salie, F.R. (2014). Attention-deficit/hyperactivity disorder with inadequate response to stimulants: Approaches to management. *CNS Drugs*, 28, 121–129.

Chou, I.C., Chang, Y.T., Chin, Z.N., Muo, C.H., Sung, F.C., Kuo, H.T., ... & Kao, C.H. (2013). Correlation between epilepsy and attention deficit hyperactivity disorder: A population-based cohort study. *PLoS One*, 8, e57926.

Coghill, D.R., Banaschewski, T., Lecendreux, M., Johnson, M., Zohadas, M., Zuddas, A., ... & Biederman, J. (2015). Maintenance of efficacy of liosexamftamine dimeylate in children and adolescents with attention-deficit/hyperactivity disorder: Randomized-withdrawal study design. *Journal of the American Academy of Child and Adolescent Psychiatry*, 53, 647–657.

DuPaul, G.J., Power, T.J., Anastopoulos, A.D., & Reid, R. (1998). *ADHD Rating Scale-IV (for children and adolescents)*: Checklists, norms, and clinical interpretation. New York, NY: Guilford Publications Inc.

European Medicines Agency (2010). Guideline on the clinical investigation of medicinal products for the treatment of attention deficit hyperactivity disorder (ADHD). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/08/WC500095686.pdf. Accessed: 17 September 2013.

Gajria, K., Kosinaki, M., Sikirica, V., Husa, M., Livote, E., Dittmann, R.W., & Erder, M.H. (2015). Psychometric validation of the Weiss Functional Impairment Rating Scale-Parent Report Form in children and adolescents with attention-deficit/hyperactivity disorder. *Health and Quality of Life Outcomes*, 13, 184.

Goodman, D.W. (2013). Sustained treatment effect in attention-deficit/hyperactivity disorder: Focus on long-term placebo-controlled randomised maintenance withdrawal and open-label studies. *Therapeutics and Clinical Risk Management*, 9, 121–130.

Guy, W. (1976). Clinical Global Impressions: Early Clinical Drug Evaluation Unit assessment manual for psychopharmacology (Gov Pubs/US: HE 20.8108: P 95/2/976). Rockville, MD: U.S. National Institute of Health, Psychopharmacology Research Branch.

Hervas, A., Huss, M., Johnson, M., McNicholas, F., van Stralen, J., Sreckovic, S., ... & Robertson, B. (2014). Efficacy and extended acceptance: guanfacine hydrochloride in children and adolescents with attention-deficit/hyperactivity disorder: A randomized, controlled, Phase III trial. *European Neuropsychopharmacology*, 24, 1861–1872.

Hu, J., Vidovic, M., Chen, M.M., Lu, Q.Y., & Song, Z.M. (2008). Activation of alpha 2A adrenoceptors alters dentritic spine development and the expression of spinophilin in cultured cortical neurones. *Brain Research*, 1199, 37–45.

Maziade, M., Rouleau, N., Lee, B., Rogers, A., Davis, L., & Dickson, R. (2009). Atomoxetine and neuropsychological function in children with attention-deficit/hyperactivity disorder: Results of a pilot study. *Journal of Child and Adolescent Psychopharmacology*, 19, 709–718.

Michelson, D., Buitelaar, J.K., Danckaerts, M., Gillberg, C., Spence, T.J., Zuddas, A., ... & Biederman, J. (2004). Relapse prevention in pediatric patients with ADHD treated with atomoxetine: A randomized, double-blind, placebo-controlled study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 43, 896–904.

Posner, K., Brent, D., Lucas, C., Gould, M., Stanley, B., Brown, G., ... & Mann, J. (2010). Columbia-suicide severity rating scale (C-SSRS). Available at: http://www.cssrs.columbia.edu/about_cssrs.html. Accessed: 16 July 2015.

Salle, F.R., Lyne, A., Wigal, T., & McGough, J.J. (2009). Long-term safety and efficacy of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology*, 19, 215–226.

Salle, F.R., McGough, J., Wigal, T., Donahue, J., Lyne, A., & Biederman, J. (2009). Guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder: A placebo-controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry*, 48, 155–165.

Song, Z.M., Abou-Zeid, O., & Fang, Y.Y. (2004). Alpha2A adrenoceptors regulate phosphorylation of microtubule-associated protein-2 in cultured cortical neurons. *CNS Drugs*, 18, 451–460.

Spencer, T.J., Greenbaum, M., Ginsberg, L.D., & Murphy, W.R. (2009). Safety and effectiveness of coadministration of guanfacine extended release and psychostimulants in children and adolescents with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology*, 19, 501–510.

Stein, M.A., Waldman, I.D., Charney, E., Aryal, S., Sable, C., Griber, R., & Newcorn, J.H. (2011). Dox effects and comparative effectiveness of extended release dexamethasone and mixed amphetamine salts. *Journal of Child and Adolescent Psychopharmacology*, 21, 581–588.

Udvardi, P.T., Fohr, K.J., Henes, C., Liebau, S., Dreyhaupt, J., Boeckers, T.M., & Ludolph, A.G. (2013). Atomoxetine affects transcription/translation of the NMDA receptor and the monoamine transporter in the rat brain – an in vivo study. *Drug Design, Development and Therapy*, 7, 1433–1446.

Upadhyaya, H., Ramos-Quiroga, J.A., Adler, L.A., Williams, D., Tanaka, Y., Lane, J., ... & Allen, A.J. (2013). Maintenance of response after open-label treatment with atomoxetine hydrochloride in international European and non-European adult outpatients with Attention-Deficit/Hyperactivity Disorder: A placebo-controlled, randomised...
withdrawal study. European Journal of Psychiatry, 27, 185–205.
Washbrook, E., Propper, C., & Sayal, K. (2013). Pre-school hyperactivity/attention problems and educational outcomes in adolescence: Prospective longitudinal study. British Journal of Psychiatry, 203, 265–271.
Weiss, M.D., Brooks, B.L., Iverson, G.L., Lee, B., Dickson, R., & Wasdell, M. (2007). Reliability and validity of the Weiss functional impairment rating scale. Presented at: AACAP 54th Annual Meeting, Boston, MA, 23–28 October.

Accepted for publication: 2 November 2015
First published online: 12 February 2016