Long-term safety and efficacy of imeglimin as monotherapy or in combination with existing antidiabetic agents in Japanese patients with type 2 diabetes (TIMES 2): A 52-week, open-label, multicentre phase 3 trial

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Abstract
Aim: To evaluate the safety and efficacy of imeglimin for 52 weeks as monotherapy or combination therapy with existing antidiabetic agents in Japanese patients with type 2 diabetes.

Materials and Methods: TIMES 2 was a phase 3, pivotal, open-label trial including patients with type 2 diabetes inadequately controlled despite diet/exercise or despite treatment with a single agent from one of several available classes of antidiabetic drugs along with diet/exercise. All patients received imeglimin 1000 mg twice-daily orally for 52 weeks as monotherapy or combination therapy. The primary endpoint was safety (adverse events, laboratory results, ECG). The secondary endpoints were changes from baseline in HbA1c and fasting plasma glucose at week 52.

Results: A total of 714 patients received the following treatments: imeglimin monotherapy (n = 134), combination with an α-glucosidase inhibitor (n = 64), biguanide (n = 64), dipeptidyl peptidase-4 inhibitor (DPP4-I; n = 63), glinide (n = 64), glucagon-like peptide-1 receptor agonist (GLP1-RA; n = 70), sodium-glucose co-transporter-2 inhibitor (n = 63), sulphonylurea (n = 127), or thiazolidinedione (n = 65). The percentage of patients experiencing at least one treatment emergent adverse event (TEAE) was 75.5%. Most of these events were mild or moderate in intensity. Serious TEAEs, none of them related to the study drug, occurred in 5.6% of all patients. No clinically significant changes in ECG, vital signs, physical examination, or laboratory tests were noted in any groups. At week 52, HbA1c decreased by 0.46% with imeglimin monotherapy, by 0.56%-0.92% with imeglimin as oral combination therapy, and by 0.12% with injectable GLP1-RA combination therapy. The greatest net HbA1c reduction (0.92%) occurred in patients receiving a DPP4-I in combination with imeglimin.

Conclusions: Imeglimin provides well-tolerated, long-term safety and efficacy in both monotherapy and oral combination therapy in Japanese patients with type 2 diabetes.
1 | INTRODUCTION

Type 2 diabetes is a widespread disease, affecting more than 500 million people worldwide. It is characterized by chronic hyperglycaemia associated with various macrovascular and microvascular complications. Diabetes is a growing public health issue worldwide; Japan is one of the nations most greatly impacted, with 18.7% of men and 9.3% of women ‘in whom diabetes is strongly suspected’. In Japan, diabetes has also been identified as a healthcare priority by the Ministry of Health, Labour and Welfare.

Imeglimin is a first-in-class novel oral antidiabetic agent to treat type 2 diabetes that was recently approved in June 2021 as a new oral antidiabetic drug by the Pharmaceuticals and Medical Devices Agency in Japan. Its mode of action is distinct from all other antihyperglycaemic classes; imeglimin’s underlying mechanism involves the targeting of mitochondrial bioenergetics and improving mitochondrial function. Imeglimin modulates mitochondrial respiratory chain complex activities while decreasing reactive oxygen species production. Imeglimin has been shown to amplify glucose-stimulated insulin secretion by improving β-cell glucose responsiveness in patients with type 2 diabetes. To improve insulin sensitivity in a rodent model of diabetes, allowing for normalization of glucose tolerance. Recently, imeglimin has been shown to prevent the death of human endothelial cells by inhibiting opening of the mitochondrial permeability transition pore—a known cause of cell death—without inhibiting mitochondrial respiration; this finding suggests the potential for end organ protection (e.g., kidney or heart).

In a phase 2, dose-ranging trial conducted in Japanese subjects, the dose of imeglimin 1000 mg twice-daily was shown to have optimal efficacy (HbA1c reduction by 0.94% vs. placebo) and favourable safety and tolerability. This dose was selected for the phase 3 programme in Japan named the Trial for Imeglimin Efficacy and Safety (TIMES). The completed phase 3 programme included three pivotal studies: TIMES 1 (assessing the efficacy of imeglimin monotherapy), TIMES 2 (reported in this article), and TIMES 3 (assessing the long-term safety and efficacy of imeglimin as an add-on to insulin for 1 year). The efficacy of imeglimin was confirmed in TIMES 1, in which 1000 mg BID as monotherapy for 6 months achieved a significant HbA1c reduction of −0.87% versus placebo. In addition, imeglimin has been previously studied in two 12-week, add-on, phase 2 studies, to metformin and sitagliptin, conducted in Caucasian subjects with imeglimin at the dose of 1500 mg BID. After 12 weeks of treatment, imeglimin decreased HbA1c versus placebo by 0.72% when combined with sitagliptin and by 0.44% when combined with metformin.

The TIMES 3—add on to insulin—trial has been completed but is not yet published. TIMES 2 long-term (52 weeks) efficacy and safety of imeglimin as monotherapy or as an add-on to other antidiabetic drugs is described herein and has not been previously published.

This article reports the findings from the largest of the three phase 3 trials in Japan (TIMES 2), which assessed 1000 mg imeglimin BID long-term monotherapy and long-term combination therapies in Japanese patients with type 2 diabetes insufficiently controlled with diet and exercise.

2 | RESEARCH DESIGN AND METHODS

2.1 | Study design

This was a phase 3, long-term (52-week), open-label, multicentre trial (TIMES 2) at 68 sites in Japan. The study protocol was approved by institutional review boards at each site according to local practice. This study was conducted in accordance with the International Conference on Harmonized Tripartite Guideline for Good Clinical Practice, the Japanese Good Clinical Practice regulations (Ministry of Health and Welfare Ordinance No. 28; 27 March 1997), and with the Helsinki Declaration of 1964, as revised in 2013. Written informed consent was obtained from all participants before the beginning of any study-related activities.

Japanese adults aged 20 years or older with type 2 diabetes treated with diet/exercise alone or together with a single antidiabetic monotherapy were enrolled in this 52-week, long-term study.

The inclusion criteria for the patients who received imeglimin long-term monotherapy included the following: treated with diet and exercise without an antihyperglycaemic agent during at least 12 weeks prior to screening, HbA1c of 7.0%-10.0%, and an estimated glomerular filtration rate (eGFR; estimated with the Japanese modification of the MDRD equation) greater than or equal to 50 ml/min/1.73m².

Patients treated with diet and exercise plus treatment with an α-glucosidase inhibitor (AGI), biguanide (BIG), dipeptidyl peptidase-4 inhibitor (DPP4-I), glinide (GLIN), injectable glucagon-like peptide-1 receptor agonist (GLP1-RA), sodium-glucose co-transporter-2 inhibitor (SGLT2-I), sulphonylurea (SU), or thiazolidinedione (TZD), were included in the long-term combination groups. Type, dose, and regimen of background antidiabetic therapy were to be unchanged for at least 12 weeks prior to screening. Other inclusion criteria for combination therapy included an HbA1c of 7.5%-10.5% and an eGFR superior to equal to 60 ml/min/1.73m².

Key exclusion criteria for all groups included insulin therapy in the 30 days before screening, heart failure (New York Heart Association class III or IV), or any acute coronary or cerebrovascular events in the 24 weeks before screening.

2.2 | Procedures

After a screening period, all participants received oral placebo BID during a 2-week, single blind, run-in period. From the start of the open-label period, participants received 1000 mg imeglimin BID for 52 weeks, followed by a 1-week, follow-up period. For the long-term combination therapy groups, patients who had been using a
background antidiabetic therapy according to the package insert of the drug continued to receive the same dose/regimen of this drug in addition to 1000 mg imeglimin BID until the end of the treatment period. Patients were assessed (physical examination, vital signs, and safety and efficacy assessments) at week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48, at the end of treatment at week 52, and at follow-up 1 week after the last dose.

The trial implemented complete follow-up for all participants, including those who discontinued treatment prematurely, meaning that all participants remained in the study, except in any case of withdrawal of consent.

Participants with unacceptable hyperglycaemia (i.e. any fasting plasma glucose [FPG] value >250 mg/dl (>13.9 mmol/L) from baseline to week 4; FPG > 240 mg/dl (>13.3 mmol/L) from week 4 to week 8; and/or any HbA1c value of at least 10.0% for the long-term monotherapy group and ≥10.5% for the long-term combination groups from week 8 to week 52) should discontinue the study drug and a rescue therapy should be initiated. The initiation, choice, and dose of rescue medication used were at the discretion of the investigator, according to local prescribing information, but insulin was not allowed. Any increase in the dosing of the background antidiabetic therapy was considered as a rescue medication. In any case of rescue medication, participants discontinued treatment prematurely but continued the study.

2.3 | Outcomes

The primary objective of this study was to assess the safety of imeglimin as monotherapy and combination therapy. Safety endpoints included vital signs, physical examination, 12-lead ECG, clinical laboratory variables, and adverse events (preferred terms coded according to the Medical Dictionary for Drug Regulatory Activities [MedDRA] version 20.1). Patients were asked to check their glucose levels, using self-monitoring blood glucose (SMBG) devices, at least twice a week. Events of hypoglycaemia were categorized into asymptomatic hypoglycaemia (an event not accompanied by typical symptoms of hypoglycaemia but with a measured capillary or plasma glucose <3.9 mmol/L), probable symptomatic hypoglycaemia (an event during which symptoms typical of hypoglycaemia are not accompanied by a capillary or plasma glucose determination), documented symptomatic hypoglycaemia (an event during which typical symptoms of hypoglycaemia are accompanied by a measured capillary or plasma glucose concentration <3.9 mmol/L), and severe hypoglycaemia (an event requiring the assistance of another person to actively administer carbohydrates, glucagon, or to take other corrective actions).12

Secondary efficacy endpoints included the change from baseline in HbA1c at week 52 (assessed at a central laboratory), the percentage of responders as defined by the percentage of patients reaching a target HbA1c of less than 7.0% at week 52, and the percentage of responders as defined by the percentage of patients with a relative decrease of at least 7% of baseline HbA1c at week 52. Efficacy was also analysed in subgroups of patients according to baseline age (<65 and ≥65 years) and baseline chronic kidney disease (CKD) stage (CKD stage 1, 2, and 3a). Other secondary efficacy endpoints included the percentage of patients requiring rescue medication and change from baseline to week 52 in FPG.

2.4 | Statistical analysis

For the long-term imeglin monotherapy group, the sample size was determined to be 125 patients to collect data from 100 patients, as required by the Japanese Guidelines for Clinical Evaluation of Hypoglycemic Agents (revised draft),13 assuming a drop-out rate of 20% during the open-label treatment period.

For the long-term combination therapy arms, in accordance with the guidance,13 and based on the knowledge of each available drug and their use as monotherapy in the Japanese population, the number of patients in each combination therapy was determined to be 63 to collect data from 50 patients (assuming a drop-out rate of 20%) in each combination group, except for SUs, where 125 patients was determined to be necessary to collect data from approximately 100 patients.

Safety analysis was performed on all as-treated patients who received at least one dose of the study drug and was descriptive in nature. Adverse events reported included those which occurred between first drug intake (open-label visit) and 7 days after cessation of drug administration, or which started before drug intake and worsened during the open-label treatment period.

Efficacy analyses were primarily performed on the safety population (i.e. patients who received at least one administration of imeglimin). Measurements after imeglimin discontinuation were censored 7 days after imeglimin discontinuation (i.e. replaced by missing data in the primary efficacy analysis). The primary efficacy analysis was performed using a mixed model for repeated measures (MMRM) fitted within each treatment arm. The MMRM included visit (categorical variable from week 4 to week 52), baseline HbA1c as a continuous covariate, and a term for baseline HbA1c by visit interaction. Least square means of change from baseline along with their 95% confidence intervals (CIs) were estimated by visit in the MMRM model fitted separately within each treatment arm. Analyses were performed using SAS version 9.4. This trial was registered on JAPIC (JapicCTI-173782).

3 | RESULTS

3.1 | Patient disposition and baseline characteristics

The TIMES 2 trial was carried out from 12 January 2018 to 23 October 2019. Of the 981 patients who provided signed informed consent, 714 entered the open-label treatment period and received at least one dose of imeglimin, including 134 patients with imeglimin long-term monotherapy, and 580 patients with imeglimin long-term combination therapy: 64 patients with an AGI, 64 patients with a BIG, 63 patients with a DPP4-I, 64 patients with a GLIN, 70 patients with a GLP1-RA, 63 patients with an SGLT2-I, 127 patients with an SU, and 65 patients with a TZD. Eighty-two (11.5%) patients prematurely discontinued treatment, including 10 (7.5%) with imeglimin long-term monotherapy, and 72 patients with imeglimin long-term combination therapy: four (6.2%) with an AGI, 11 (17.2%) with a BIG, eight (12.7%)
|                          | Imeglimin monotherapy | Combination with AGI | Combination with BIG | Combination with DDP4-I | Combination with GLIN | Combination with SGLT2-I | Combination with SU | Combination with TZD | Combination with GLP1-RA |
|---------------------------|-----------------------|----------------------|----------------------|------------------------|-----------------------|-------------------------|----------------------|----------------------|------------------------|
| **Number of patients**    | 134                   | 64                   | 64                   | 63                     | 64                    | 63                      | 127                  | 65                   | 70                     |
| **Sex**                   |                       |                      |                      |                        |                       |                         |                      |                      |                        |
| Female                    | 28 (20.9%)            | 16 (25.0%)           | 18 (28.1%)           | 24 (38.1%)             | 21 (32.8%)            | 18 (28.6%)              | 26 (20.5%)           | 11 (16.9%)           | 26 (37.1%)             |
| Male                      | 106 (79.1%)           | 48 (75.0%)           | 46 (71.9%)           | 39 (61.9%)             | 43 (67.2%)            | 45 (71.4%)              | 101 (79.5%)          | 54 (83.1%)           | 44 (62.9%)             |
| **Age (y)**               | 59.4 (10.8%)          | 56.6 (12.0)          | 57.6 (10.8)          | 63.6 (8.95)            | 58.1 (10.8)           | 57.1 (10.0)             | 60.3 (10.4)          | 57.1 (10.0)          | 57.4 (11.0)            |
| **Age group (y)**         |                       |                      |                      |                        |                       |                         |                      |                      |                        |
| <65                       | 86 (64.2%)            | 41 (64.1%)           | 47 (73.4%)           | 28 (44.4%)             | 42 (65.6%)            | 45 (71.4%)              | 76 (59.8%)           | 44 (67.7%)           | 46 (65.7%)             |
| ≥65                       | 48 (35.8%)            | 23 (35.9%)           | 17 (26.6%)           | 35 (55.6%)             | 22 (34.4%)            | 18 (28.6%)              | 51 (40.2%)           | 21 (32.3%)           | 24 (34.3%)             |
| **HbA1c (%)**             | 7.92 (0.705)          | 8.44 (0.758)         | 8.22 (0.618)         | 8.28 (0.653)           | 8.46 (0.747)          | 8.52 (0.725)            | 8.69 (0.824)         | 8.70 (0.889)         | 8.64 (0.728)            |
| **Diabetes duration (y)** | 5.9 (6.0)             | 7.5 (6.8)            | 9.0 (6.3)            | 8.0 (5.6)              | 7.9 (4.9)             | 9.6 (5.7)               | 10.6 (6.6)           | 9.3 (6.6)            | 10.7 (5.9)             |
| **Body weight (kg)**      | 71.3 (13.7)           | 73.1 (16.9)          | 72.6 (11.4)          | 65.0 (12.8)            | 68.3 (13.8)           | 73.1 (16.4)             | 70.7 (13.7)          | 75.5 (16.0)          | 71.0 (15.1)            |
| **BMI (kg/m²)**           | 25.7 (3.9)            | 26.4 (4.8)           | 26.3 (3.7)           | 24.6 (3.4)             | 25.3 (4.6)            | 26.5 (4.4)              | 25.6 (4.2)           | 27.2 (4.9)           | 26.3 (4.3)             |
| **eGFR (MDRD; ml/ min/ 1.73 m²)** | 75.5 (15.0)         | 78.9 (15.5)          | 81.4 (14.7)          | 77.2 (11.6)            | 80.2 (13.0)           | 81.5 (13.1)             | 77.3 (11.5)          | 78.3 (12.6)          | 80.0 (14.6)            |
| **CKD stage**             |                       |                      |                      |                        |                       |                         |                      |                      |                        |
| CKD stage 1               | 24 (17.9%)            | 13 (20.3%)           | 15 (23.4%)           | 11 (17.5%)             | 14 (21.9%)            | 21 (33.3%)              | 18 (14.2%)           | 15 (23.1%)           | 17 (24.3%)             |
| CKD stage 2               | 89 (66.4%)            | 51 (79.7%)           | 49 (76.6%)           | 52 (82.5%)             | 50 (78.1%)            | 42 (66.7%)              | 109 (85.8%)          | 50 (76.9%)           | 53 (75.7%)             |
| CKD stage 3a              | 21 (15.7%)            | 0                    | 0                    | 0                      | 0                     | 0                       | 0                    | 0                    | 0                      |

Note: Data are mean (SD) or n (%).

Abbreviations: AGI, α-glucosidase inhibitor; BIG, biguanide; BMI, body mass index; CKD, chronic kidney disease; DDP4-I, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLIN, glinide; GLP1-RA, glucagon-like peptide-1 receptor agonist; MDRD, modified diet in renal disease; SGLT2-I, sodium glucose cotransporter 2 inhibitor; SU, sulphonylurea; TZD, thiazolidinedione.
### TABLE 2  Patients with adverse events

|                   | Imeglimin monotherapy, n (%) [95% CI] | Combination with AGI, n (%) [95% CI] | Combination with BIG, n (%) [95% CI] | Combination with DDP4-I, n (%) [95% CI] | Combination with GLIN, n (%) [95% CI] | Combination with SGLT2-I, n (%) [95% CI] | Combination with SU, n (%) [95% CI] | Combination with TZD, n (%) [95% CI] | Combination with GLP1-RA, n (%) [95% CI] |
|-------------------|---------------------------------------|--------------------------------------|--------------------------------------|----------------------------------------|---------------------------------------|----------------------------------------|-------------------------------------|--------------------------------------|-------------------------------------|
| **Number of patients** | 134 (73.1%) [65.6-80.6] | 64 (51.6%) [39.4-63.8] | 64 (51.6%) [39.4-63.8] | 63 (51.6%) [39.4-63.8] | 64 (51.6%) [39.4-63.8] | 63 (51.6%) [39.4-63.8] | 127 (66.7%) [65.7-86.7] | 65 (78.6%) [70.6-89.4] | 70 (80.0%) [70.6-89.4] |
| **Any TEAEs**     | 98 (73.1%) [65.6-78.6] | 50 (79.4%) [69.4-89.4] | 50 (79.4%) [69.4-89.4] | 50 (79.4%) [69.4-89.4] | 54 (84.4%) [75.5-93.3] | 48 (76.2%) [65.7-86.7] | 50 (80.3%) [73.4-87.2] | 56 (80.0%) [66.7-87.1] | 56 (80.0%) [70.6-89.4] |
| **Mild**          | 32 (64.4%) [37.8-62.3] | 45 (70.3%) [59.1-81.5] | 50 (79.4%) [69.4-89.4] | 53 (82.8%) [73.6-92.0] | 53 (82.8%) [69.4-89.4] | 47 (74.6%) [63.9-85.3] | 50 (78.7%) [71.6-85.8] | 55 (78.6%) [69.0-88.2] | 55 (78.6%) [69.0-88.2] |
| **Moderate**      | 9 (6.3%) [0.3-12.3] | 8 (12.7%) [4.5-20.9] | 5 (7.8%) [1.2-14.4] | 6 (10.6%) [3.7-26.3] | 4 (6.3%) [0.3-12.3] | 4 (6.3%) [0.3-12.3] | 15 (11.8%) [6.2-17.4] | 12 (18.5%) [9.1-27.9] | 4 (5.7%) [0.3-11.1] |
| **Severe**        | 2 (1.6%) [0.0-4.7] | 6 (3.3%) [0.3-12.3] | 1 (1.6%) [0.0-4.7] | 0 | 1 (1.6%) [0.0-4.7] | 5 (3.9%) [0.5-7.3] | 1 (1.5%) [0.0-4.5] | 2 (2.9%) [0.0-6.8] | 3 (4.6%) [0.0-9.7] |
| **Drug-related TEAEs** | 13 (9.7%) [4.7-14.7] | 24 (37.5%) [25.6-49.4] | 14 (22.2%) [11.9-32.5] | 10 (15.6%) [6.7-24.5] | 7 (11.1%) [3.3-18.9] | 27 (21.3%) [14.2-28.4] | 6 (9.2%) [2.2-16.2] | 8 (11.4%) [4.0-18.8] | 8 (11.4%) [4.0-18.8] |
| **Serious TEAEs** | 4 (3.0%) [0.1-5.9] | 4 (6.3%) [0.3-12.3] | 3 (4.8%) [0.0-10.1] | 1 (1.6%) [0.0-4.7] | 4 (6.3%) [0.3-12.3] | 11 (8.7%) [3.8-13.6] | 4 (6.2%) [0.3-12.1] | 5 (7.1%) [1.1-13.1] | 5 (7.1%) [1.1-13.1] |
| **Serious drug-related TEAEs** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Death**         | 1 (0.7%) [0.0-2.1] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **TEAE leading to study drug discontinuation** | 3 (2.2%) [0.0-4.7] | 7 (10.9%) [3.3-18.5] | 5 (7.9%) [1.2-14.6] | 1 (1.6%) [0.0-4.7] | 1 (1.6%) [0.0-4.7] | 9 (7.1%) [2.6-11.6] | 4 (6.2%) [0.3-12.1] | 15 (21.4%) [11.8-31.0] | 15 (21.4%) [11.8-31.0] |
| **TEAEs occurring in more than 5% of patients in any treatment group** | | | | | | | | | |
| **Nasopharyngitis** | 40 (29.9%) [22.1-37.7] | 16 (25.0%) [14.4-35.6] | 19 (30.2%) [18.9-41.5] | 27 (42.2%) [30.1-54.3] | 20 (31.7%) [20.2-43.2] | 39 (30.7%) [22.7-48.1] | 18 (27.7%) [16.8-38.6] | 20 (28.6%) [18.0-39.2] | 20 (28.6%) [18.0-39.2] |
| **Pharyngitis**    | 8 (6.0%) [2.0-10.0] | 0 | 3 (4.8%) [0.0-10.1] | 4 (6.3%) [0.3-12.3] | 5 (7.9%) [1.2-14.6] | 5 (3.9%) [0.5-7.3] | 3 (4.6%) [0.9-7.9] | 1 (1.4%) [0.0-4.2] | 1 (1.4%) [0.0-4.2] |
| **Influenza**      | 4 (3.0%) [0.1-5.9] | 1 (1.6%) [0.0-4.7] | 2 (3.3%) [0.0-7.3] | 2 (3.3%) [0.0-7.3] | 9 (7.1%) [2.6-11.6] | 3 (4.6%) [0.9-7.9] | 1 (1.4%) [0.0-4.2] | 1 (1.4%) [0.0-4.2] | 1 (1.4%) [0.0-4.2] |
| **Bronchitis**     | 1 (0.7%) [0.0-2.1] | 2 (3.1%) [0.0-7.3] | 4 (6.3%) [0.3-12.3] | 2 (3.2%) [0.0-7.5] | 1 (0.8%) [0.0-2.3] | 4 (6.2%) [0.3-12.1] | 0 | | |
| **Nausea**         | 9 (6.7%) [2.5-10.9] | 1 (1.6%) [0.0-4.7] | 5 (7.9%) [1.2-14.6] | 0 | 4 (6.2%) [0.3-12.3] | 1 (0.8%) [0.0-2.3] | 1 (1.5%) [0.0-4.5] | 3 (4.3%) [0.0-9.1] | 3 (4.3%) [0.0-9.1] |
| **Diarrhoea**      | 4 (3.0%) [0.1-5.9] | 11 (17.2%) [8.0-26.4] | 4 (6.3%) [0.3-12.3] | 3 (2.4%) [0.0-5.1] | 2 (3.1%) [0.0-7.3] | 3 (4.3%) [0.0-9.1] | | | |
| **Constipation**   | 5 (3.7%) [0.5-6.9] | 2 (3.1%) [0.0-4.7] | 5 (7.9%) [1.2-14.6] | 2 (3.1%) [0.0-7.3] | 2 (3.2%) [0.0-7.5] | 8 (6.3%) [2.1-10.5] | 1 (1.5%) [0.0-4.5] | 1 (1.4%) [0.0-4.2] | 1 (1.4%) [0.0-4.2] |
| **Death**         | 1 (0.7%) [0.0-2.1] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Condition                        | Imeglimin monotherapy, n (%) [95% CI] | Combination with AGI, n (%) [95% CI] | Combination with BIG, n (%) [95% CI] | Combination with DDP4-I, n (%) [95% CI] | Combination with GLIN, n (%) [95% CI] | Combination with SGLT2-I, n (%) [95% CI] | Combination with SU, n (%) [95% CI] | Combination with TZD, n (%) [95% CI] | Combination with GLP1-RA, n (%) [95% CI] |
|----------------------------------|---------------------------------------|--------------------------------------|--------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|-----------------------------------|--------------------------------------|----------------------------------------|
| Gastroesophageal reflux disease  | 3 (2.2%) [0.0-4.7]                    | 2 (3.1%) [0.0-7.3]                   | 1 (1.6%) [0.0-4.7]                   | 9 (7.1%) [2.6-11.6]                    |                                        |                                        |                                   |                                     |                                        |
| Vomiting                         | 1 (0.7%) [0.0-2.1]                    | 0                                    | 4 (6.3%) [0.3-12.3]                  | 0                                      | 1 (1.6%) [0.0-4.7]                    | 0                                      | 2 (3.1%) [0.0-7.3]                  | 2 (2.9%) [0.0-6.8]                   |
| Back pain                        | 5 (3.7%) [0.5-6.9]                    | 2 (3.1%) [0.0-7.3]                   | 1 (1.6%) [0.0-4.7]                   | 3 (4.7%) [0.0-9.9]                     | 0                                      | 10 (7.9%) [3.2-12.6]                | 4 (6.2%) [0.3-12.1]                 | 0                                    |
| Spinal osteoarthritis            | 1 (0.7%) [0.0-2.1]                    | 1 (1.6%) [0.0-4.7]                   | 0                                    | 4 (6.3%) [0.3-12.3]                    | 0                                      | 1 (1.6%) [0.0-4.7]                   | 0                                 | 0                                    | 1 (1.4%) [0.0-4.2]                   |
| Intervertebral disc protrusion   | 0                                     | 1 (1.6%) [0.0-4.7]                   | 0                                    | 4 (6.3%) [0.3-12.3]                    | 1 (1.6%) [0.0-4.7]                    | 0                                      | 0                                 | 0                                    | 1 (1.4%) [0.0-4.2]                   |
| Hypoglycaemia                    | 5 (3.7%) [0.5-6.9]                    | 2 (3.1%) [0.0-7.3]                   | 6 (9.4%) [2.3-16.5]                  | 5 (7.9%) [1.2-14.6]                    | 9 (14.1%) [5.6-22.6]                  | 4 (6.3%) [0.3-12.3]                   | 21 (16.5%) [10.0-23.0]              | 2 (3.1%) [0.0-7.3]                   | 2 (2.9%) [0.0-6.8]                   |
| Hyperglycaemia                   | 5 (3.7%) [0.5-6.9]                    | 1 (1.6%) [0.0-4.7]                   | 0                                    | 2 (3.2%) [0.0-7.5]                     | 0                                      | 1 (1.6%) [0.0-4.7]                   | 7 (5.5%) [1.5-9.5]                  | 1 (1.5%) [0.0-4.5]                   | 8 (11.4%) [4.0-18.8]                 |
| Eczema                           | 2 (1.5%) [0.0-3.6]                    | 0                                    | 0                                    | 5 (7.9%) [1.2-14.6]                    | 3 (4.7%) [0.0-9.9]                     | 2 (3.2%) [0.0-7.5]                    | 4 (3.1%) [0.1-6.1]                  | 1 (1.5%) [0.0-4.5]                   | 4 (5.7%) [0.3-11.1]                  |
| Hypertension                     | 0                                     | 3 (4.7%) [0.0-9.9]                   | 1 (1.6%) [0.0-4.7]                   | 2 (3.3%) [0.0-7.3]                     | 1 (1.6%) [0.0-4.7]                    | 7 (5.5%) [1.5-9.5]                   | 3 (4.6%) [0.0-9.7]                  | 2 (2.9%) [0.0-6.8]                   |

Abbreviations: AGI, α-glucosidase inhibitor; BIG, biguanide; DDP4-I, dipeptidyl peptidase-4 inhibitor; GLIN, glinide; GLP1-RA, glucagon-like peptide-1 receptor agonist; SGLT2-I, sodium glucose cotransporter 2 inhibitor; SU, sulphonylurea; TEAE, treatment emergent adverse event; TZD, thiazolidinedione.
with a DPP4-I, six (9.4%) with a GLIN, 19 (27.1%) with a GLP1-RA, three (4.7%) with an SGLT2-I, 17 (13.4%) with an SU, and four (6.2%) with a TZD. The main reason for premature treatment discontinuation was withdrawal of consent for imeglimin long-term monotherapy and for long-term combination with an AGI/GLIN/SU/SGLT2-I, or, occurrence of a treatment emergent adverse event (TEAE) or serious TEAE for long-term combination with a BIG/DPP4-I/GLP1-RA/TZD.

Demographic and baseline characteristics in each treatment group are shown in Table 1. Mean age ranged from 56.6 to 63.6 years. Baseline HbA1c ranged from 7.92% to 8.70%.

3.2 | Safety

Overall, during the 52-week, open-label treatment period, the percentage of patients experiencing at least one TEAE was 75.5% (Table 2). Of note, this overall TEAE rate was similar to the rate observed in either the imeglimin (62%-73%) or placebo (68%) arms of the 24-week Japanese phase 2b trial.8

The percentage of patients with mild, moderate, and severe TEAEs was 73.5% (525/714) (95% CI: 70.3-76.7), 9.1% (65/714) (95% CI: 7.0-11.2), and 2.4% (95% CI: 1.3-3.5) (17/714), respectively. Serious TEAEs occurred in 5.6% of all patients, including one death as a result of a traffic accident in the imeglimin long-term monotherapy arm.

No clinically significant changes in 12-lead ECG, vital signs, physical examination, or laboratory tests were noted in any groups.

3.2.1 | Imeglimin long-term monotherapy

The percentage of patients experiencing at least one TEAE was 73.1%. Nasopharyngitis, pharyngitis, and nausea were experienced by 5% or more patients. TEAEs leading to study drug discontinuation were reported in three (2.2%) patients because of mild events of hyperglycaemia.

Hypoglycaemia was reported in 3.7% (5/134) of patients. All hypoglycaemia events were asymptomatic and self-reported by patients using SMBG. No severe hypoglycaemia was reported.

Serious TEAEs occurred in 3.0% of patients. One patient presented with a serious event of appendicitis, one with postprocedural haemorrhage, and another with atrial fibrillation. None of these events were considered drug-related. One patient died from a subarachnoid haemorrhage, which resulted from injuries caused by a traffic accident as a pedestrian.

3.2.2 | Imeglimin long-term combination therapy

The percentage of patients experiencing at least one TEAE ranged from 51.6% (AGI arm) to 84.4% (GLIN arm). The most frequently reported TEAE was nasopharyngitis in all background therapies. The TEAEs experienced by 5% or more of patients are shown in Table 2. Gastrointestinal events increased in combination with a BIG.

TEAEs leading to study drug discontinuation were reported in 1.6% to 21.4% of patients, including: two patients with an AGI (one mild hyperglycaemia and one decreased appetite); seven patients with a BIG (one severe unrelated cholangiocarcinoma, four gastrointestinal events [nausea, diarrhoea, abdominal pain upper, and dyspepsia], one with a decreased platelet count, and the other with a decreased appetite); five patients with a DPP4-I (one serious unrelated [multiple fracture] and one each of mild hyperglycaemia, decreased appetite, nausea, and erectile dysfunction); one patient with a GLIN (one serious unrelated testicular cancer); 15 patients with a GLP1-RA (one serious unrelated [invasive duct cell carcinoma], eight mild hyperglycaemias, three gastrointestinal events [nausea, abdominal pain upper, and dyspepsia], and one each of cholelithiasis, diabetic neuropathy, and decreased appetite); one patient with an SU (one mild hyperglycaemia); nine patients with an SU (two serious unrelated colon cancer and rectal cancer, and seven mild hyperglycaemias); and four patients with a TZD (one serious unrelated enterovesical fistula, and one each of nausea, vomiting, and mild hyperglycaemia).

Hypoglycaemia was reported in 3.1% to 16.5% of patients. No severe hypoglycaemia was reported in combination with any of the background therapies. There was a greater number of hypoglycaemic events in combination therapy with a GLIN (nine patients [14.1%]) and with an SU (21 patients [16.5%]). In these two groups, most of the hypoglycaemia events were asymptomatic and self-reported by patients using SMBG. In combination with a GLIN, two patients reported seven events of symptomatic hypoglycaemic events and, in combination with an SU, nine patients reported 15 events of symptomatic hypoglycaemic events.

Serious TEAEs, none of them related to the study drug, occurred in 1.6% to 8.7% of patients, including: four patients with an AGI (drug-induced liver injury attributed to another drug in the same patient, ovarian cyst, unstable angina pectoris, and heat stroke); four patients with a BIG (myocardial infarction, cholangiocarcinoma, appendicitis, and colorectal polyp); three patients with a DPP4-I (multiple fracture, colorectal polyp, and endometrial carcinoma stage 3); one patient with a GLIN (testicular cancer); five patients with a GLP1-RA (lumbar spinal stenosis, invasive ductal carcinoma, dermoid cyst, coronary artery stenosis, and cerebral infarction/coronary stenosis); four patients with an SGLT2-I (heart failure/pneumonia, lacunar infarction, colon polyp, and vertebral fracture); 11 patients with an SU (clavicle fracture, colon cancer stage 1, rectal cancer, unstable angina pectoris, acute myocardial infarction, contusion, subdural haematoma, traumatic pneumothorax, uterine leiomyoma, lower gastrointestinal haemorrhage, and synovitis); and four patients with a TZD (enterovesical fistula, craniocerebral injury, inflammation, and bacterial pneumonia).

3.3 | Efficacy

3.3.1 | Imeglimin long-term monotherapy

The adjusted mean (standard error) change from baseline in HbA1c at week 52 with imeglin as monotherapy was ~0.46% (0.07%)
The reduction in HbA1c was sustained over 52 weeks (Figure 1). At week 52, the percentage of patients achieving an HbA1c of less than 7% and a relative decrease of at least 7% versus baseline HbA1c was 40.3% and 48.6%, respectively (Table S1).

The HbA1c decrease was consistent across age groups (Table S2). At week 52, HbA1c decreased by 0.37% (0.09%) in patients aged younger than 65 years and by 0.63% (0.06%) in those patients aged 65 years or older patients. The HbA1c decrease was also consistent across CKD stage groups (Table S3). At week 52, HbA1c decreased by 0.32% (0.17%) in CKD stage 1 patients, by 0.48% (0.09%) in CKD stage 2 patients, and by 0.50% (0.07%) in CKD stage 3a patients.

3.3.2 Imeglimin long-term combination therapy

Adjusted mean (standard error) changes from baseline in HbA1c at week 52 ranged from −0.12% (0.13%) to −0.92% (0.11%). In combination with other oral agent classes, the mean HbA1c change from baseline ranged from −0.56% (with an SU) to −0.92% (with a DPP4-I), as

![Figure 1](image1.png)

![Figure 2](image2.png)
week 52 ranged from 2 patients. With an SGLT2-I, six (4.7%) patients with an SU, and one patient with DPP4-I, eight patients (11.4%) with a GLP1-RA, one patient (1.6%) with mon metformin side effects. However, imeglimin has been shown to dose-dependently increase gastrointestinal events at higher doses, from 1500 up to 6000 mg, the maximal tolerated doses. In this context, the most commonly observed events are nausea, vomiting, and diarrhoea, and these are mainly mild in intensity. When related to imeglimin, these events tend to start immediately after treatment initiation and are resolved within 1 month. The mechanisms underlying such effects are unknown, but tend to correlate better with the dose of imeglimin delivered in the gastrointestinal tract, rather than with the circulating concentrations (Cmax) of the drug, based on studies in healthy subjects (unpublished results). Importantly, in the two previous studies conducted in Japan as a monotherapy regimen (phase 2b and TIMES 1), imeglimin—up to the dose of 1000 mg BID—was observed to have a safety/tolerability profile that was similar to the control placebo groups. Moreover, in a prior phase 2 metformin combination study conducted in Caucasian subjects, imeglimin at the dose of 1500 mg BID produced only a slight increase (23% of subjects) in TEAEs versus metformin alone (19%). In previous studies, imeglimin showed a low risk of hypoglycaemia. In randomized placebo-controlled trials, imeglimin did not exhibit an increased incidence of hypoglycaemia and no severe hypoglycaemia was reported. This is consistent with the mechanism of action of imeglimin, which only induces insulin secretion in response to glucose via enhancing β-cell function and amplifying glucose-stimulated insulin secretion. In the current study, the low incidence of hypoglycaemia was confirmed in both monotherapy and combination use, except when combined with an SU or a GLIN, where the incidence was twice as high as in the other groups. This could be attributed to the background therapy, because both GLINs and SUs trigger insulin secretion independently of glucose levels, and also because it was not planned to adjust the dose of the background therapy during the course of the study. As imeglimin improved the overall glucose control, this tended to increase the incidence of hypoglycaemia, although no severe hypoglycaemia was reported. Indeed, the risk of hypoglycaemia with the use of these two background therapies is well known, and physicians should carefully adjust doses according to glucose monitoring data when using these drugs in either monotherapy or combination therapy.

In this study, approximately one-third of patients were elderly (i.e. aged ≥65 years), and 76.3% presented with evidence of mild renal impairment (CKD stage 2) considering their baseline eGFR measurements. The efficacy and safety profile of imeglimin among elderly and CKD patients was consistent with a previous report showing no influence of older age or decreased renal function on imeglimin’s profile. The current study provides evidence to support imeglimin as a favourable option in monotherapy, as well as in combination therapy. Imeglimin was previously shown to provide benefits on glycaemic control in Japanese patients with type 2 diabetes during two randomized placebo-controlled trials. In this trial, the imeglimin 1000 mg BID long-term monotherapy arm confirmed its efficacy with a similar decrease in HbA1c and a sustained effect after 1 year of treatment.

The effect of imeglimin to enhance glucose-dependent insulin secretion may be of particular interest because Japanese patients with type 2 diabetes have a different profile compared with Caucasians, with an earlier defect in insulin secretion and, in general, fewer degrees of insulin resistance. The effect of imeglimin was observed both as a monotherapy and as an add-on to all oral antidiabetic classes, suggesting favourable complementarity with other therapies.

Treatment with imeglimin also led to sustained improvements in glycaemic control in Japanese patients with type 2 diabetes when added to all oral background therapies available on the Japanese market. Thus, imeglimin led to clinically meaningful HbA1c reductions of −0.56% to −0.92% from a mean HbA1c baseline of 8.22% to 8.70% in these arms of the trial. Furthermore, 8.1% to 37.2% of patients achieved an HbA1c of less than 7%, the target recommended by the Japan Diabetes Society to prevent complications of type 2 diabetes.
The efficacy of imeglimin as an add-on to metformin or to sitagliptin was previously described in two dedicated studies in Caucasian patients with type 2 diabetes, showing a −0.44% and a −0.72% decrease, respectively, after 12 weeks of treatment with imeglimin 1500 mg BID.10,11 This potential for utility when combined with metformin was confirmed in Japanese patients with type 2 diabetes, where sustained efficacy, with an HbA1c decrease from baseline of −0.67% after 52 weeks of treatment, was evident. This finding also highlights the complementary mode of action of the two compounds: metformin acts primarily to suppress excessive hepatic glucose output, whereas imeglimin targets both insulin sensitivity and insulin secretion in response to glucose.4

The current study also strongly supports the utility of combination therapy with a DPP4-I. DPP4-Is are the most frequently prescribed class of antidiabetic agents for type 2 diabetes in Japan and are associated with the greatest drug adherence, as reported in a retrospective real-world evidence study.19 This study is also noteworthy because more than half of the patients treated with DPP4-Is were older than 65 years.17 In the present trial, imeglimin, in combination with a DPP4-I, produced a clinically meaningful HbA1c reduction of 0.92%, with a favourable safety/tolerability profile, in line with the effects observed in the short Caucasian add-on study.10 These observations also support the concept that, although both DPP4-Is and imeglimin induce an increase in insulin secretion in response to glucose, their mechanisms of action are different, and their effects on glucose control complement one another to achieve greater efficacy when combined. DPP4-Is have been shown to slightly increase endogenous GLP1 concentrations by inhibiting their degradation. By contrast, imeglimin has direct effects on pancreatic β-cells to amplify glucose-stimulated insulin release.4 The underlying mechanism is distinct from GLP1 receptor activation and involves increases in the cellular NAD⁺ pool along with augmentation of glucose-induced ATP levels. These recently reported findings unveil a novel mode of action for imeglimin.5 Therefore, considering the very good safety and efficacy profile of this combination, imeglimin add-on to a DPP4-I appears to be a very promising option in Japanese patients to enhance insulin secretion in response to glucose without incurring an additional risk of hypoglycaemia in patients with type 2 diabetes.

Although the safety/tolerability profile was favourable, only minimal efficacy was observed when imeglimin was used in combination with an injectable GLP1-RA, another incretin-based therapeutic class. This might be explained by greater severity of the disease (e.g. lower β-cell mass at baseline) in this subpopulation because an injectable GLP1-RA is not typically prescribed as monotherapy, and is most frequently employed later in the treatment continuum when several existing oral agents have failed to provide acceptable glycaemic control.20 The baseline demographic features of the GLP1-RA group (including age, body mass index, and baseline HbA1c) were not distinctly different from other combination groups; however, relative to the other combination groups, this cohort had the longest duration of disease. Alternatively, GLP1-RAs—unlike DPP4-Is—have direct, and much more robust, effects on β-cells to augment glucose-responsive insulin secretion. It is plausible that imeglimin and GLP1-RA mediated pathways converge downstream from their respective mechanisms to drive insulin release in response to glucose; therefore, there may be a limited ability for imeglimin to further augment β-cell function when both approaches are used together. This concept is potentially consistent with important differences in efficacy between the two distinct incretin-based therapeutic classes; DPP4-Is primarily target postprandial plasma glucose, while GLP1-RAs also drive substantial effects on FPG.21

This study had several limitations. The first is the lack of a placebo control or other monotherapy as an active comparator, although such a comparator is not required for long-term studies, according to the Pharmaceuticals and Medical Devices Agency.13 This lack of a control group should be taken into consideration when interpreting the study data. The study was conducted in Japanese patients only, therefore, the results cannot be extrapolated to other populations. Currently, the longest follow-up period studied in clinical trials of imeglimin is 1 year. Considering that type 2 diabetes is a chronic condition, even longer follow-up assessments will be needed in the future to better characterize the safety/efficacy profile of imeglimin and to confirm its durability. This could potentially be achieved by further clinical trials or real-world evidence postapproval of imeglimin in Japan. Lastly, the comparatively small sample size in each combination group does not allow for the detection of rare adverse events. Further postmarket surveillance in Japan will allow for improved knowledge of the safety profile of this new oral antidiabetic drug.

In conclusion, imeglimin monotherapy and, in combination with oral antidiabetic drugs in Japanese individuals with type 2 diabetes, was well tolerated and led to clinically meaningful and sustained improvements in glycaemic control.

CONFLICT OF INTEREST
JD, PF, and DQ are employees of Poxel. JMG is a consultant for Poxel. KK has been an advisor to, received honoraria for lectures from, and received scholarship grants from Astellas, AstraZeneca, Eli Lilly Japan, Novo Nordisk Pharma, Sanwa Kagaku Kenkyusho, Takeda Pharmaceuticals, Taisho Pharmaceutical, MSD, Kowa, Sumitomo Dainippon Pharma, Poxel, Mitsubishi Tanabe Pharma, Boehringer Ingelheim Japan, and Daiichi Sankyo.

AUTHOR CONTRIBUTIONS
JD contributed to the study design, interpretation of data, drafted and edited the report. PF, DQ, and JMG contributed to the study design, interpretation of data, and reviewed the report. KK contributed to interpretation of data and reviewed the report. All the authors read the manuscript critically and approved the submitted version. The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development, and have approved the final version.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study can be available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.
REFERENCES

1. Kaiser A, Zhang N, der Pluijm W. Global prevalence of type 2 diabetes over the next ten years (2018-2028). Diabetes. 2018;67:202-LB.

2. Ministry of Health LaW. The National Health and Nutrition Survey (NHNS) Japan. Tokyo, Japan: National Institutes of Biomedical Innovation; 2018.

3. Pirags V, Lebovitz H, Fouqueray P. Imeglimin, a novel glimin oral anti-diabetic, exhibits a good efficacy and safety profile in type 2 diabetic patients. Diabetes Obes Metab. 2012;14:852-858.

4. Hallakou-Bozec S, Vial G, Kergoat M, et al. Mechanism of action of Imeglimin: a novel therapeutic agent for type 2 diabetes. Diabetes Obes Metab. 2021;23:664-673.

5. Vial G, Chauvin MA, Bendridi N, et al. Imeglimin normalizes glucose tolerance and insulin sensitivity and improves mitochondrial function in liver of a high-fat, high-sucrose diet mice model. Diabetes. 2015;64:2254-2264.

6. Pacini G, Mari A, Fouqueray P, Bolze S, Roden M. Imeglimin increases glucose-dependent insulin secretion and improves beta-cell function in patients with type 2 diabetes. Diabetes Obes Metab. 2015;17:541-545.

7. Detaille D, Vial G, Borel AL, et al. Imeglimin prevents human endothelial cell death by inhibiting mitochondrial permeability transition without inhibiting mitochondrial respiration. Cell Death Discovery. 2016;2:15072.

8. Dubourg J, Ueki K, Grouin JM, Fouqueray P. Efficacy and safety of imeglimin in Japanese patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled, dose-ranging phase 2b trial. Diabetes Obes Metab. 2021;23:800-810.

9. Dubourg J, Fouqueray P, Thang C, Grouin JM, Ueki K. Efficacy and safety of omeglimin monotherapy versus placebo in Japanese patients with type 2 diabetes (TIMES 1): a double-blind, randomized, placebo-controlled, parallel-group, multicenter phase 3 trial. Diabetes Care. 2021;44:952-959.

10. Fouqueray P, Pirags V, Diamant M, et al. The efficacy and safety of imeglimin as add-on therapy in patients with type 2 diabetes inadequately controlled with sitagliptin monotherapy. Diabetes Care. 2014;37:1924-1930.

11. Fouqueray P, Pirags V, Inzucchi SE, et al. The efficacy and safety of imeglimin as add-on therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy. Diabetes Care. 2013;36:565-568.

12. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. J Clin Endocrinol Metab. 2013;98:1845-1859.

13. PMDA, Pharmaceutical and Food Safety Bureau MoH, Labour and Welfare. On Release of the Guideline for Clinical Evaluation of Oral Hypoglycemic Agents, Tokyo, Japan; PMDA; 2010.

14. Bouchoucha M, Uzzan B, Cohen R. Metformin and digestive disorders. Diabetes Metab. 2011;37:90-96.

15. Hallakou-Bozec S, Kergoat M, Fouqueray P, Bolze S, Moller DE. Imeglimin amplifies glucose-stimulated insulin release from diabetic islets via a distinct mechanism of action. PLoS One. 2021;16:e0241651.

16. International Hypoglycaemia Study Group. Minimizing hypoglycemia in diabetes. Diabetes Care. 2015;38:1583-1591.

17. Muller JB, Pedersen M, Tanaka H, et al. Body composition is the main determinant for the difference in type 2 diabetes pathophysiology between Japanese and Caucasians. Diabetes Care. 2014;37:796-804.

18. Yabe D, Seino Y. Type 2 diabetes via β-cell dysfunction in east Asian people. Lancet Diabetes Endocrinol. 2016;4:2-3.

19. Kadowaki T, Sarai N, Hirakawa T, Taki K, Iwasaki K, Urushihara H. Persistence of oral antidiabetic treatment for type 2 diabetes characterized by drug class, patient characteristics and severity of renal impairment: a Japanese database analysis. Diabetes Obes Metab. 2018;20:2830-2839.

20. Nishimura R, Kato H, Kisanuki K, et al. Treatment patterns, persistence and adherence rates in patients with type 2 diabetes mellitus in Japan: a claims-based cohort study. BMJ Open. 2019;9:e025806.

21. Fineman MS, Cirincione BB, Maggs D, Diamant M. GLP-1 based therapies: differential effects on fasting and postprandial glucose. Diabetes Obes Metab. 2012;14:675-688.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher’s website.

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