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Efficacy and safety of guanfacine extended-release in Japanese adults with attention-deficit/hyperactivity disorder: Exploratory post hoc subgroup analyses of a randomized, double-blind, placebo-controlled study

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Abstract

Aim: Previously, we reported on the efficacy and safety of guanfacine extended-release (GXR) in Japanese adults with attention-deficit/hyperactivity disorder (ADHD) from a phase 3, double-blind, placebo-controlled, randomized trial. In this exploratory post hoc analysis, we assessed the efficacy and/or safety of GXR in the following subgroups: ADHD-combined (ADHD-C) and ADHD-predominantly inattentive (ADHD-I) subtypes, age (≥31, <31 years), sex (male, female), and body weight (≥50, <50 kg).

Methods: The primary efficacy endpoint was change from baseline in the Japanese version of the investigator-rated ADHD-Rating Scale-IV (ADHD-RS-IV) with adult prompts (total scores) at week 10.

Results: The efficacy analysis population included 200 patients (GXR, 100; placebo, 100). ADHD-RS-IV total score effect sizes (GXR vs placebo) were similar across all subgroups (total population: 0.52, ADHD-C: 0.51, ADHD-I: 0.52, ≥31 years: 0.61, <31 years: 0.47, male: 0.50, female: 0.57). There were no major differences in the incidence/types of treatment-emergent adverse events (TEAEs) across the subgroups. The incidence of significant TEAEs (34.3%, 10.6%) and TEAEs leading to discontinuation (34.3%, 12.1%) were approximately three times higher in females than males, respectively. The incidence of TEAEs in patients weighing <50 kg and ≥50 kg was 100% and 73.6% during dose optimization and 40% and 24.4% during the maintenance period, respectively.

Conclusion: Findings from this post hoc analysis in adults with ADHD support the efficacy and safety of GXR regardless of ADHD subtype, age, or sex and suggest that careful monitoring for TEAEs and GXR dose optimization is considered for all patients, as needed.

KEYWORDS
adult, attention-deficit/hyperactivity disorder, guanfacine extended-release, safety, treatment efficacy

1 | INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common developmental disorders to be diagnosed in children and adolescents.[1] ADHD can also persist into or be newly diagnosed in adulthood,[1] making it a common disorder in adults, with a prevalence of 2.5% to 2.8% globally[2,3] and 1.7% in Japan.[4] The clinical presentation of ADHD varies between children and adults, and, as individuals mature, there is a decrease in overt hyperactivity symptoms and increases in more subtle symptoms, such as inattention and disorganization.[5-7] This makes it difficult to diagnose ADHD in adults and can result in decreased quality of life (QoL) and psychosocial function.[8,9]

Guanfacine extended-release (GXR) is a selective α_{2A}-adrenergic receptor agonist approved for the treatment of ADHD in children, adolescents, and in Japan only, in adults.[10-12] The overall efficacy and safety profiles of GXR in adults with ADHD have been demonstrated in a phase 3, double-blind, placebo-controlled, randomized trial[13] and in an open-label extension study[14] conducted in Japan. In the placebo-controlled trial, dose-optimized GXR (4-6 mg/day) significantly reduced ADHD symptoms at week 10 compared with placebo and improved QoL.[13] In addition, the overall safety profile of GXR was consistent with that observed in studies of children and adolescents,[11,15-18] and the most commonly observed treatment-related adverse events (AEs; somnolence, thirst, blood pressure decrease, postural dizziness, and constipation) were consistent with the mechanism of action of GXR.[13] In the extension study, no major safety concerns were noted following 50 weeks of treatment, and adults had significant improvements in ADHD symptoms.[14]

As management of ADHD is complex, the selection and use of medication should be tailored to an individual's needs and responses.[19] Several studies in children and adolescents with ADHD suggest that GXR reduces both hyperactivity-impulsivity and inattentiveness[20] and has consistent effects in those with ADHD-combined (ADHD-C) or ADHD-predominantly inattentive (ADHD-I) subtypes.[21] However, there are no studies in adults that have assessed the efficacy or safety of GXR in ADHD subtypes or in subgroups of adults by age or sex.

In this study, we performed an exploratory post hoc analysis of the previous randomized placebo-controlled trial[13] to assess the efficacy and safety of GXR in subgroups of Japanese adults with ADHD.

2 | METHODS

2.1 | Study design

This was a post hoc analysis of a phase 3, multicenter, dose-optimized, randomized, placebo-controlled trial in adults with ADHD (Japan Primary Registries Network identifier: JapicCTI-163231: https://rctportal.niph.go.jp/en/). Further details of the study design have been described previously.[13] The post hoc analysis focuses on the double-blind phase of the trial and does not include data captured during the open-label extension phase. The study was approved by the local ethics committees, was conducted at 71 Japanese centers from October 2016 to July 2017, and was compliant with the Japanese Ethical Guidelines for Clinical Studies and the Declaration of Helsinki. All patients provided written informed consent before participating in the study.

2.2 | Study population

The study population has been described previously.[13] Briefly, patients were included if they were aged ≥18 years with a diagnosis of ADHD (*Diagnostic and Statistical Manual of Mental Disorders*, fifth edition [DSM-5])[22] and had a total score ≥24 as assessed by the Japanese version of the ADHD-Rating Scale-IV (ADHD-RS-IV) with adult prompts and a score ≥4 on the Clinical Global Impression-Severity of Illness (CGI-S) scale. Patients were excluded if they had a documented diagnosis of moderate or severe psychiatric disorder based on the DSM-5 that necessitated treatment or a history of substance use disorder or seizures. Patients with a diagnosis of a serious tic disorder or considered at suicide risk, as well as patients with a history of cardiovascular disease or patients requiring medications affecting blood pressure, were also excluded from the study.

2.3 | Treatment protocol

Patients were randomized 1:1 to oral GXR or placebo and treated for 5 weeks (dose optimization, forced dose escalation) before a 5-week maintenance phase, 2-week tapering phase, and 1 week of follow-up.[13] All patients received a single dose of GXR or placebo once daily at approximately the same time in the morning or afternoon, and a minimum maintenance dose of GXR was set at 4 mg/day. By week 3 (Figure 1), patients received a minimum dose of GXR of 4 mg/day and from week 4 were allowed to increase their dose in increments of 1 mg weekly (or after at least 5 days) at the investigator's discretion. The criteria for an increase in dose were CGI-S ≥3 and no safety concerns (defined as systolic blood pressure [SBP] ≤90 mmHg and a decrease ≥20 mmHg from baseline, diastolic blood pressure [DBP] ≤50 mmHg and a decrease ≥15 mmHg from baseline, pulse rate ≤50 beats per minute [bpm] and a decrease ≥15 bpm from baseline, and newly occurring or persistent symptoms related to SBP, DBP, or pulse

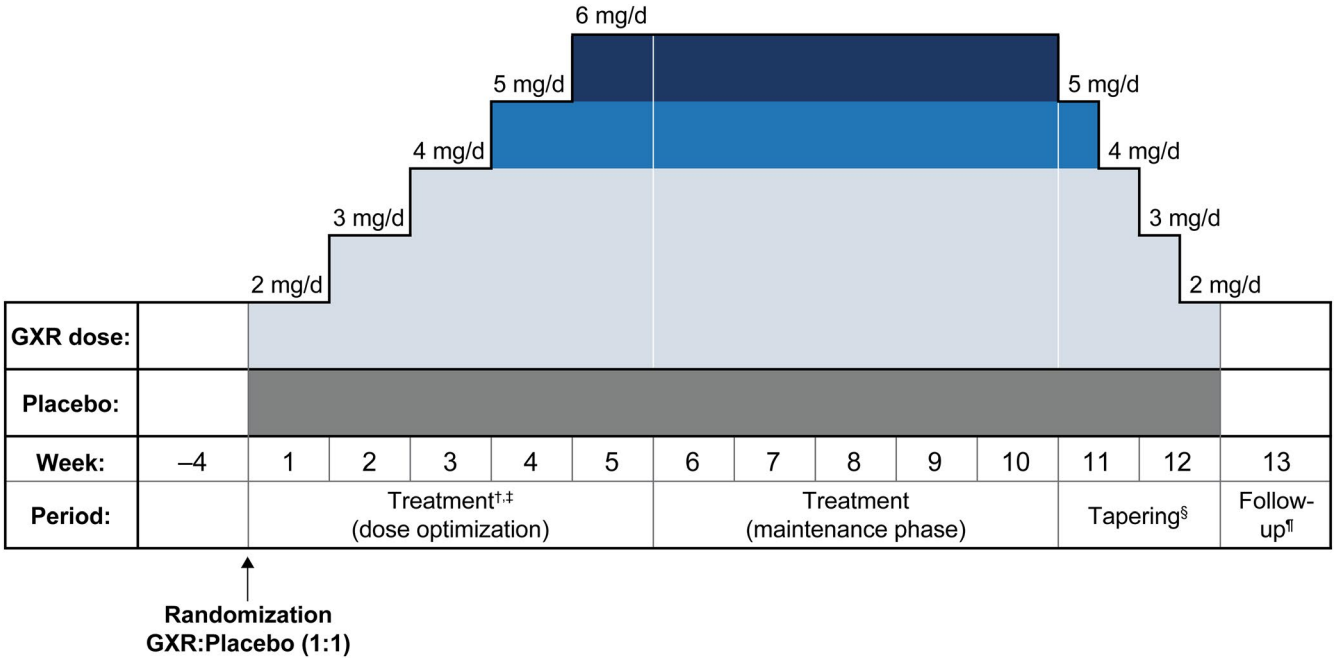

FIGURE 1 Study design. †Patients randomized to guanfacine extended-release (GXR) or placebo received 2 mg/d as a starting dose for the first week. The dose increased by 1 mg each week for the next 2 wk. ‡Patients who received the minimum GXR dose of 4 mg/d from week 3 were allowed to increase their dose in increments of 1 mg weekly (or after at least 5 d) from week 4 up to a maximum of 6 mg/d. §Treatment was tapered down over 2 wk from week 11 or when patients discontinued before the end of the treatment period. ¶Patients underwent 1 wk of follow-up from week 13 or the week after treatment discontinuation

rate). The mean dose of GXR during the maintenance phase was 5.07 mg.[13]

2.4 | Outcome measures

Efficacy outcomes included in this analysis were the Japanese version of the investigator-rated ADHD-RS-IV with adult prompts (total and subscale scores),[16,23] the patient-rated Adult ADHD Quality of Life Questionnaire (AAQoL),[24,25] and the Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A).[26] The primary efficacy endpoint was the least-squares (LS) mean change from baseline in ADHD-RS-IV total score at week 10. Safety outcome measures included in this analysis were the type and incidence of treatment-emergent AEs (TEAEs) (Medical Dictionary for Regulatory Activities, v19.0) and treatment-related AEs. Significant TEAEs were severe TEAEs or TEAEs resulting in study discontinuation that were not serious. Vital signs (including SBP, DBP, and pulse rate) and electrocardiogram (ECG) parameters were also measured.

2.5 | Statistical analysis

Because most subgroup analyses were conducted post hoc and all subgroups had small sample sizes, comparisons between subgroups in this analysis were not designed or powered for statistical significance. Efficacy analyses were conducted on the full analysis set (FAS), defined as all randomized patients who received ≥1 dose of study drug and had ≥1 ADHD-RS-IV score measured (at baseline and after the start of study drug administration). Safety analyses were conducted on the safety analysis set (SAS), defined as all patients who received ≥1 dose of study drug and had ≥1 safety measure. Exploratory subgroup analyses were conducted on efficacy and safety outcomes by ADHD subtype (ADHD-C and ADHD-I), age (median ≥31 and <31 years), and sex (male and female), and for the incidence of TEAEs by body weight (≥50 and <50 kg). The ADHD-predominantly hyperactive/impulsive (ADHD-H) subtype was not analyzed because of the small number of patients for this subgroup. For ADHD-RS-IV total score, the subgroup analysis by sex was pre-planned and for other subgroups was post hoc.

A mixed model for repeated measures (MMRM) method with an unstructured covariance matrix was used to assess ADHD-RS-IV total score (effect size was calculated at 10 weeks), ADHD-RS-IV Inattention and Hyperactivity-Impulsivity subscale scores, AAQoL total score and subscores, and BRIEF-A subscale T-scores. Fixed effects included treatment group, time point, and treatment group-by-time point interaction, and covariates included the respective baseline values for each measure and ADHD subtype (except for the ADHD subtype subgroup analyses). Descriptive statistics were used to describe the incidences of TEAEs, treatment-related AEs, vital signs, and ECG parameters in the subgroups. Statistical analyses were performed using SAS v9.2 (SAS Institute Inc, Cary, NC, USA).

TABLE 1 Patient demographics and baseline characteristics (FAS)

	Total population N = 200		Subgroups ADHD-C n = 100		ADHD-I n = 96		Age <31 y n = 99		Age ≥31 y n = 101		Male n = 129		Female n = 71	
Subgroup/ characteristic	**GXR n = 100**	**PBO n = 100**	**GXR n = 51**	**PBO n = 49**	**GXR n = 47**	**PBO n = 49**	**GXR n = 53**	**PBO n = 46**	**GXR n = 47**	**PBO n = 54**	**GXR n = 66**	**PBO n = 63**	**GXR n = 34**	**PBO n = 37**
Subtypes														
ADHD-C, n (%)	51 (51.0)	49 (49.0)	51 (100)	49 (100)	0 (0)	0 (0)	25 (47.2)	24 (52.2)	26 (55.3)	25 (46.3)	37 (56.1)	34 (54.0)	14 (41.2)	15 (40.5)
ADHD-I, n (%)	47 (47.0)	49 (49.0)	0 (0)	0 (0)	47 (100)	49 (100)	27 (50.9)	21 (45.7)	20 (42.6)	28 (51.9)	27 (40.9)	28 (44.4)	20 (58.8)	21 (56.8)
ADHD-H, n (%)	2 (2.0)	2 (2.0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.9)	1 (2.2)	1 (2.1)	1 (1.9)	2 (3.0)	1 (1.6)	0 (0)	1 (2.7)
ADHD-RS-IV total score														
BL score, mean	31.5	31.7	34.7	35.5	27.8	27.9	30.8	32.7	32.1	30.8	31.7	32.2	30.9	30.8
BL score <30, n (%)	49 (49.0)	48 (48.0)	10 (19.6)	11 (22.4)	38 (80.9)	36 (73.5)	29 (54.7)	16 (34.8)	20 (42.6)	32 (59.3)	28 (42.4)	27 (42.9)	21 (61.8)	21 (56.8)
BL score ≥30, n (%)	51 (51.0)	52 (52.0)	41 (80.4)	38 (77.6)	9 (19.1)	13 (26.5)	24 (45.3)	30 (65.2)	27 (57.4)	22 (40.7)	38 (57.6)	36 (57.1)	13 (38.2)	16 (43.2)
Age														
Mean, years	31.1	33.8	31.5	33.3	30.6	34.3	24.6	25.3	38.4	41.1	31.7	31.3	29.9	38.1
Sex														
Male, n (%)	66 (66.0)	63 (63.0)	37 (72.5)	34 (69.4)	27 (57.4)	28 (57.1)	33 (62.3)	36 (78.3)	33 (70.2)	27 (50.0)	66 (100)	63 (100)	0 (0)	0 (0)
Female, n (%)	34 (34.0)	37 (37.0)	14 (27.5)	15 (30.6)	20 (42.6)	21 (42.9)	20 (37.7)	10 (21.7)	14 (29.8)	27 (50.0)	0 (0)	0 (0)	34 (100)	37 (100)
Weight														
Mean, kg	65.3	66.1	66.6	67.3	63.6	65.2	64.0	64.7	66.8	67.2	69.1	70.8	58.0	58.0
Weight <50 kg, n (%)	9 (9.0)	12 (12.0)	3 (5.9)	6 (12.2)	6 (12.8)	6 (12.2)	6 (11.3)	6 (13.0)	3 (6.4)	6 (11.1)	0 (0)	2 (3.2)	9 (26.5)	10 (27.0)
Weight ≥50 kg, n (%)	91 (91.0)	88 (88.0)	48 (94.1)	43 (87.8)	41 (87.2)	43 (87.8)	47 (88.7)	40 (87.0)	44 (93.6)	48 (88.9)	66 (100)	61 (96.8)	25 (73.5)	27 (73.0)
Concurrent disease														
Yes, n (%)	74 (74.0)	80 (80.0)	39 (76.5)	40 (81.6)	33 (70.2)	38 (77.6)	36 (67.9)	36 (78.3)	38 (80.9)	44 (81.5)	47 (71.2)	49 (77.8)	27 (79.4)	31 (83.8)
Prior drug treatment														

(Continues)

TABLE 1 (Continued)

Subgroup/ characteristic	Total population N = 200		Subgroups									
			ADHD-C n = 100		ADHD-I n = 96		Age <31 y n = 99		Age ≥31 y n = 101		Male n = 129		Female n = 71	
	GXR n = 100	PBO n = 100	GXR n = 51	PBO n = 49	GXR n = 47	PBO n = 49	GXR n = 53	PBO n = 46	GXR n = 47	PBO n = 54	GXR n = 66	PBO n = 63	GXR n = 34	PBO n = 37
Yes, n (%)	43 (43.0)	47 (47.0)	19 (37.3)	25 (51.0)	22 (46.8)	22 (44.9)	19 (35.8)	20 (43.5)	24 (51.1)	27 (50.0)	27 (40.9)	30 (47.6)	16 (47.1)	17 (45.9)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ADHD-C, ADHD-combined subtype; ADHD-H, ADHD-predominantly hyperactive/impulsive subtype; ADHD-I, ADHD-predominantly inattentive subtype; ADHD-RS-IV, ADHD-Rating Scale-IV with adult prompts; BL, baseline; FAS, full analysis set; GXR, guanfacine extended-release; PBO, placebo; y, years.

3 | RESULTS

3.1 | Demographic and baseline clinical characteristics

Of the 200 patients in the total population, 50% had ADHD-C, 48% had ADHD-I, and 2% had ADHD-H (Table 1). Because of the small number of patients with ADHD-H, this subtype was not included as an individual subgroup in the analysis but patients with ADHD-H were included in the age and sex subgroups. The median age was 31 years, 65% of patients were male, and 90% had a body weight ≥50 kg. The percentage of patients with ADHD-RS-IV total scores <30 and ≥30 were 49% and 52%, respectively, 77% of patients had concurrent disease, and 45% had received drug therapy for ADHD previously.

In general, baseline characteristics were similar between the subgroups (Table 1). However, a greater proportion of patients in the ADHD-C subgroup were male, patients in the ADHD-I and female subgroups had lower baseline ADHD symptom severity (ADHD-RS-IV total score) compared with the other subgroups, and the mean body weight of female patients was 11 to 13 kg lower than male patients.

3.2 | ADHD-RS-IV total and subscale scores

Significant improvements in ADHD symptoms after 10 weeks of treatment with GXR compared with placebo were reported in all patient subgroups (Table 2). The magnitude of the effects of GXR compared with placebo on ADHD-RS-IV total scores after 10 weeks of treatment were consistent between the ADHD-C and ADHD-I subgroups and between the age and sex subgroups (Table 2). The effect size for GXR compared with placebo was 0.52 for the total population, 0.51 and 0.52 for the ADHD-C and ADHD-I subgroups, respectively, 0.61 and 0.47 for the ≥31- and <31-year subgroups, respectively, and 0.50 and 0.57 for the male and female subgroups, respectively. Numerically, there were no major differences in the change in ADHD-RS-IV total scores from baseline over time between the ADHD-C and ADHD-I subgroups or between the age and sex subgroups (Figure 2). However, no statistical comparisons between subgroups were conducted.

Although significant improvements in ADHD-RS-IV subscale scores for Inattention and for Hyperactivity-Impulsivity with GXR compared with placebo were not reported in all patient subgroups, the magnitude of the treatment effect was numerically similar between each of the subgroups (ADHD subtypes, age, sex) (Table 2). The mean difference from placebo across each of the subgroups ranged from −2.07 to −3.11 for the ADHD-RS-IV Inattention subscale scores and from −0.63 to −2.75 for the ADHD-RS-IV Hyperactivity-Impulsivity subscale scores. The mean difference from placebo for the ADHD-RS-IV Hyperactivity-Impulsivity subscale scores was −0.63 for the ADHD-I subgroup and −2.75 for the ADHD-C subgroup, and significant improvements after 10 weeks of treatment with GXR compared

TABLE 2 Change in ADHD-RS-IV total and subscale scores for the total population and subgroups at week 10 from baseline (FAS)

	Total population N = 200		Subgroups											
			ADHD-C n = 100		ADHD-I n = 96		Age <31 y n = 99		Age ≥31 y n = 101		Male n = 129		Female n = 71	
Variable	GXR n = 100	PBO n = 100	GXR n = 51	PBO n = 49	GXR n = 47	PBO n = 49	GXR n = 53	PBO n = 46	GXR n = 47	PBO n = 54	GXR n = 66	PBO n = 63	GXR n = 34	PBO n = 37
ADHD-RS-IV total score														
BL score, mean	31.45	31.70	34.73	35.49	27.83	27.94	30.83	32.72	32.15	30.83	31.74	32.22	30.88	30.81
Change from BL, LS mean	−11.55	−7.27	−13.56	−8.56	−11.28	−7.85	−10.79	−7.09	−12.45	−7.20	−10.86	−6.88	−13.03	−8.10
Difference vs PBO, mean (95% CI)	−4.28*** (−6.67, −1.88)		−5.00* (−8.97, −1.04)		−3.42* (−6.24, −0.61)		−3.70* (−6.99, −0.41)		−5.25** (−8.77, −1.74)		−3.98** (−6.86, −1.11)		−4.92* (−9.30, −0.55)	
ADHD-RS-IV Inattention subscale score														
BL score, mean	21.24	21.88	21.43	22.43	21.49	21.84	21.42	22.24	21.04	21.57	21.03	22.00	21.65	21.68
Change from BL, LS mean	−7.39	−4.89	−7.72	−5.45	−8.05	−5.23	−7.49	−5.41	−7.44	−4.53	−6.41	−4.29	−8.89	−5.78
Difference vs PBO, mean (95% CI)	−2.51** (−4.16, −0.85)		−2.28 (−4.66, 0.11)		−2.81* (−5.22, −0.41)		−2.07 (−4.40, 0.26)		−2.92* (−5.35, −0.49)		−2.12* (−4.11, −0.13)		−3.11* (−6.13, −0.09)	
ADHD-RS-IV Hyperactivity-Impulsivity subscale score														
BL score, mean	10.21	9.82	13.29	13.06	6.34	6.10	9.42	10.48	11.11	9.26	10.71	10.22	9.24	9.14
Change from BL, LS mean	−3.84	−2.10	−6.46	−3.71	−3.16	−2.53	−3.19	−1.84	−4.41	−2.29	−3.53	−1.78	−3.99	−2.27
Difference vs PBO, mean (95% CI)	−1.74** (−2.84, −0.64)		−2.75** (−4.62, −0.88)		−0.63 (−1.61, 0.34)		−1.35 (−2.91, 0.21)		−2.12** (−3.71, −0.53)		−1.74** (−2.95, −0.53)		−1.71 (−3.98, 0.56)	

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ADHD-C, ADHD-combined subtype; ADHD-I, ADHD-predominantly inattentive subtype; ADHD-RS-IV, ADHD-Rating Scale-IV with adult prompts; BL, baseline; CI, confidence interval; FAS, full analysis set; GXR, guanfacine extended-release; LS, least-squares; PBO, placebo; y, years.

Mixed model for repeated measures:

*$P < .05$ vs placebo.

**$P < .01$ vs placebo.

***$P < .001$ vs placebo.

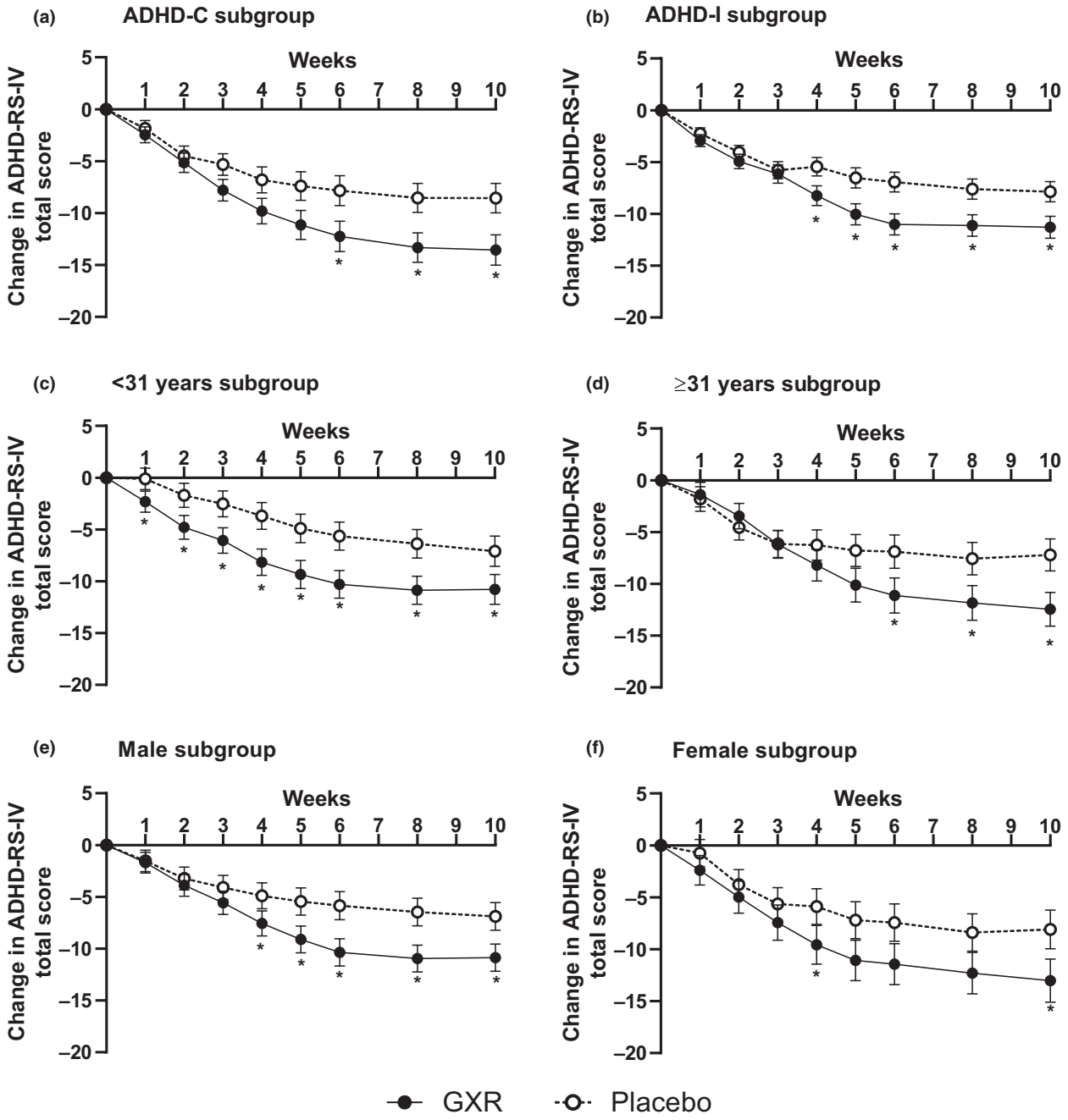

FIGURE 2 Change from baseline in ADHD-Rating Scale-IV (ADHD-RS-IV) with adult prompts total score. Data are the least-squares mean (standard error of the mean) change from baseline for patients in the following subgroups: (A) ADHD-C, (B) ADHD-I, (C) <31 years, (D) ≥31 years, (E) male, and (F) female. Mixed model for repeated measures: *$P < .05$ compared with placebo. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ADHD-C, ADHD-combined subtype; ADHD-I, ADHD-inattentive subtype; GXR, guanfacine extended-release

with placebo were reported for ADHD-RS-IV Inattention subscale scores in the ADHD-I subgroup and for Hyperactivity-Impulsivity subscale scores in the ADHD-C subgroup (Table 2).

3.3 | Quality of life and executive functioning

Significant differences in the effect of treatment with GXR compared with placebo at 10 weeks from baseline were observed for AAQoL total scores in the ADHD-I subgroup and for life productivity in the ADHD-I, ≥31 years, and male subgroups (Table 3). However, most differences compared with placebo were within the 95% confidence intervals across the subgroups (Table 3). Similarly, significant differences in several BRIEF-A subscale T-scores following 10 weeks of treatment with GXR compared with placebo were observed in the ADHD-C and ADHD-I subgroups, and in the ≥31-year, male, and female subgroups (Table 3), but all mean differences compared with placebo were within the 95% confidence intervals across each of the subgroups.

TABLE 3 Change in quality of life and executive functioning for each subgroup for guanfacine extended-release compared with placebo at week 10 from baseline (FAS)

		Subgroup					
Measure	Total population N = 200	ADHD-C n = 100	ADHD-I n = 96	Age <31 y n = 99	Age ≥31 y n = 101	Male n = 129	Female n = 71
AAQoL score							
Total	3.74 (−0.30, 7.77)	0.81 (−4.67, 6.28)	7.17* (0.99, 13.35)	3.91 (−2.12, 9.94)	3.84 (−1.83, 9.51)	3.95 (−0.91, 8.80)	3.13 (−4.63, 10.88)
Life productivity	6.78** (1.86, 11.71)	1.63 (−5.46, 8.71)	12.35*** (5.26, 19.44)	5.61 (−1.85, 13.08)	8.66* (1.92, 15.40)	6.90* (0.73, 13.06)	6.49 (−2.37, 15.35)
Psychological health	2.42 (−3.31, 8.15)	0.11 (−7.60, 7.82)	5.84 (−3.14, 14.82)	3.93 (−4.17, 12.04)	1.02 (−7.40, 9.44)	3.87 (−3.27, 11.02)	0.47 (−9.72, 10.67)
Life outlook	0.32 (−3.57, 4.22)	−1.17 (−6.28, 3.94)	2.59 (−3.71, 8.90)	1.77 (−3.51, 7.05)	−0.83 (−6.81, 5.15)	1.16 (−3.43, 5.74)	−1.07 (−8.86, 6.73)
Relationships	4.48 (−0.79, 9.76)	5.65 (−2.13, 13.44)	3.72 (−3.74, 11.19)	5.76 (−2.15, 13.68)	2.71 (−4.60, 10.03)	4.18 (−2.47, 10.83)	5.57 (−3.40, 14.53)
BRIEF-A subscale T-scores							
Inhibit	−2.91* (−5.30, −0.52)	−3.70* (−7.35, −0.04)	−2.42 (−5.61, 0.77)	−1.89 (−5.72, 1.93)	−3.74* (−6.82, −0.66)	−2.15 (−5.04, 0.74)	−4.66* (−9.23, −0.08)
Shift	−1.33 (−4.34, 1.68)	−1.68 (−6.05, 2.69)	−1.22 (−5.52, 3.08)	−2.81 (−7.41, 1.79)	−0.14 (−4.25, 3.96)	−2.57 (−6.20, 1.06)	0.87 (−4.74, 6.47)
Emotional control	−1.57 (−3.79, 0.66)	−0.82 (−3.95, 2.31)	−2.11 (−5.39, 1.16)	−1.20 (−4.26, 1.87)	−1.85 (−5.20, 1.50)	−1.47 (−4.09, 1.15)	−1.06 (−5.26, 3.15)
Self-monitor	−1.80 (−4.93, 1.33)	1.19 (−3.17, 5.56)	−5.03* (−9.65, −0.41)	−0.55 (−5.09, 4.00)	−2.48 (−6.89, 1.94)	−1.85 (−5.72, 2.02)	−2.32 (−7.68, 3.04)
Behavioral regulation index	−2.17 (−4.72, 0.38)	−1.06 (−4.65, 2.53)	−3.32 (−7.08, 0.44)	−1.64 (−5.40, 2.12)	−2.55 (−6.13, 1.03)	−1.69 (−4.91, 1.00)	−2.30 (−7.20, 2.62)
Initiate	−3.32* (−6.49, −0.14)	−2.80 (−7.35, 1.74)	−4.13 (−8.88, 0.63)	−1.72 (−6.53, 3.09)	−4.70* (−9.05, −0.36)	−2.99 (−6.58, 0.61)	−3.62 (−10.30, 3.06)
Working memory	−2.92 (−6.19, 0.34)	−0.70 (−5.34, 3.95)	−4.98* (−9.80, −0.15)	−1.65 (−6.76, 3.46)	−4.42* (−8.73, −0.12)	−4.32* (−8.17, −0.47)	−0.23 (−6.10, 6.55)
Plan/organize	−3.76* (−6.85, −0.67)	−3.41 (−7.85, 1.62)	−3.92 (−8.45, 0.61)	−2.49 (−7.35, 2.36)	−5.13* (−9.20, −1.06)	−4.35* (−8.05, −0.66)	−2.24 (−8.21, 3.74)
Task monitor	−2.59 (−5.92, 0.74)	−0.90 (−5.31, 3.51)	−4.38 (−9.73, 0.97)	−0.51 (−5.91, 4.88)	−4.36* (−8.57, −0.15)	−1.89 (−5.85, 2.08)	−4.17 (−10.65, 2.31)
Organization of materials	−2.38 (−4.88, 0.13)	−0.77 (−4.46, 2.91)	−3.90* (−7.33, −0.46)	−1.99 (−5.71, 1.72)	−2.68 (−6.18, 0.82)	−2.20 (−5.30, 0.89)	−2.52 (−7.07, 2.03)

(Continues)

TABLE 3 (Continued)

Measure	Total population N = 200	Subgroup ADHD-C n = 100	ADHD-I n = 96	Age <31 y n = 99	Age ≥31 y n = 101	Male n = 129	Female n = 71
Metacognition index	−3.04 (−6.11, 0.03)	−1.48 (−5.84, 2.88)	−4.64* (−9.23, −0.05)	−1.79 (−6.66, 3.08)	−4.25* (−8.23, −0.26)	−3.16 (−6.74, 0.41)	−2.65 (−8.83, 3.54)
GEC index	−3.06* (−5.99, −0.14)	−1.67 (−5.85, 2.51)	−4.51* (−8.82, −0.20)	−2.04 (−6.61, 2.52)	−3.99* (−7.86, −0.12)	−2.90 (−6.28, 0.48)	−3.18 (−9.06, 2.69)

Note: Data are the difference between guanfacine extended-release and placebo for the least-squares mean change at week 10 from baseline (95% confidence interval).

Abbreviations: AAQoL, Adult ADHD quality of life; ADHD, attention-deficit/hyperactivity disorder; ADHD-C, ADHD-combined subtype; ADHD-I, ADHD-predominantly inattentive subtype; BRIEF-A, Behavior Rating Inventory of Executive Function-Adult Version; FAS, full analysis set; GEC, Global Executive Composite; y, years.

Mixed model for repeated measures:

*$P < .05$ vs placebo.

**$P < .01$ vs placebo.

***$P < .001$ vs placebo.

3.4 | Safety measures

There were no major differences during the treatment period in the incidence of TEAEs or types of TEAEs across the ADHD subtype, age, and sex subgroups (Table 4). For placebo-treated patients, 62.0% of all patients had at least 1 TEAE and the percentage of TEAEs ranged from 56.5% to 66.7% across the subgroups. For GXR-treated patients, the percentage of patients who had at least 1 TEAE was 81.2% for all patients; the percentages were 83.0% and 78.8% for the ADHD-I and ADHD-C subgroups, respectively; 91.5% and 72.2% for the ≥31- and <31-year subgroups, respectively; and 97.1% and 72.7% for the female and male subgroups, respectively. The percentages of patients with significant TEAEs (34.3%, 10.6%) and TEAEs leading to discontinuation (34.3%, 12.1%) were approximately three times higher in the female subgroup than in the male subgroup, respectively (Table 4). In general, the types of treatment-related TEAEs reported by ≥10% of GXR-treated patients in the subgroups were similar (Figure 3). However, approximately 40% of patients reported somnolence in the ADHD-C, ≥31-year, and female subgroups, and the percentages of patients with blood pressure decrease (37.1%, 12.1%, respectively) and postural dizziness (25.7%, 9.1%, respectively) were approximately three times higher in the female subgroup than the male subgroup.

Overall, mean differences in the change from baseline over the treatment period in vital signs and ECG parameters between GXR-treated patients and placebo were consistent across each of the subgroups (Table 5). All values were within the normal range and reflected the mechanism of action of GXR (Table 5).

During the dose optimization and maintenance periods, the percentage of patients with at least 1 TEAE appeared to be higher in patients of lower body weight (<50 kg weight subgroup) than those of higher body weight (≥50 kg subgroup) in both GXR- and placebo-treated patients (Table S1). During dose optimization, all (100%, 10 of 10) GXR-treated patients and 66.7% (8 of 12 patients) of placebo-treated patients in the <50 kg subgroup had at least 1 TEAE and 73.6% (67 of 91 patients) of GXR-treated patients and 44.3% (39 of 88 patients) of placebo-treated patients had at least 1 TEAE in the ≥50 kg subgroup (Table S1). The incidence of TEAEs was lower during the dose maintenance period than during the dose optimization period (Table S1). During the dose maintenance period, 40.0% (2 of 5 patients) of GXR-treated patients and 36.4% (4 of 11 patients) of placebo-treated patients had at least 1 TEAE in the <50 kg subgroup, and 24.4% (19 of 78 patients) of GXR-treated patients and 27.4% (23 of 84 patients) of placebo-treated patients had at least 1 TEAE in the ≥50 kg subgroup (Table S1).

4 | DISCUSSION

Findings from this exploratory post hoc analysis in adults with ADHD support the efficacy of GXR regardless of ADHD subtype, age, or sex. Significant improvements in all core symptoms of ADHD were evident following 10 weeks of treatment and there were no major

TABLE 4 Summary of adverse events by subgroup during the treatment period (SAS)

	Total population		Subgroup											
			ADHD-C		ADHD-I		Age <31 y		Age ≥31 y		Male		Female	
Type of event, n (%)	GXR n = 101	PBO n = 100	GXR n = 52	PBO n = 49	GXR n = 47	PBO n = 49	GXR n = 54	PBO n = 46	GXR n = 47	PBO n = 54	GXR n = 66	PBO n = 63	GXR n = 35	PBO n = 37
TEAEs	82 (81.2)*	62 (62.0)	41 (78.8)	31 (63.3)	39 (83.0)*	30 (61.2)	39 (72.2)	26 (56.5)	43 (91.5)*	36 (66.7)	48 (72.7)	39 (61.9)	34 (97.1)*	23 (62.2)
Deaths	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Serious TEAEs	1 (1.0)	0 (0)	0 (0)	0 (0)	1 (2.1)	0 (0)	1 (1.9)	0 (0)	0 (0)	0 (0)	1 (1.5)	0 (0)	0 (0)	0 (0)
Significant TEAEs[a]	19 (18.8)*	3 (3.0)	9 (17.3)*	0 (0)	10 (21.3)*	3 (6.1)	9 (16.7)	2 (4.3)	10 (21.3)*	1 (1.9)	7 (10.6)	2 (3.2)	12 (34.3)*	1 (2.7)
TEAEs leading to study discontinuation	20 (19.8)*	3 (3.0)	9 (17.3)*	0 (0)	11 (23.4)*	3 (6.1)	10 (18.5)*	2 (4.3)	10 (21.3)*	1 (1.9)	8 (12.1)	2 (3.2)	12 (34.3)*	1 (2.7)
Treatment-related TEAEs	72 (71.3)*	19 (19.0)	38 (73.1)*	8 (16.3)	32 (68.1)*	10 (20.4)	35 (64.8)*	10 (21.7)	37 (78.7)*	9 (16.7)	39 (59.1)*	12 (19.0)	33 (94.3)*	7 (18.9)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ADHD-C, ADHD-combined subtype; ADHD-I, ADHD-predominantly inattentive subtype; GXR, guanfacine extended-release; PBO, placebo; SAS, safety analysis set; TEAE, treatment-emergent adverse event; y, years.

[a]Significant TEAEs were those that were severe or resulted in study discontinuation but were not serious.

*$P < .05$, Fisher's exact test for GXR compared with placebo.

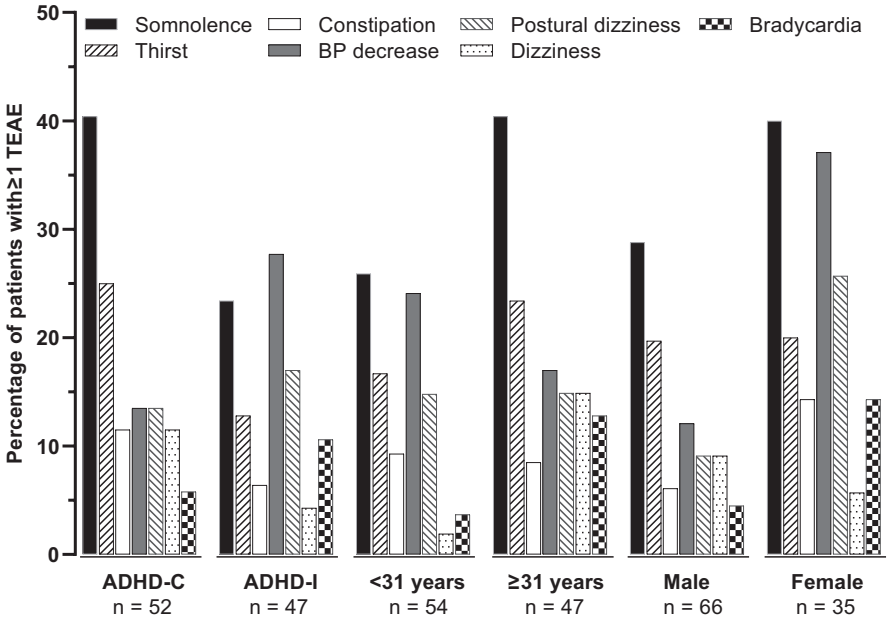

FIGURE 3 Summary of the most common treatment-related treatment-emergent adverse events (TEAEs) by subgroup in patients treated with guanfacine extended-release. Data are reported for TEAEs with an incidence ≥10% in at least one subgroup. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ADHD-C, ADHD-combined subtype; ADHD-I, ADHD-predominantly inattentive subtype; BP, blood pressure; y, years

differences in safety between the patient subgroups. Consistent with the total population,[13] these improvements in symptoms were, in general, associated with numerical improvements in patient-rated QoL (AAQoL) and executive functioning (BRIEF-A). However, the lack of significant differences in GXR-treated patients compared with placebo for patient-rated QoL measures was likely a reflection of the smaller sample sizes in this subgroup analysis compared with the total population.

This post hoc analysis showed that the efficacy and safety of GXR across each of the subgroups was consistent with those of the primary analysis in adults,[13] with previous studies of GXR in Japanese and non-Japanese children and adolescents,[11,15-18] and with pooled analyses of non-Japanese children and adolescents with ADHD-C and ADHD-I subtypes.[20,21] After 10 weeks of treatment, the ADHD-RS-IV total score effect sizes for GXR- versus placebo-treated patients across each of the subgroups were comparable to those of the total population, and the magnitude of the treatment effect on the change in ADHD-RS-IV subscale scores for Inattention and Hyperactivity-Impulsivity subscale scores was similar in each of the subgroups. Although a smaller improvement in ADHD-RS-IV Hyperactivity-Impulsivity subscale scores was observed in the ADHD-I subgroup, this is most likely because of the low level of hyperactive-impulsive symptoms at baseline in patients with ADHD-I. The differences in ADHD-RS-IV scores compared with placebo were statistically significant for the Inattention subscale in patients with ADHD-I and for the Hyperactivity-Impulsivity subscale in patients with ADHD-C, providing further support for the benefit of GXR in both ADHD subtypes. In addition, the ADHD-RS-IV total score effect sizes for the ADHD-C (0.51) and ADHD-I (0.52) subtypes in this study of adults were consistent with the effect sizes calculated from a pooled analysis of children and adolescents with ADHD-C (0.64) and ADHD-I (0.50, 0.52) who were treated with GXR.[20]

Analysis of the primary population for this trial[13] showed that the types of TEAEs during treatment with GXR in adults are similar to those in children and adolescents.[11,15-18] Although the incidence of TEAEs is higher among adults than in children and adolescents, the most frequently reported TEAEs related to GXR across all groups are somnolence, thirst, decreased blood pressure, postural dizziness, and constipation. Thirst has been reported more frequently in Japanese adults[13,14] than in Japanese children and adolescents,[16,17] but this finding is similar to findings in non-Japanese adults[27,28] and is not thought to be clinically relevant. In the primary population for this trial, the incidence of TEAEs with GXR was higher than placebo and the discontinuations owing to TEAEs in GXR-treated patients during dose optimization were most likely to have been related to the forced dose titration. Similar to the findings in children and adolescents,[11,15-18] most discontinuations were because of blood pressure decrease or somnolence, but these TEAEs were transitory and occurred during the first week of titration.[13] In this post hoc analysis, female patients appeared to report a higher incidence of TEAEs, including decreased blood pressure and postural dizziness, than male patients, which may be because of the known physiological differences between males and females that can affect response to treatment, related side effects, and the pharmacokinetics of many medications.[29] In addition, female patients had mean body weight of 58 kg, which was 11 to 13 kg lower compared with men. Hence, it is possible that the higher incidence of TEAEs in female patients may have been related to the forced dose titration and minimum maintenance dose of 4 mg/day GXR. The selected doses for GXR in adults in this study were based on studies in children and adolescents and assumed that weight-based dosing for adults was not required. Despite this, the subgroup analysis by weight showed that the incidence of TEAEs in GXR-treated patients may have been higher in those who were <50 kg than in those who were ≥50 kg. However,

TABLE 5 Vital signs and electrocardiogram parameters for each subgroup for guanfacine extended-release compared with placebo (SAS)

Parameter		Total population N = 201	Subgroup ADHD-C n = 101	ADHD-I n = 96	Age <31 y n = 100	Age ≥31 y n = 101	Male n = 129	Female n = 72
SBP, mmHg								
Mean value at week 10	GXR	107.07	107.72	105.96	105.01	109.41	111.09	97.29
	PBO	114.78	115.58	114.40	111.79	117.13	117.03	111.05
Mean difference vs PBO[a]		−10.10	−8.57	−11.62	−10.08	−10.23	−8.58	−13.76
DBP, mmHg								
Mean value at week 10	GXR	65.79	66.08	64.94	63.44	68.46	67.76	61.01
	PBO	73.35	72.83	74.39	69.77	76.17	73.73	72.72
Mean difference vs PBO[a]		−7.73	−5.35	−10.59	−6.64	−8.79	−7.22	−9.27
Pulse rate, beats/min								
Mean value at week 10	GXR	66.18	67.48	64.68	65.42	67.05	66.49	65.42
	PBO	74.51	73.43	75.58	75.74	73.54	74.81	74.02
Mean difference vs PBO[a]		−6.83	−6.61	−6.13	−5.85	−7.57	−5.79	−8.88
Heart rate, bpm								
Mean value at week 10	GXR	58.9	59.9	57.6	57.6	60.3	58.6	59.6
	PBO	66.2	65.9	66.3	65.8	66.5	65.8	66.9
Mean difference vs PBO[a]		−6.4	−5.31	−6.65	−6.08	−6.26	−5.31	−8.08
RR interval, msec								
Mean value at week 10	GXR	1041.5	1020.0	1070.2	1069.8	1009.5	1046.2	1030.2
	PBO	919.5	923.6	919.8	924.8	915.4	925.2	910.3
Mean difference vs PBO[a]		108.47	84.24	124.49	118.25	93.19	96.12	128.16
PR interval, msec								
Mean value at week 10	GXR	153.6	157.9	148.9	148.9	159.1	155.9	148.2
	PBO	154.1	153.8	155.3	151.3	156.3	153.3	155.4
Mean difference vs PBO[a]		0.81	3.66	−2.07	1.36	0.80	1.24	−0.16
QRS interval, msec								
Mean value at week 10	GXR	99.7	99.4	100.0	99.5	99.9	102.8	92.1
	PBO	99.2	99.7	98.3	101.8	97.1	102.1	94.3
Mean difference vs PBO[a]		−1.06	−0.64	−1.72	−0.84	−1.20	−2.08	1.09
QT interval, msec								
Mean value at week 10	GXR	412.2	406.8	418.4	417.2	406.5	407.9	422.7
	PBO	395.1	392.6	398.9	387.1	401.4	388.3	406.3
Mean difference vs PBO[a]		17.57	16.05	17.28	17.59	16.74	15.88	20.49
QTcB interval, msec								
Mean value at week 10	GXR	405.8	404.3	406.8	405.6	406.0	400.6	418.3
	PBO	413.2	409.9	417.0	403.6	420.8	404.8	427.2
Mean difference vs PBO[a]		−4.11	−1.17	−6.95	−5.60	−2.34	−2.68	−6.56
QTcF interval, msec								
Mean value at week 10	GXR	407.7	405.0	410.4	409.2	406.1	402.9	419.6
	PBO	407.0	403.9	410.7	398.0	414.1	399.2	419.9
Mean difference vs PBO[a]		3.10	4.69	0.96	1.93	4.18	3.39	2.62

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ADHD-C, ADHD-combined subtype; ADHD-I, ADHD-predominantly inattentive subtype; bpm, beats per minute; DBP, diastolic blood pressure; GXR, guanfacine extended-release; PBO, placebo; QTcB, QT interval corrected by Bazett's formula; QTcF, QT interval corrected by Fridericia's formula; SAS, safety analysis set; SBP, systolic blood pressure; y, years.

[a]Mean difference vs PBO for the change from baseline over the treatment period.

because of the post hoc nature of the analyses and the small sample size of the subgroups, it is not possible to conclude that the safety profile of GXR in adults is truly influenced by patient sex and weight.

The main limitations of this study were the post hoc nature of the analyses and the small sample sizes of the subgroups, such that formal statistical comparisons between subgroups were not conducted. In addition, the subgrouping may have contributed to bias in patient background demographics and, because the characteristics of the subgroups were restricted by the eligibility criteria in the primary study, may not reflect subgroups of patients in real-world clinical practice or in populations outside Japan.

In conclusion, the efficacy and safety of GXR in the subgroups in this analysis were shown to be consistent with previous studies of GXR in adults. This analysis provides clinically practical information on the efficacy and safety of GXR for treatment of adults who have hyperactive-impulsive and/or inattentive ADHD symptoms, and subgroups of adults categorized by sex, age, and weight. In clinical practice, patient and physician awareness of the potential for adverse effects is recommended, and careful monitoring for TEAEs and dose optimization, particularly at the start of administration, is considered for all patients.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Shionogi & Co., Ltd. was involved in the study design, data collection, data analysis, and preparation of the manuscript. Medical writing assistance was provided by Serina Stretton, PhD, CMPP and Rebecca Lew, PhD, CMPP of ProScribe – Envision Pharma Group, and was funded by Shire International GmbH (manufacturer/licensee of Intuniv®), a member of the Takeda group of companies, and Shionogi & Co., Ltd. ProScribe's services complied with international guidelines for Good Publication Practice (GPP3). All authors participated in the interpretation of study results, and in the drafting, critical revision, and approval of the final version of the manuscript. Akira Iwanami was a coordinating investigator in the study. Chika Sakai, Daiki Okutsu, Ryo Kiguchi, Noriyuki Naya, Toshinaga Tsuji, and Masakazu Fujiwara were involved in the development of the study design, Daiki Okutsu was involved in data collection, and Masakazu Fujiwara and Ryo Kiguchi were involved in the statistical analyses.

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This study was funded by Shire International GmbH (manufacturer/licensee of Intuniv®), a member of the Takeda group of companies, and Shionogi & Co., Ltd. Intuniv is approved for adults with ADHD only in Japan.

ETHICS APPROVAL STATEMENT

The study was approved by the local ethics committees and was compliant with the Japanese Ethical Guidelines for Clinical Studies and the Declaration of Helsinki.

INFORMED CONSENT

All patients provided written informed consent before participating in the study.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY

Japan Primary Registries Network (https://rctportal.niph.go.jp/en/): JapicCTI-163232, registered 04/21/2016.

DATA AVAILABILITY STATEMENT

The data for this study are not available in a public repository because Shionogi takes suitable measures to protect personal information and the sponsor's intellectual property. The nature of the information protected will be tailored to the specific request. Researchers can request access to detailed information about Shionogi's clinical trials, including trial protocols and individual patient data, through the portal site: https://clinicalstudydatarequest.com/. Sharable information includes data about Shionogi's clinical trials conducted in patients in Japan. The information will become sharable after the medicinal products for which the trials are performed have been approved in Japan. Note that all documents will be provided in Japanese language only as they have been prepared in Japanese.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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