Safety and efficacy of guanfacine extended-release in adults with attention-deficit/hyperactivity disorder: an open-label, long-term, phase 3 extension study

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Abstract

Background: To assess the safety and efficacy of long-term administration of guanfacine extended-release (GXR) in adults with attention-deficit/hyperactivity disorder (ADHD).

Methods: In this open-label, long-term, phase 3 extension study in Japan, 150 patients transitioned from a double-blind trial, and 41 newly enrolled patients received once daily GXR (starting dose 2 mg/day, maintenance dose 4–6 mg/day) for 50 weeks. Primary outcome measures were the frequency and nature of treatment-emergent adverse events (TEAEs); secondary outcome measures included the change from week 0 in ADHD Rating Scale IV with Adult Prompts (ADHD-RS-IV; Japanese version) total and subscale scores, Conners’ Adult ADHD Rating Scales (CAARS), Clinical Global Impression-Improvement (CGI-I) and Patient Global Impression-Improvement (PGI-I) scales, and quality of life (QoL) and executive functioning measures.

Results: Of all patients, 94.2% (180/191) reported ≥ 1 TEAE and 19.9% (38/191) discontinued because of a TEAE. Most TEAEs were mild to moderate in severity; there were two serious TEAEs and no deaths. Commonly reported TEAEs (≥ 10% of patients) were somnolence, thirst, nasopharyngitis, decreased blood pressure, postural dizziness, bradycardia, malaise, constipation, and dizziness. Mean changes from week 0 in ADHD-RS-IV total and subscale scores and CAARS subscale scores were significantly improved in former placebo or GXR patients and new patients at last observation (p < .0001), and the percentage of patients with very much or much improved CGI-I and PGI-I scores increased.

Conclusions: There were no major safety concerns during long-term GXR administration in adults with ADHD. After long-term treatment, patients had significant improvements from baseline in ADHD symptoms, QoL, and executive functioning.

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

Keywords: Adult, Attention deficit disorder with hyperactivity, Guanfacine, Safety, Treatment outcome
Background
Although attention-deficit/hyperactivity disorder (ADHD) is commonly considered a childhood disorder, it is estimated to affect up to 3% of adults worldwide [1, 2]. Adult ADHD can persist from childhood into adulthood or be newly diagnosed in adults [3] and differs from childhood ADHD in several respects. ADHD symptoms change as patients mature, with decreases in overt hyperactivity symptoms and increases in more subtle symptoms, such as inattention and disorganization [4–6]. Comorbid psychiatric and behavioral symptoms can be associated with ADHD in children and adults, which may obscure initial diagnosis of ADHD in adults [6, 7]. Nonpsychiatric comorbidities, particularly obesity, sleep disorders, and asthma, are also associated with ADHD in adults [8]. Overall, underdiagnosis and undertreatment of ADHD in adults can result in impaired quality of life (QoL) [9] and psychosocial functioning [10], addictive or risky behaviors (including substance use disorders) [6], high rates of accidental death [11], and suicide [12].

Guanfacine extended-release (GXR) is a nonstimulant, selective, α2A-adrenergic receptor agonist approved worldwide for ADHD in children and adolescents and was first approved for treatment of ADHD in adults in Japan in June 2019. As clinical trial data for the use of GXR in adults have only recently become available [13], GXR for adults was not included in a comprehensive systematic review and metaanalysis of medications for ADHD, published in 2018 [14], and is not included in current international guidelines [15]. In the first phase 3, double-blind, randomized trial conducted in adults, dose-optimized GXR treatment significantly reduced ADHD symptoms at week 10 compared with placebo, with improvements in QoL and functioning [13]. Compared with placebo, GXR was associated with an increased incidence of treatment-emergent adverse events (TEAEs) that were related to its effect on α2A-adrenergic receptors (somnolence, thirst, blood pressure decrease, postural dizziness, and constipation), but most were mild to moderate in severity and resolved during treatment [13]. Given the differences between children and adults in the clinical presentation of ADHD and associated comorbidities, assessment of the safety and efficacy of prolonged GXR treatment in adults is required.

The primary objective of this study was to assess the safety of long-term administration of once-daily GXR in adults with ADHD over 50 weeks of treatment. The secondary objective was to assess the efficacy of GXR.

Methods
This was an open-label, long-term, phase 3 study in adults with ADHD. The study (conducted at 71 Japanese centers from December 2016 through December 2018) was approved by the following local ethics committees:

- Mizuo Clinic Institutional Review Board (IRB); Ehime University Hospital IRB; IHL Shinagawa East One Medical Clinic IRB; Dr. Mano Medical Clinic IRB; Odori Park Mental Clinic IRB; Tokyo Midtown Clinic IRB; Tokyo-Eki Center-Building Clinic IRB; Riverside Internal and Circulatory Medical Clinic IRB; Goryokai Hospital IRB; Himorogi Psychiatric Institute IRB; Nanko Clinic of Psychiatry IRB; Iwata Buddy’s Clinic IRB; Suzuki Internal and Circulatory Medical Clinic IRB; Koijinkai Sapporo Skin Clinic IRB; Shoda Hospital IRB; Kondo Hospital IRB; Tomisaka Clinic IRB; Yokohama Sakae Kyosai Hospital IRB; Hokkaido University Hospital IRB; Yamate Dermatological Clinic IRB; Chibune General Hospital IRB; IRB of Showa University Karasuyama Hospital; Yoyogi Mental Clinic IRB; Tokai University Hospital IRB; The Jikei University Hospital IRB for Medicinal Products; Non-Profit Organization Tokyo Allergy and Respiratory Disease Research Institute IRB; Review Board of Human Rights and Ethics for Clinical Studies; Nara Medical University Hospital IRB; University of Fukui Hospital IRB; Hayashi Diabetes Clinic IRB, and conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent before participating in the study. The previous double-blind trial (DBT) [13] and this study were registered at the Japan Primary Registries Network (JapicCTI-163231).

Study population
Newly enrolled patients and the patients who completed the previous DBT and who consented to transition to this open-label study were eligible for inclusion. The main inclusion criteria for new patients were adult men or women (age ≥18 years) with a diagnosis of ADHD (Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) [DSM-5]) [16], ADHD Rating Scale IV with Adult Prompts (ADHD-RS-IV; Japanese version) total score ≥24, and a Clinical Global Impression-Severity of Illness (CGI-S) scale score ≥4. Exclusion criteria were reported in detail previously [13]. In brief, the main exclusion criteria were a diagnosed or documented moderate/severe psychiatric disorder (based on DSM-5) requiring drug treatment, a history of substance use disorder or seizures, persons considered at risk of suicide, a history or evidence of cardiovascular disease, and use of medications affecting blood pressure or heart rate.

Study design
This open-label study was dose optimized and noncontrolled and comprised a 50-week treatment period, a 2-week tapered dose-reduction period, and a 1-week follow-up period (Additional file 1). All patients received a single dose of GXR once daily at approximately the same time (morning or afternoon), starting at a
minimum dose of 2 mg/day and increasing to a maintenance dose of 4–6 mg/day for 50 weeks. Forced dose increments of 1-mg increases up to a total of 4 mg, followed by 1-mg increases or reductions at ≥5-day intervals to maintain the dose between 4 and 6 mg, were allowed at the investigator’s discretion for patients with no safety concerns and CGI-S scores ≥3. During the tapered dose-reduction period, doses were decreased by 1 mg at ≥3-day intervals over 2 weeks.

Outcome measures
Safety measures included the type and frequency of TEAEs (Medical Dictionary for Regulatory Activities, v19.0) and vital signs at each visit, and electrocardiogram (ECG) parameters and clinical laboratory tests (weeks 0, 10, 22, 34, 50, and study discontinuation).

Efficacy outcomes included physician-rated measures (ADHD-RS-IV total and subscale scores, Conners’ Adult ADHD Rating Scales [CAARS], and CGI-Improvement [CGI-I and CGI-S scales]) [17–20] and patient-rated measures (Patient Global Impression-Improvement [PGI-I] scale, the Adult ADHD Quality of Life Questionnaire [AAQoL], and the Behavior Rating Inventory of Executive Function-Adult Version [BRIEF-A]) [19, 21–23]. ADHD-RS-IV and CGI-S were assessed at each visit from weeks 0–50 or discontinuation. CGI-I and PGI-I were assessed at each visit from weeks 1–50 or discontinuation, CAARS was assessed at weeks 0, 22, and 50 or discontinuation, and AAQoL and BRIEF-A were assessed at weeks 0, 10, 22, 34, and 50 or discontinuation.

Statistical analysis
The target sample size was 190 patients to allow for 100 patients completing 1 year of treatment. All patients who received at least one dose of GXR were included in the analyses. All TEAEs between the first intake of study drug and follow-up observation were analyzed. For analyses of ADHD-RS-IV total and subscale scores, CAARS scores, AAQoL scores, and BRIEF-A, mean (95% confidence intervals [CIs]) at each visit were reported. Mean differences in scores from week 0 (screening period) were assessed at each visit using two-sided t tests for ADHD-RS-IV total and subscale scores, CAARS scores, and AAQoL scores. Illness severity and improvement (CGI-S, CGI-I, or PGI-I) rates at each visit from week 0 were used to assess statistical analyses were performed using SAS Version 9.2 or higher (SAS Institute Inc., Cary, NC, USA).

Results
Patient disposition and baseline characteristics
A total of 191 patients were enrolled, received at least one dose of study drug, and were included in the analyses (Fig. 1); 150 had transitioned from the previous DBT (former placebo or GXR patients) and 41 were newly enrolled (new patients). Of the enrolled patients, 124 (95 transitioned, 29 new) completed the study. The main reason for discontinuation was adverse events from all populations (Fig. 1).

During the study, mean (standard deviation) treatment duration was 254.9 (136.5) days for all patients (transitioned: 247.6 [140.1]; new: 281.7 [120.3]), and the most frequently taken doses of GXR were 6 mg (38% of patients), 4 mg (35% of patients), and 5 mg (17% of patients).

In all patients, approximately half had combined presentation or predominantly inattentive presentation, and approximately half had been treated with ADHD medication previously (Table 1). At the start of the DBT for those who transitioned and at the start of long-term treatment for new patients, mean ADHD-RS-IV total scores were approximately 32 among all patients, but there was a higher proportion of new patients (70.7%) with ADHD-RS-IV total scores ≥30 than former placebo (51.6%) or GXR (53.4%) patients.

Safety and tolerability
In general, no new or unexpected adverse events were reported during long-term treatment (Table 2). A total of 830 TEAEs were reported by 180 patients (94.2%), with most considered to be drug related (83.8% of all patients). Most TEAEs were mild to moderate in severity, and no deaths were reported (Table 2). Compared with former placebo patients and new patients, a smaller proportion of former GXR patients experienced treatment-related TEAEs or moderate severity TEAEs or discontinued because of a TEAE (Table 2).

Two patients experienced a serious TEAE. One continuing patient was diagnosed with acute myeloid leukemia 380 days after starting treatment (81 days after completing the tapering period), which was considered unrelated to study drug. One new patient, with a preexisting condition requiring prescription of verapamil, experienced supraventricular tachycardia of moderate severity 255 days after starting GXR; the patient recovered following treatment and discontinuation of GXR.

The most commonly reported TEAEs (incidence ≥10%) in all patients were somnolence, thirst, nasopharyngitis, decreased blood pressure, postural dizziness, bradycardia, malaise, constipation, and dizziness (Table 2). Except for nasopharyngitis, most events were considered related to GXR. Study drug discontinuation because of TEAEs was reported for 19.9% of all patients (Table 2). The main TEAEs resulting in GXR discontinuation were somnolence (nine patients), blood pressure reduction (eight patients), malaise (six patients), bradycardia (four patients), and postural dizziness (three patients) or...
dizziness (three patients). All events resulting in GXR discontinuation were of mild or moderate severity except for one event of severe bradycardia, which occurred 70 days after commencing treatment. The GXR dose at onset was 6 mg. The patient discontinued GXR and recovered without treatment.

There were no clinically relevant changes in blood pressure, pulse rate, or ECG parameters (Table 3) or clinical laboratory tests after 50 weeks of treatment with GXR. For all patients, the mean change from week 0 in systolic blood pressure and diastolic blood pressure between week 1 and week 50 ranged from $-9.54$ to $-3.82$ mmHg and from $-8.37$ to $-2.93$ mmHg, respectively; the mean change in pulse rate ranged from $-9.04$ to $-2.12$ beats/minute; and the mean change in body weight between week 4 and week 50 ranged from $-0.33$ to $-0.15$ kg.

### Table 1: Patient Demographics and Baseline Characteristics

| Characteristic                             | Former placebo patients | Former GXR patients | New patients | All patients |
|--------------------------------------------|-------------------------|---------------------|--------------|-------------|
| Male, n (%)                                | 56 (63.6)               | 47 (75.8)           | 27 (65.9)    | 130 (68.1)  |
| Age, y, mean (SD)                          | 34.2 (10.1)             | 30.6 (8.2)          | 34.3 (9.2)   | 33.1 (9.4)  |
| <30 y, n (%)                               | 32 (36.4)               | 32 (51.6)           | 15 (36.6)    | 79 (41.4)   |
| 30 to <40 y, n (%)                         | 31 (35.2)               | 18 (29.0)           | 13 (31.7)    | 62 (32.5)   |
| ≥40 y, n (%)                               | 25 (28.4)               | 12 (19.4)           | 13 (31.7)    | 50 (26.2)   |
| Previous disease recorded in medical history, yes, n (%) | 46 (52.3)               | 29 (46.8)           | 16 (39.0)    | 91 (47.6)   |
| Prior ADHD medicationb, yes, n (%)         | 42 (47.7)               | 30 (48.4)           | 19 (46.3)    | 91 (47.6)   |
| Atomoxetine                                | 24 (27.3)               | 15 (24.2)           | 11 (26.8)    | 50 (26.2)   |
| Methylphenidate                            | 22 (25.0)               | 15 (24.2)           | 10 (24.4)    | 47 (24.6)   |
| Other                                      | 0 (0.0)                 | 3 (4.8)             | 0 (0.0)      | 3 (1.6)     |
| ADHD presentation, n (%)                   |                         |                     |              |             |
| Combined presentation                      | 46 (52.3)               | 31 (50.0)           | 20 (48.8)    | 97 (50.8)   |
| Predominantly inattentive presentation     | 40 (45.5)               | 29 (46.8)           | 21 (51.2)    | 90 (47.1)   |
| Predominantly hyperactive-impulsive
presentation | 2 (2.3)                 | 2 (3.2)             | 0 (0.0)      | 4 (2.1)     |
| Baseline ADHD-RS-IV total score, mean (SD) | 32 (7.1)                | 31.7 (6.0)          | 32.8 (5.9)   | 32.1 (6.5)  |
| <30, n (%)                                 | 41 (46.6)               | 30 (48.4)           | 12 (29.3)    | 83 (42.5)   |
| ≥30, n (%)                                 | 47 (53.4)               | 32 (51.6)           | 29 (70.7)    | 108 (56.5)  |

*ADHD* Attention-deficit/hyperactivity disorder, *ADHD-RS-IV* Attention-Deficit/Hyperactivity Disorder Rating Scale IV with Adult Prompts, *DBT* Double-blind trial, *GXR* Guanfacine extended-release, *SD* Standard deviation

a Baseline data are at enrollment in the previous DBT
b Patients might have more than one prior ADHD medication
to 0.28 kg. For all patients, small changes in ECG parameters were observed during long-term treatment, which gradually recovered to the levels observed at week 0 by the end of treatment (weeks 50–52). The mean change from week 0 at last observation in the treatment period was a decrease in heart rate of 6.75 beats/minute, an increase in RR interval of 115.12 msec, an increase in PR interval of 3.55 msec, an increase in QT interval of 12.96 msec, and a decrease in QTc corrected by Bazett’s formula (QTcB) interval of 9.91 msec and a decrease in QTc corrected by Fridericia’s formula (QTcF) interval of 2.36 msec. The changes in QRS interval were variable during long-term treatment.

**Efficacy**

**ADHD-RS-IV**

Significant improvements in ADHD symptoms were reported in all patient populations during long-term treatment with GXR (Table 4). ADHD-RS-IV total and subscale scores significantly decreased (improved) compared with week 0 up to last observation and week 50 (Table 4; all \( p < .0001 \)). The mean (95% CI) ADHD-RS-IV total scores at last observation were 18.82 (16.47, 21.16) for former placebo patients, 14.44 (12.08, 16.79) for former GXR patients, and 16.27 (13.21, 19.32) for new patients. Rapid improvements in ADHD-RS-IV total scores were observed within the first 1–6 weeks of long-term treatment, which were sustained up to week 50 for all populations (Fig. 2).

**CAARS**

The mean (95% CI) CAARS total scores at last observation were 20.61 (18.27, 22.95) for former placebo patients, 15.66 (13.20, 18.11) for former GXR patients, and 16.68 (13.84, 19.51) for new patients. In addition, there were significant decreases (improvements) from week 0 at last observation and week 50 in all CAARS subscale scores (\( p < .0001 \); Table 4).

**CGI-I, PGI-I, and CGI-S**

The percentage of patients with “very much improved” or “much improved” physician-rated (CGI-I) and patient-rated (PGI-I) scores, and with “normal” or “borderline mentally ill” physician-rated CGI-S scores, increased during long-term GXR treatment (Table 4). Eighteen patients were rated as severely ill at week 0 (eight former placebo patients, four former GXR patients, and six new patients). At week 50, three were markedly ill (two former placebo patients, one new patient) and three remained severely ill (all former placebo patients), with the remainder rated as borderline, mildly, or moderately ill.

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**Table 2 Patients Experiencing TEAEs During Long-term Treatment With GXR**

| Variable                              | Former placebo patients (N = 88) | Former GXR patients (N = 62) | New patients (N = 41) | All patients (N = 191) |
|---------------------------------------|----------------------------------|------------------------------|-----------------------|------------------------|
| All TEAEs, n (%)                      | 82 (93.2)                        | 58 (93.5)                    | 40 (97.6)             | 180 (94.2)             |
| Related                               | 74 (84.1)                        | 49 (79.0)                    | 37 (90.2)             | 160 (83.8)             |
| Mild\(^a\)                            | 46 (52.3)                        | 39 (62.9)                    | 20 (48.8)             | 105 (50.0)             |
| Moderate\(^a\)                        | 35 (39.8)                        | 17 (27.4)                    | 20 (48.8)             | 72 (37.7)              |
| Severe\(^a\)                          | 1 (1.1)                          | 2 (3.2)                      | 0                     | 3 (1.6)                |
| Leading to study discontinuation, n (%) | 22 (25.0)                        | 6 (9.7)                      | 10 (24.4)             | 38 (19.9)              |
| Serious TEAEs, n (%)                  | 0                               | 1 (1.6)                      | 1 (2.4)               | 2 (1.0)                |
| Death, n (%)                          | 0                               | 0                            | 0                     | 0                      |
| TEAEs occurring in \( \geq 10\% \) of all patients, n (%) | | | | |
| Somnolence                            | 34 (38.6)                        | 27 (43.5)                    | 19 (46.3)             | 80 (41.9)              |
| Thirst                                | 34 (38.6)                        | 13 (21.0)                    | 12 (29.3)             | 59 (30.9)              |
| Nasopharyngitis                        | 19 (21.6)                        | 20 (32.3)                    | 14 (34.1)             | 53 (27.7)              |
| Blood pressure decrease               | 16 (18.2)                        | 11 (17.7)                    | 11 (26.8)             | 38 (19.9)              |
| Postural dizziness                     | 18 (20.5)                        | 8 (12.9)                     | 10 (24.4)             | 36 (18.8)              |
| Bradycardia                            | 16 (18.2)                        | 10 (16.1)                    | 7 (17.1)              | 33 (17.3)              |
| Malaise                                | 17 (19.3)                        | 6 (9.7)                      | 7 (17.1)              | 30 (15.7)              |
| Constipation                           | 8 (9.1)                          | 7 (11.3)                     | 6 (14.6)              | 21 (11.0)              |
| Dizziness                              | 13 (14.8)                        | 5 (8.1)                      | 2 (4.9)               | 20 (10.5)              |

GXR Guanfacine extended-release, TEAE Treatment-emergent adverse event

\(^a\) For patients experiencing the same coded event more than once, the severest category was reported
Patient-reported QoL and executive functioning significantly improved in former DBT patients who transitioned and in new patients during long-term treatment (Table 4). AAQoL total scores increased (improved) significantly from week 0 to 49.11 for former placebo patients, 58.27 for former GXR patients, and 52.39 for new patients at last observation. At last observation and week 50, significant improvements from week 0 were reported for AAQoL life productivity for former placebo and GXR patients, life outlook for new patients, and relationships for former placebo patients (Table 4). In addition, significant improvements were reported for almost all BRIEF-A T-score subscales in all populations (Table 4).

### Discussion
This is the first study to assess long-term safety and efficacy of dose-optimized GXR in adult ADHD. The safety

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**Table 3** Change in Body Weight and Cardiovascular Parameters During Long-term Treatment With GXR

| Parameter          | Patient population          | Week 0 Mean (SD) | Mean (SD) change from week 0 at last observation in the treatment period |
|--------------------|-----------------------------|------------------|-------------------------------------------------------------------------|
| Body weight, kg    | Former placebo patients     | 66.89 (15.1)     | 0.12 (2.8)                                                              |
|                    | Former GXR patients         | 67.34 (12.7)     | −0.34 (4.4)                                                             |
|                    | New patients                | 68.40 (15.2)     | −0.34 (3.4)                                                             |
| Pulse rate, bpm    | Former placebo patients     | 73.56 (8.5)      | −5.60 (12.4)                                                            |
|                    | Former GXR patients         | 72.94 (11.7)     | −5.48 (9.8)                                                             |
|                    | New patients                | 77.22 (11.7)     | −6.74 (11.8)                                                            |
| Systolic BP, mmHg  | Former placebo patients     | 115.39 (14.2)    | −6.19 (11.9)                                                            |
|                    | Former GXR patients         | 117.58 (13.2)    | −7.31 (11.7)                                                            |
|                    | New patients                | 119.54 (16.9)    | −8.27 (14.7)                                                            |
| Diastolic BP, mmHg | Former placebo patients     | 72.38 (10.5)     | −4.11 (10.1)                                                            |
|                    | Former GXR patients         | 74.51 (11.2)     | −6.88 (10.6)                                                            |
|                    | New patients                | 75.06 (14.0)     | −6.52 (10.8)                                                            |
| ECG parameters     |                             |                  |                                                                         |
| Heart rate, bpm    | Former placebo patients     | 65.7 (8.5)       | −7.9 (10.0)                                                             |
|                    | Former GXR patients         | 63.5 (9.9)       | −3.8 (9.5)                                                              |
|                    | New patients                | 69.30 (9.4)      | −8.70 (12.4)                                                            |
| RR interval, msec  | Former placebo patients     | 926.0 (114.2)    | 135.7 (165.3)                                                           |
|                    | Former GXR patients         | 964.6 (147.3)    | 72.9 (161.8)                                                            |
|                    | New patients                | 881.55 (134.5)   | 134.30 (192.9)                                                          |
| PR interval, msec  | Former placebo patients     | 153.1 (20.5)     | 3.1 (12.0)                                                              |
|                    | Former GXR patients         | 149.2 (19.5)     | 4.2 (11.6)                                                              |
|                    | New patients                | 150.87 (21.0)    | 3.44 (15.3)                                                             |
| QRS interval, msec | Former placebo patients     | 98.6 (10.4)      | 0.5 (6.5)                                                               |
|                    | Former GXR patients         | 100.7 (16.0)     | −0.1 (6.4)                                                              |
|                    | New patients                | 98.58 (7.9)      | 0.58 (5.7)                                                              |
| QT interval, msec  | Former placebo patients     | 396.9 (29.0)     | 169.2 (25.9)                                                            |
|                    | Former GXR patients         | 403.5 (24.3)     | 4.6 (25.6)                                                              |
|                    | New patients                | 387.86 (28.3)    | 17.05 (27.3)                                                            |
| QTcB, msec         | Former placebo patients     | 413.5 (23.3)     | −9.9 (18.1)                                                             |
|                    | Former GXR patients         | 413.1 (21.9)     | −9.5 (16.8)                                                             |
|                    | New patients                | 414.85 (21.4)    | −10.56 (21.4)                                                           |
| QTcF, msec         | Former placebo patients     | 407.8 (22.5)     | −1.0 (14.4)                                                             |
|                    | Former GXR patients         | 407.9 (17.0)     | −5.0 (13.4)                                                             |
|                    | New patients                | 405.41 (19.8)    | −1.21 (14.8)                                                            |

BP Blood pressure, bpm Beats per minute, ECG Electrocardiogram, GXR Guanfacine extended-release, QTcB QTc corrected by Bazett’s formula, QTcF QTc corrected by Fridericia’s formula, SD Standard deviation
## Table 4: Key Efficacy Measures During Long-term Treatment With GXR

| Endpoint                  | Patient populations       | Week 0 | Week 50 | Change from week 0 | p-value | Last observation in the treatment period | Change from week 0 | p-value |
|---------------------------|---------------------------|--------|---------|--------------------|---------|------------------------------------------|--------------------|---------|
| ADHD-RS-IV<sup>a</sup>, mean (95% CI) | Former placebo patients   | 24.76  | (22.53, 26.99) | −8.31 (−10.72, −5.89) | <.0001 | −5.94 (−7.53, −4.36) | <.0001 |
|                           | Former GXR patients       | 22.31  | (19.65, 24.97) | −9.11 (−11.19, −7.03) | <.0001 | −7.87 (−9.68, −6.06) | <.0001 |
|                           | New patients              | 32.80  | (30.93, 34.68) | −19.69 (−23.35, −16.03) | <.0001 | −16.54 (−19.77, −13.31) | <.0001 |
| Inattention score         | Former placebo patients   | 17.36  | (15.97, 18.76) | −5.51 (−7.15, −3.87) | <.0001 | −3.90 (−5.03, −2.76) | <.0001 |
|                           | Former GXR patients       | 15.37  | (13.68, 17.07) | −5.82 (−7.22, −4.42) | <.0001 | −4.87 (−6.04, −3.70) | <.0001 |
|                           | New patients              | 21.68  | (20.12, 23.24) | −12.10 (−14.70, −9.51) | <.0001 | −10.02 (−12.28, −7.76) | <.0001 |
| Hyperactivity-impulsivity | Former placebo patients   | 7.40   | (6.15, 8.65)   | −2.80 (−4.00, −1.59) | <.0001 | −2.05 (−2.77, −1.32) | <.0001 |
|                           | Former GXR patients       | 6.94   | (5.55, 8.32)   | −3.29 (−4.40, −2.17) | <.0001 | −3.00 (−3.96, −2.04) | <.0001 |
|                           | New patients              | 11.12  | (9.50, 12.74)  | −7.59 (−9.81, −5.36) | <.0001 | −6.51 (−8.25, −4.78) | <.0001 |
| CAARS scores (DSM-IV)<sup>a</sup>, mean (95% CI) | Former placebo patients   | 25.08  | (22.93, 27.23) | −6.27 (−8.65, −3.89) | <.0001 | −4.60 (−6.17, −3.02) | <.0001 |
|                           | Former GXR patients       | 22.74  | (20.07, 25.42) | −8.38 (−10.90, −5.86) | <.0001 | −7.30 (−9.49, −5.10) | <.0001 |
|                           | New patients              | 31.32  | (28.64, 33.99) | −17.31 (−20.89, −13.73) | <.0001 | −15.08 (−18.49, −11.66) | <.0001 |
| Inattentive symptoms      | Former placebo patients   | 17.40  | (16.14, 18.65) | −3.96 (−5.57, −2.35) | <.0001 | −2.90 (−4.02, −1.79) | <.0001 |
|                           | Former GXR patients       | 15.55  | (13.90, 17.19) | −5.40 (−7.03, −3.77) | <.0001 | −4.51 (−5.89, −3.13) | <.0001 |
|                           | New patients              | 20.39  | (18.48, 22.30) | −11.00 (−13.54, −8.46) | <.0001 | −9.15 (−11.47, −6.83) | <.0001 |
| Hyperactive-impulsive     | Former placebo patients   | 7.68   | (6.38, 8.98)   | −2.31 (−3.55, −1.06) | .0005  | −1.69 (−2.47, −0.92) | <.0001 |
|                           | Former GXR patients       | 7.19   | (5.79, 8.60)   | −2.98 (−4.30, −1.65) | <.0001 | −2.79 (−3.92, −1.66) | <.0001 |
|                           | New patients              | 10.93  | (9.36, 12.49)  | −6.31 (−8.17, −4.45) | <.0001 | −5.93 (−7.56, −4.29) | <.0001 |
| CGI-I response rates<sup>b</sup>, % of patients (95% CI) | Improvement rate (disease scores 1 or 2) | Former placebo patients | 3.4 (0.7, 9.6)<sup>c</sup> | 51.0 (36.3, 65.6) | NA | 35.2 (25.3, 46.1) | NA |
|                           | Former GXR patients       | 4.8 (1.0, 13.5)<sup>c</sup> | 64.4 (48.8, 78.1) | NA | 53.2 (40.1, 66.0) | NA |
|                           | New patients              | 0.0 (0.0, 8.6)<sup>c</sup> | 79.3 (60.3, 92.0) | NA | 65.9 (49.4, 79.9) | NA |
| PGI-I response rates<sup>b</sup>, % of patients (95% CI) | Improvement rate (disease scores 1 or 2) | Former placebo patients | 8.0 (3.3, 15.7)<sup>c</sup> | 28.6 (16.6, 43.3) | NA | 19.3 (11.7, 29.1) | NA |
|                           | Former GXR patients       | 9.7 (3.6, 19.9)<sup>c</sup> | 42.2 (27.7, 57.8) | NA | 33.9 (22.3, 47.0) | NA |
|                           | New patients              | 9.8 (2.7, 23.1)<sup>c</sup> | 37.9 (20.7, 57.5) | NA | 31.7 (18.1, 48.1) | NA |

Patients not ill or borderline mentally ill<sup>b</sup>, % of patients (95% CI)
| Endpoint                          | Patient populations        | Week 0       | Week 50       | Change from week 0 | p-value | Last observation in the treatment period | Change from week 0 | p-value |
|----------------------------------|---------------------------|--------------|---------------|-------------------|---------|----------------------------------------|-------------------|---------|
|                                  |                           |              |               |                   |         |                                        |                   |         |
| CGI-S scores 1 or 2              | Former placebo patients   | 0.0 (0.0, 4.1) | 14.3 (5.9, 27.2) | NA                |         | 8.0 (3.3, 15.7)                        | NA                |         |
|                                  | Former GXR patients       | 0.0 (0.0, 5.8) | 26.7 (14.6, 41.9) | NA                |         | 22.6 (12.9, 35.0)                      | NA                |         |
|                                  | New patients              | 0.0 (0.0, 8.6) | 20.7 (8.0, 39.7) | NA                |         | 17.1 (7.2, 32.1)                       | NA                |         |
| AAQoL^a, mean (95% CI)           |                           |              |               |                   |         |                                        |                   |         |
|                                  | Total score               |              |               |                   |         |                                        |                   |         |
|                                  | Former placebo patients   | 46.43 (43.21, 49.64) | 4.13 (0.50, 7.75) | .0266             |         | 2.81 (0.31, 5.30)                      | .0282             |         |
|                                  | Former GXR patients       | 54.27 (49.78, 58.77) | 4.29 (0.35, 8.23) | .0334             |         | 4.04 (0.88, 7.20)                      | .0131             |         |
|                                  | New patients              | 43.28 (38.38, 48.17) | 12.75 (6.68, 18.81) | .0002             |         | 9.22 (4.11, 14.34)                     | .0008             |         |
|                                  |                           |              |               |                   |         |                                        |                   |         |
|                                  | Life productivity         |              |               |                   |         |                                        |                   |         |
|                                  | Former placebo patients   | 48.04 (43.75, 53.33) | 2.64 (−3.32, 8.61) | .0275             |         | 2.89 (−0.94, 6.72)                     | .1377             |         |
|                                  | Former GXR patients       | 57.88 (52.69, 63.08) | 8.74 (4.69, 12.79) | <.0001            |         | 8.08 (4.76, 11.41)                     | <.0001            |         |
|                                  | New patients              | 44.29 (37.72, 50.86) | 17.08 (9.11, 25.06) | .0001             |         | 14.38 (7.75, 21.00)                    | <.0001            |         |
|                                  |                           |              |               |                   |         |                                        |                   |         |
|                                  | Psychological health       |              |               |                   |         |                                        |                   |         |
|                                  | Former placebo patients   | 47.02 (42.20, 51.83) | 5.27 (0.57, 9.97) | .0286             |         | 2.60 (−1.14, 6.34)                     | .1710             |         |
|                                  | Former GXR patients       | 54.91 (48.88, 60.93) | 2.78 (−2.69, 8.25) | .3117             |         | 1.57 (−2.82, 5.96)                     | .4771             |         |
|                                  | New patients              | 43.39 (36.92, 49.86) | 11.35 (4.29, 18.41) | .0027             |         | 5.62 (−0.57, 11.82)                    | .0739             |         |
|                                  |                           |              |               |                   |         |                                        |                   |         |
|                                  | Life outlook              |              |               |                   |         |                                        |                   |         |
|                                  | Former placebo patients   | 41.93 (38.20, 45.66) | 2.59 (−1.97, 7.15) | .2597             |         | 1.37 (−1.76, 4.51)                     | .3868             |         |
|                                  | Former GXR patients       | 46.10 (41.64, 50.56) | −1.90 (−6.44, 2.63) | .4016             |         | −0.35 (−4.08, 3.37)                    | .8510             |         |
|                                  | New patients              | 40.17 (35.10, 45.24) | 8.23 (1.25, 15.21) | .0225             |         | 6.06 (0.71, 11.41)                     | .0275             |         |
|                                  |                           |              |               |                   |         |                                        |                   |         |
|                                  | Relationships             |              |               |                   |         |                                        |                   |         |
|                                  | Former placebo patients   | 48.47 (44.01, 52.92) | 8.16 (2.70, 13.63) | .0042             |         | 4.88 (1.15, 8.61)                      | .0109             |         |
|                                  | Former GXR patients       | 57.02 (50.97, 63.06) | 5.00 (−1.10, 11.10) | .1058             |         | 4.26 (−0.82, 9.34)                     | .0984             |         |
|                                  | New patients              | 45.24 (38.72, 51.77) | 11.21 (3.26, 19.16) | .0074             |         | 6.63 (−0.12, 13.37)                    | .0542             |         |
|                                  |                           |              |               |                   |         |                                        |                   |         |
|                                  | BRIEF-A T-score^a, mean (95% CI) |              |               |                   |         |                                        |                   |         |
|                                  | Inhibit                   |              |               |                   |         |                                        |                   |         |
|                                  | Former placebo patients   | 57.24 (54.81, 59.66) | −3.69 (−6.39, −0.99) | .0084             |         | −2.39 (−4.15, −0.63)                    | .0084             |         |
|                                  | Former GXR patients       | 51.68 (49.20, 54.16) | −1.84 (−4.04, 0.35) | .0977             |         | −2.66 (−4.65, −0.66)                    | .0098             |         |
|                                  | New patients              | 59.68 (56.49, 62.87) | −8.07 (−11.76, −4.38) | .0001             |         | −8.25 (−11.28, −5.22)                   | <.0001            |         |
|                                  |                           |              |               |                   |         |                                        |                   |         |
|                                  | Shift                     |              |               |                   |         |                                        |                   |         |
|                                  | Former placebo patients   | 69.55 (66.63, 72.27) | −5.84 (−9.00, −2.68) | .0005             |         | −3.29 (−5.51, −1.08)                    | .0040             |         |
|                                  | Former GXR patients       | 62.73 (59.04, 66.41) | −4.60 (−8.30, −0.90) | .0159             |         | −3.70 (−6.57, −0.84)                    | .0121             |         |
|                                  | New patients              | 70.07 (66.33, 73.81) | −8.86 (−11.81, −5.91) | .0001             |         | −8.63 (−11.18, −6.07)                   | <.0001            |         |
|                                  |                           |              |               |                   |         |                                        |                   |         |
|                                  | Emotional control         |              |               |                   |         |                                        |                   |         |
|                                  | Former placebo patients   | 57.80 (55.51, 60.08) | −4.39 (−7.55, −1.23) | .0075             |         | −3.26 (−5.34, −1.18)                    | .0025             |         |
Table 4  Key Efficacy Measures During Long-term Treatment With GXR (Continued)

| Endpoint                   | Patient populations | Week 0            | Week 50           | Last observation in the treatment period | Change from week 0 | p-value | Change from week 0 | p-value |
|----------------------------|---------------------|-------------------|-------------------|------------------------------------------|--------------------|---------|--------------------|---------|
|                            |                     |                   |                   |                                          |                    |         |                    |        |
|                            | Former GXR patients | 53.32 (50.75, 55.89) | −2.22 (−4.97, 0.53) | .1104 | −1.52 (−3.72, 0.67) | .1703 |
|                            | New patients        | 59.98 (56.74, 63.22) | −5.41 (−7.60, −3.23) | <.0001 | −4.53 (−6.68, −2.37) | .0001 |
|                            | Self-monitor        |                   |                   |                                          |                    |         |                    |        |
|                            | Former placebo patients | 61.81 (58.70, 64.91) | −6.39 (−8.98, −3.79) | <.0001 | −4.48 (−6.45, −2.52) | <.0001 |
|                            | Former GXR patients | 56.06 (52.73, 59.40) | −4.93 (−8.10, −1.76) | .031 | −4.23 (−6.87, −1.58) | .0022 |
|                            | New patients        | 61.24 (56.70, 65.79) | −7.86 (−11.77, −3.96) | .0003 | −6.23 (−10.05, −2.40) | .0021 |
|                            | Behavioral regulation index |                   |                   |                                          |                    |         |                    |        |
|                            | Former placebo patients | 63.09 (60.46, 65.73) | −6.02 (−9.06, −2.98) | <.0001 | −4.06 (−6.05, −2.07) | .0001 |
|                            | Former GXR patients | 56.39 (53.43, 59.35) | −3.71 (−6.52, −0.90) | .0109 | −3.26 (−5.52, −1.01) | .0053 |
|                            | New patients        | 64.73 (61.24, 68.23) | −8.72 (−11.53, −5.92) | <.0001 | −7.98 (−10.72, −5.23) | <.0001 |
|                            | Initiate            |                   |                   |                                          |                    |         |                    |        |
|                            | Former placebo patients | 68.51 (65.65, 71.38) | −5.49 (−8.51, −2.46) | <.0001 | −3.87 (−5.94, −1.80) | .0004 |
|                            | Former GXR patients | 59.71 (56.58, 62.84) | −3.31 (−6.64, 0.02) | .0514 | −2.03 (−4.87, 0.80) | .1563 |
|                            | New patients        | 69.10 (64.97, 73.22) | −10.38 (−13.98, −6.78) | <.0001 | −8.95 (−12.11, −5.79) | <.0001 |
|                            | Working memory      |                   |                   |                                          |                    |         |                    |        |
|                            | Former placebo patients | 73.91 (71.07, 76.75) | −4.80 (−8.45, −1.15) | .0111 | −3.31 (−5.68, −0.93) | .0069 |
|                            | Former GXR patients | 66.18 (62.57, 69.78) | −4.78 (−8.24, −1.32) | .0079 | −3.92 (−6.70, −1.13) | .0066 |
|                            | New patients        | 74.10 (70.29, 77.91) | −10.93 (−14.98, −6.88) | <.0001 | −10.15 (−13.73, −6.57) | <.0001 |
|                            | Plan/organize       |                   |                   |                                          |                    |         |                    |        |
|                            | Former placebo patients | 70.51 (67.74, 73.28) | −3.86 (−6.94, −0.78) | .0152 | −2.32 (−4.37, −0.27) | .0270 |
|                            | Former GXR patients | 63.02 (59.52, 66.51) | −3.69 (−7.09, −0.29) | .0340 | −3.00 (−5.90, −0.10) | .0426 |
|                            | New patients        | 70.51 (66.57, 74.45) | −8.90 (−12.63, −5.16) | <.0001 | −8.75 (−11.90, −5.60) | <.0001 |
|                            | Task monitor        |                   |                   |                                          |                    |         |                    |        |
|                            | Former placebo patients | 72.63 (69.56, 75.69) | −6.76 (−9.95, −3.56) | <.0001 | −4.07 (−6.35, −1.79) | .0006 |
|                            | Former GXR patients | 63.85 (60.22, 67.49) | −7.02 (−11.06, −2.99) | <.0001 | −4.89 (−8.34, −1.43) | .0063 |
|                            | New patients        | 70.71 (66.07, 75.34) | −8.93 (−13.17, −4.70) | <.0001 | −8.35 (−12.12, −4.58) | <.0001 |
|                            | Organization of materials |                   |                   |                                          |                    |         |                    |        |
|                            | Former placebo patients | 65.97 (63.95, 67.98) | −5.00 (−7.82, −2.18) | <.0008 | −3.24 (−5.21, −1.26) | .0016 |
|                            | Former GXR patients | 58.61 (55.77, 61.45) | −3.31 (−5.55, −1.08) | .0046 | −2.87 (−4.62, −1.11) | .0018 |
|                            | New patients        | 65.73 (62.43, 69.03) | −8.41 (−11.90, −4.93) | <.0001 | −7.88 (−11.03, −4.72) | <.0001 |
|                            | Metacognition index |                   |                   |                                          |                    |         |                    |        |
|                            | Former placebo patients | 73.36 (70.51, 76.21) | −5.80 (−9.04, −2.55) | <.0008 | −3.75 (−5.86, −1.65) | .0007 |
|                            | Former GXR patients | 64.16 (60.65, 67.68) | −5.02 (−8.21, −1.83) | .0028 | −3.82 (−6.44, −1.20) | .0050 |
|                            | New patients        | 73.24 (69.29, 77.20) | −11.14 (−14.95, −7.33) | <.0001 | −10.35 (−13.69, −7.01) | <.0001 |
findings during treatment for 50 weeks were consistent with the previous 10-week DBT [13] and the known safety profile of GXR, and no new or unexpected safety signals were identified. Adult patients experienced improvements in ADHD symptoms, QoL, and executive functioning that were sustained for up to 1 year. Given the complexity of treating ADHD, nonstimulant medications are not effective or well tolerated [6]. The findings from this study support the use of GXR as an alternative treatment for adult patients with ADHD in Japan.

Consistent with the known safety profile of GXR in children [24–27], the most frequently reported TEAEs were sedative and included somnolence, decreased blood pressure, thirst, postural dizziness, bradycardia, malaise, constipation, and dizziness. Although nasopharyngitis was reported frequently, this TEAE was not considered related to GXR. Similar to the previous DBT [13], thirst was reported more frequently in adults than in studies of GXR in children [28, 29]. This finding was not considered to be clinically relevant or related to any differences in ethnicity between Japanese and non-Japanese populations because thirst (dry mouth) has been reported in studies conducted with GXR in adults in the United States [30, 31] and because direct comparison of the pharmacokinetics, safety, and tolerability of GXR were similar to the improvements in patient-reported QoL and all aspects of executive functioning.

Table 4. Key Efficacy Measures During Long-term Treatment With GXR (Continued)

| Endpoint | Patient populations | Week 0 | Week 50 | Last observation in the treatment period |
|----------|---------------------|--------|---------|----------------------------------------|
|          |                     |        | Change from week 0 | p-value | Change from week 0 | p-value |
| GEC index Former placebo patients | 70.52 (67.76, 73.29) | −6.41 (−9.59, −3.22) | .0002 | −4.22 (−6.30, −2.15) | .0001 |
| Former GXR patients | 61.73 (58.32, 65.13) | −4.84 (−7.96, −1.73) | .0031 | −3.90 (−6.45, −1.36) | .0032 |
| New patients | 71.10 (67.26, 74.93) | −10.86 (−14.29, −7.43) | <.0001 | −10.05 (−13.21, −6.89) | <.0001 |

AAQoL, Adult ADHD Quality of Life Questionnaire; ADHD-RS-IV, Attention-Deficit/Hyperactivity Disorder Rating Scale IV; Conners’ Adult ADHD Rating Scales; CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity of Illness; CI, confidence interval; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition); GEC, Global Executive Composite; GXR, guanfacine extended-release; NA, not applicable; PG1-I, Patient Global Impression-Improvement.

*Change from start of long-term treatment calculated using week 50 or last observation in the treatment period and assessed using two-sided t tests.

Data are response rates at each time point. Differences in response rates from the start of long-term treatment or week 1 and week 50 or last observation in the treatment period were assessed using two-sided t tests.

Data are response rates at week 1 of long-term treatment.

Treatments that provide sustained long-term improvements in ADHD symptoms are needed for adults because of the substantial impact of ADHD in adults on general health, psychosocial and neuropsychological functioning, and productivity [9, 10, 33]. During the previous DBT, significant improvements in ADHD symptoms (ADHD-RS-IV total and subscale scores) were observed for GXR-treated patients at 4 weeks [13]. In the current study, rapid improvement in ADHD symptoms was seen for GXR-treated patients within the first 6 weeks, which continued to improve for up to 50 weeks. These improvements were similar to the improvements in patient-reported QoL and all aspects of executive functioning.

The main strength of this study is that the flexible-dosing regimen allowed individualized treatment in all patients for 50 weeks of treatment. Furthermore, multiple physician- and patient-specific rating instruments were included to assess the effects of treatment. Although all patients underwent titration at the start of the long-term treatment, patients who transitioned from GXR in the previous DBT did not undergo a washout...
phase and received continuous GXR treatment through the end of long-term treatment. There was a potential for observer bias because of the open-label nature of the study, and the findings may not be representative of real-world settings because patients with psychiatric or cardiovascular comorbidities, which are common in patients with ADHD, were excluded. In addition, there was a potential bias favoring safety and efficacy for continuing patients because those who discontinued owing to adverse events or lack of efficacy were not eligible for inclusion. However, these effects are balanced by the inclusion of newly enrolled patients.

**Conclusions**

In conclusion, there were no new or unexpected safety concerns during long-term administration of GXR in Japanese adults with ADHD. During long-term treatment for up to 50 weeks, patients who received dose-optimized GXR had improvements in multiple aspects of ADHD, including symptoms, QoL, and executive functioning.

**Supplementary information**

Supplementary information accompanies this paper at https://doi.org/10.1186/s12888-020-02867-8.

**Fig. 2** Change from baseline in ADHD-RS-IV total scores. Data are the mean change from baseline (i.e., the start of the previous double-blind trial [DBT]) for patients who transitioned from the placebo arm and guanfacine extended-release (GXR) arm and the mean change from week 0 of the long-term treatment study for new patients. Error bars denote standard deviations. ADHD-RS-IV: Attention-Deficit/Hyperactivity Disorder Rating Scale IV with Adult Prompts

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**Authors’ contributions**

Hi was an expert medical advisor for the study, AI and KS were coordinating investigators in the study and involved in data collection, DO was the study leader, and MF was involved in the statistical analyses. All authors participated in the interpretation of the study results and in the drafting, critical revision, and approval of the final version of the manuscript.

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**Availability of data and materials**

Researchers can request access to detailed information about Shionogi’s clinical trials, including trial protocols and individual patient data, on the portal site: 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.
Ethics approval and consent to participate
This study was approved by the following local ethics committees: Mizuo Clinic Institutional Review Board (IRB), Ehime University Hospital IRB; IHL Shingawara East One Medical Clinic IRB; Dr. Mano Medical Clinic IRB; Odori Park Mental Clinic IRB; Tokyo Midtown Clinic IRB; Tokyo-Eki Center-Building Clinic IRB; Riverside Internal and Circulatory Medical Clinic IRB; Goyokai Hospital IRB; Himorogi Psychiatric Institute IRB; Nankio Clinic of Psychiatry IRB; Ivata Buddy's Clinic IRB; Suzuki Internal and Circulatory Medical Clinic IRB; Kojinkai Sapporo Skin Clinic IRB; Shoda Hospital IRB; Kondo Hospital IRB; Tomisaka Hospital IRB; Yokohama Sakae Koyoai Hospital IRB; Hokkaido University Hospital IRB; Yamate Dermatological Clinic IRB; Chibune General Hospital IRB; IRB of Showa University Karasuyama Hospital; Yoyogi Mental Clinic IRB; Tokai University Hospital IRB; The Jikei University Hospital IRB for Medicinal Products; Non-Profit Organization Tokyo Allergy and Respiratory Disease Research Institute IRB; Review Board of Human Rights and Ethics for Clinical Studies; Nara Medical University Hospital IRB; University of Fukui Hospital IRB; Hayashi Diabetes Clinic IRB. All patients provided written informed consent before participating in the study.

Consent for publication
Not applicable.

Competing interests
AI has received honoraria and other payments from Eisai, Eli Lilly Japan, Janssen Japan, Kyowa, Meiji Seika Pharma, Mitsubishi Tanabe Pharma, MSD KK, Otsuka, Pfizer Japan, Sumitomo Dainippon Pharma, and Yoshitomiyakuhin Corporation. KS has received honoraria and other payments from Eli Lilly Japan, Hisamitsu, Janssen Japan, Meiji Seika Pharma, Mitsubishi Tanabe Pharma, Otsuka, Shionogi, Shire Japan (now part of the Takeda group of companies), Sumitomo Dainippon Pharma, Taisho, and Yoshitomiyakuhin Corporation. MF and DO are employees of and own shares in Shionogi. HI has received honoraria and other payments from AbbVie GK, Eli Lilly Japan, Hisamitsu Pharmaceutical, Janssen Japan, Meiji Seika Pharma, Otsuka, Shionogi, and Taisho.

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