Efficacy and Safety of Imeglimin Monotherapy Versus Placebo in Japanese Patients With Type 2 Diabetes (TIMES 1): A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicenter Phase 3 Trial

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OBJECTIVE

The aim of this study was to investigate the efficacy and safety of imeglimin, the first in a new class of oral antidiabetic agent, in Japanese patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

This was a double-blind, randomized, parallel-group, placebo-controlled phase 3 trial in 30 sites in Japan. Eligible participants were individuals aged ≥20 years with type 2 diabetes treated with diet and exercise, stable for ≥12 weeks prior to screening, and whose HbA_{1c} was 7.0–10.0% (53–86 mmol/mol). Patients were randomly assigned (1:1) to either oral imeglimin (1,000 mg twice daily) or matched placebo for 24 weeks. Investigators, participants, and the sponsor of the study remained blinded throughout the trial. The primary end point was the change in mean HbA_{1c} from baseline to week 24, and the key secondary end point was the percentage of responders (according to two definitions) at week 24.

RESULTS

Between 26 December 2017 and 1 February 2019, 106 and 107 patients were randomly assigned to treatment with imeglimin and placebo, respectively. Compared with placebo, the adjusted mean difference in change from baseline HbA_{1c} at week 24 was −0.87% (95% CI −1.04 to −0.69 [−9.5 mmol/mol; 95% CI −11.4 to −7.5]; $P < 0.0001$). Forty-seven (44.3%) patients reported ≥1 adverse event in the imeglimin group versus 48 adverse events (44.9%) in the placebo group.

CONCLUSIONS

Imeglimin significantly improved HbA_{1c} in Japanese patients with type 2 diabetes compared with placebo and had a similar safety profile to placebo. Imeglimin represents a potential new treatment option for this population.

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Type 2 diabetes is a widespread disease, affecting >500 million people worldwide (1). It is characterized by pancreatic islet β-cell dysfunction and peripheral insulin resistance leading to hyperglycemia (2,3). In addition to long-term lifestyle modifications, pharmacologic management is usually required to maintain effective glycemic control. In Japan, the prevalence of type 2 diabetes is increasing. Type 2 diabetes affects ~7.6% of adults aged 20–79 years and accounts for ~6% of the Japanese national health care expenditure (4). The consensus-based guidelines provided by the Japan Diabetes Society recommend a stepwise treatment algorithm for effective management of type 2 diabetes (5). Unfortunately, although monotherapies and combination therapies improve glycemic control, they also cause adverse events, particularly in the elderly population. This population is also often burdened with additional therapies for treatment of comorbidities. Consequently, unmet medical needs are still a reality in type 2 diabetes, and new therapeutic agents with durable efficacy and improved safety profiles are still needed.

Imeglimin is a first-in-class, novel, oral antidiabetic investigational agent to treat type 2 diabetes. Its mode of action is distinct from all other antihyperglycemic classes; imeglimin's underlying mechanism involves targeting of mitochondrial bioenergetics (6) and improving mitochondrial function. Imeglimin modulates mitochondrial respiratory chain complex activities while decreasing reactive oxygen species production (7). Imeglimin has been shown to amplify glucose-stimulated insulin secretion by improving β-cell glucose responsiveness in patients with type 2 diabetes (8) and to improve insulin sensitivity in a rodent model of diabetes, allowing for normalization of glucose tolerance (7). 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 (9); this finding suggests the potential for end organ protection (e.g., kidney or heart).

Previous phase 1 and phase 2 clinical trials in Caucasian patients with type 2 diabetes demonstrated that imeglimin is efficacious as monotherapy and has an adequate safety and tolerability profile (6,10). In addition, imeglimin had demonstrated efficacy and was well-tolerated as add-on therapy to metformin and sitagliptin, highlighting the potential for add-on therapy with common oral antidiabetic agents (11,12). The dose of 1,000 mg twice daily was selected for the Japanese phase 3 program in Japan in which 1,000 mg imeglimin twice daily as monotherapy demonstrated the optimal efficacy (−0.94% [−10.3 mmol/mol] HbA_{1c} reduction vs. placebo) and safety and tolerability profile (13).

In this article, we report the findings of one of the phase 3 trials in Japan (Trials of Imeglimin for Efficacy and Safety 1 [TIMES 1]), in which 1,000 mg imeglimin twice-daily monotherapy was assessed. The trial was designed to confirm the efficacy, safety, and tolerability of imeglimin monotherapy compared with placebo in Japanese patients with type 2 diabetes insufficiently controlled with diet and exercise.

RESEARCH DESIGN AND METHODS

Study Design and Participants

This was a phase 3, randomized, double-blind, parallel-group, multicenter trial (TIMES 1) conducted at 30 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 Harmonization 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 beginning any study-related activities.

Eligible participants were Japanese adults aged ≥20 years with type 2 diabetes treated with diet and exercise and with or without a stable dose of a single oral antidiabetic agent for ≥12 weeks prior to screening, and an HbA_{1c} of 7.0–10.0% (53–86 mmol/mol). Key exclusion criteria included insulin therapy or any injectable glucose-lowering drugs in the 30 days before screening, estimated glomerular filtration rate (eGFR; estimated with the Japanese MDRD equation) of <45 mL/min/1.73 m^2, heart failure (New York Heart Association class III or IV), or any acute coronary or cerebrovascular events in the 24 weeks before screening.

Randomization and Masking

Eligible participants were randomly assigned (1:1) to receive either oral imeglimin (1,000 mg twice daily) or matched placebo. Participants were allocated to treatment groups via an interactive web response system and stratified by HbA_{1c} 1 week before randomization (<8% [64 mmol/mol] and ≥8% [64 mmol/mol]) and previous treatment status (treatment-naive patients and previously treated patients). The investigators, participants, and sponsor remained blinded throughout the trial.

Procedures

After a screening period, all participants received oral placebo during a 4-week run-in period. Participants treated with a single oral hypoglycemic agent had an additional 8-week washout period before the start of the run-in period. After randomization, participants received 1,000 mg imeglimin twice daily or matched placebo for 24 weeks, followed by a 1-week follow-up period.

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 case of withdrawal of consent.

Participants with unacceptable hyperglycemia (i.e., any fasting plasma glucose [FPG] value >250 mg/dL [13.9 mmol/L] from baseline to week 4 or 240 mg/dL [13.3 mmol/L] from week 4 to week 8, and/or any HbA_{1c} value ≥10.0% [86 mmol/mol] from week 8 to week 24) could be offered rescue medication. The initiation, choice, and dose of rescue medication used were at the discretion of the investigator, according to local prescribing information, but injectable glucose-lowering drugs were not allowed. In case of rescue medication, participants discontinued treatment prematurely but continued the study.

Outcomes

The primary efficacy end point was the change from baseline in HbA_{1c} at week 24 with imeglimin versus placebo, assessed at a central laboratory. Key secondary end points were the percentage of responders, based on two different definitions:

1. the percentage of patients reaching a target HbA_{1c} <7.0% (53 mmol/mol) at week 24
2. the percentage of responders as defined by the percentage of patients with a relative decrease of ≥7% from baseline HbA_{1c} at week 24.

Exploratory end points included the percentage of patients requiring rescue therapy and change from baseline to week 24 in FPG levels, laboratory measurements associated with β-cell function and glycemic control (i.e., proinsulin to insulin ratio, proinsulin to C-peptide ratio, the QUICKI, and a HOMA of β-cell function [HOMA-β] and insulin resistance [HOMA-IR]—all fasting) and lipid parameters (concentrations of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides). Change from baseline in HbA_{1c} at week 24 was also analyzed in subgroups of patients according to baseline age (<65 years and ≥65 years), baseline chronic kidney disease (CKD) stage (CKD stages 1, 2, and 3A), and previous diabetes therapy (treatment-naive patients vs. patients treated with a sodium–glucose cotransporter inhibitor vs. patients treated with another oral hypoglycemic agent). A post hoc analysis was performed to assess change from baseline in HbA_{1c} at week 24 according to previous diabetes therapy (treatment-naive patients vs. previously treated patients).

Safety end points included vital signs, physical examination, 12-lead electrocardiogram, clinical laboratory parameters, and adverse events (preferred terms coded according to the Medical Dictionary for Drug Regulatory Activities, version 20.1). Patients were asked to check their glucose levels, using self-monitoring of blood glucose (SMBG) devices, at least twice a week. Events of hypoglycemia were categorized into asymptomatic hypoglycemia (i.e., an event not accompanied by typical symptoms of hypoglycemia but with a measured capillary or plasma glucose <3.9 mmol/L), probable symptomatic hypoglycemia (i.e., an event during which symptoms typical of hypoglycemia are not accompanied by a capillary or plasma glucose determination), documented symptomatic hypoglycemia (i.e., an event during which typical symptoms of hypoglycemia are accompanied by a measured capillary or plasma glucose concentration <3.9 mmol/L), and severe hypoglycemia (i.e., an event requiring assistance of another person to actively administer carbohydrates or glucagon, or take other corrective actions) (14).

Statistical Analysis

A sample size of 106 participants per randomized treatment group was required to ensure 90% power to show an expected 0.5% (5.5 mmol/mol) treatment difference in mean changes of HbA_{1c} between imeglimin and placebo at the two-sided $\alpha = 0.05$ level, assuming an SD of 1.0% and a drop-out rate of 20%.

Multiplicity raised by the primary analysis and key secondary analyses was addressed considering a three-step testing procedure that strongly controls the two-sided type I error to 0.05. If (and only if) the primary end point was significant at the two-sided nominal level of 0.05, then the first key secondary end point was tested at the same two-sided nominal level of 0.05; and only if this was also significant, the second key secondary end point was tested at the same two-sided nominal level of 0.05.

Efficacy analyses were primarily performed on a modified intention-to-treat analysis, comprising all randomly assigned patients who were exposed to ≥1 dose of double-blind study medication and who had ≥1 post baseline assessment of HbA_{1c}. The change of HbA_{1c} (%) from baseline to week 24 was assessed using a mixed model for repeated measures assuming an unstructured covariance matrix and including fixed factors for treatment, visit (categorical variable), treatment-by-visit interaction, randomization strata of previous treatment status, and baseline HbA_{1c} as a continuous covariate. Measurements after treatment discontinuation were censored at the time of study drug discontinuation. Least square means of change from baseline for each treatment group and the differences in least square means between imeglimin and placebo groups was estimated in this model along with 95% CIs and the *P* value. A two-sided nominal significance level of 0.05 was used for treatment comparison.

Safety analysis was performed on all as-treated patients who received ≥1 dose of study drug and was descriptive. Adverse events reported included those that occurred between first drug intake (at randomization) and 7 days after cessation of drug administration or that started before drug intake and worsened during the double-blind treatment period.

Analyses were performed using SAS, version 9.4. This trial was registered with the Japan Pharmaceutical Information Center (registration no. JapicCTI-173769).

RESULTS

Between 26 December 2017 and 1 February 2019, 213 patients were randomly assigned to treatment (Fig. 1). Of these, 194 (91%) completed the 24-week, double-blind treatment period. Among the 213 randomized patients, 212 received ≥1 dose of double-blind trial medication, had ≥1 post-baseline HbA_{1c} value, and were included in the modified intention-to-treat analysis (Fig. 1). Eight participants (7.5%) treated with imeglimin and 11 (10.3%) treated with placebo prematurely discontinued treatment. The main reason for premature treatment discontinuation was withdrawal of consent (Fig. 1).

Baseline characteristics were similar between treatment groups (Table 1) with regard to mean age, diabetes duration, HbA_{1c}, BMI, and eGFR. Mean age was 62.0 years and 100 (46.9%) were elderly (≥65 years). Mean eGFR was 71.31 mL/min/1.73 m^2 and the majority of patients were treatment naive (71.8%).

At week 24, HbA_{1c} had significantly decreased by 0.72% (95% CI −0.86 to −0.58 [7.9 mmol/mol, 95% CI −9.4 to −6.3]) with imeglimin versus a nonsignificant increase of 0.15% (95% CI 0.01 to 0.29 [1.6 mmol/mol, 95% CI 0.1 to 3.2]) with placebo (estimated treatment difference vs. placebo: −0.87%, 95% CI −1.04 to −0.69 [−9.5 mmol/mol, 95% CI −11.4 to −7.5]; $P < 0.0001$) (Fig. 2).

At week 24, HbA_{1c} <7% (53 mmol/mol) was achieved by significantly more patients in the imeglimin group ($n = 38$ of 106 patients; 35.8%) compared with the placebo group ($n = 8$ of 106 patients [7.5%]; $P < 0.0001$). At week 24, a relative decrease of ≥7% from baseline HbA_{1c} was achieved by significantly more patients in the imeglimin group ($n = 61$ of 106 patients; 57.5%) compared with the placebo group ($n = 12$ of 106 patients [11.3%]; $P < 0.0001$).

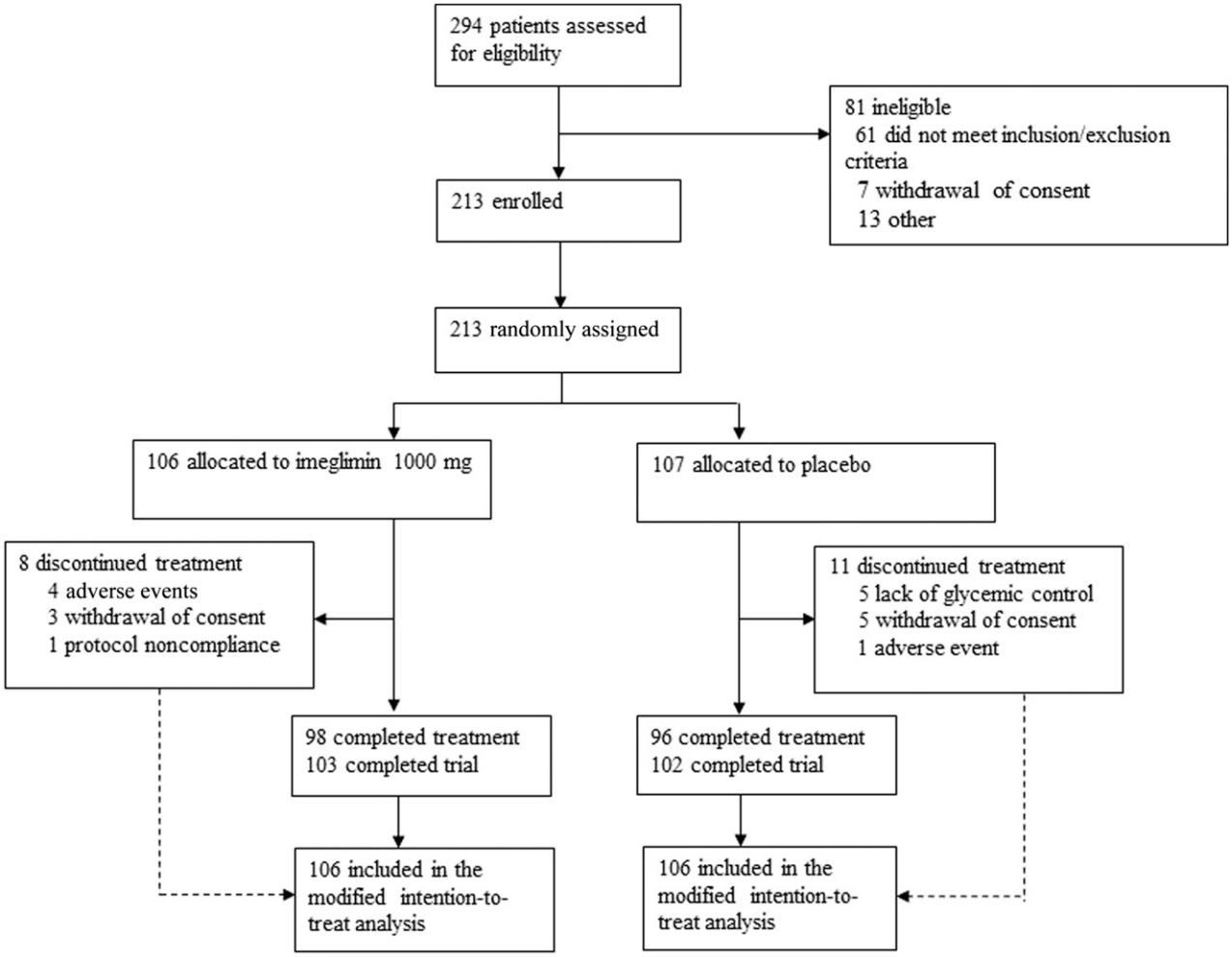

Figure 1—Diagram of trial flow.

The HbA_{1c} decrease was consistent across age-groups. At week 24, HbA_{1c} decreased by 0.70% (95% CI −0.92 to −0.49 [7.7 mmol/mol, 95% CI −10.1 to −5.4]) in patients younger than 65 years and by 0.75% (95% CI −0.96 to −0.54 [8.2 mmol/mol, 95% CI −10.5 to −5.9]) in elderly patients. The HbA_{1c} decrease was also consistent across CKD stage groups. At week 24, HbA_{1c} decreased by 0.33% (95% CI −0.77 to 0.10 [3.6 mmol/mol, 95% CI −8.4 to 1.1]) in patients with stage 1 CKD; by 0.82% (95% CI −0.99 to −0.65 [9.0 mmol/mol, 95% CI −10.8 to −7.1] in patients with stage 2 CKD; and by 0.66% (95% CI −0.93 to −0.40 [7.2 mmol/mol, 95% CI −10.2 to −4.4]) in patients with stage 3 CKD.

In treatment-naive patients, at week 24, HbA_{1c} had significantly decreased by 0.81% (95% CI −0.96 to −0.67 [8.9 mmol/mol, 95% CI −10.5 to −7.3]) with imeglimin versus an increase of 0.06% (95% CI −0.08 to 0.20 [0.7 mmol/mol, 95% CI −0.9 to 2.2]) with placebo (estimated treatment difference vs. placebo: −0.87%, 95% CI −1.07 to −0.67 [−9.5 mmol/mol, 95% CI −11.7 to −7.3]; $P < 0.0001$).

In previously treated patients, at week 24, HbA_{1c} had significantly decreased by 0.51% (95% CI −0.73 to −0.29 [5.6 mmol/mol, 95% CI −8.0 to −3.2]) with imeglimin versus an increase of 0.33% (95% CI 0.09 to 0.56 [3.6 mmol/mol, 95% CI 1.0 to 6.1]) with placebo (estimated treatment difference vs. placebo: −0.84%, 95% CI −1.16 to −0.52 [−9.2 mmol/mol, 95% CI −12.7 to −5.7]; $P < 0.0001$).

Other efficacy parameters are shown in Table 2. FPG and fasting proinsulin/C-peptide ratio were significantly decreased compared with placebo after 24 weeks of treatment, whereas QUICKI and HOMA-β values were significantly increased.

All patients requiring rescue therapy were in the placebo group ($n = 6$; 5.7%). The rescue therapy used was metformin by three patients, dipeptidyl peptidase-4 inhibitor by two patients, and sodium–glucose cotransporter 2 inhibitor (SGLT2-I) by one patient.

No deaths were reported in any of the groups. The proportion of participants reporting any adverse events was similar between groups (Supplementary Table 1). Most reported adverse events were of mild intensity. A total of five patients experienced a serious adverse event during the trial: four (3.8%) in the imeglimin group and one (0.9%) in the placebo group. No patient experienced a serious adverse event considered by the investigator to be related to treatment. There was no difference between groups in term of incidence of gastrointestinal disorders (Supplementary Table 2).

Table 1—Baseline characteristics of the modified intention-to-treat population

	Treatment group		
	Imeglimin 1,000 mg (n = 106)	Placebo (n = 107)	Total (N = 213)
Sex			
Female	17 (16.0)	29 (27.1)	46 (21.6)
Male	89 (84.0)	78 (72.9)	167 (78.4)
Age (years)	62.2 (9.61)	61.9 (10.17)	62.0 (9.87)
Age-group (years)			
<65	54 (50.9)	59 (55.1)	113 (53.1)
≥65	52 (49.1)	48 (44.9)	100 (46.9)
HbA_{1c} (%)	7.99 (0.764)	7.93 (0.682)	7.96 (0.723)
HbA_{1c} (mmol/mol)	64 (8.4)	63 (7.5)	63 (7.9)
Diabetes duration (years)	7.70 (5.59)	7.28 (6.15)	7.49 (5.87)
Previous diabetes therapy			
Treatment naive	76 (71.7)	77 (72.0)	153 (71.8)
SGLT2-I	4 (3.8)	4 (3.7)	8 (3.8)
Another oral hypoglycemic agent	26 (24.5)	26 (24.3)	52 (24.4)
Body weight (kg)	70.98 (14.12)	69.29 (12.85)	70.13 (13.49)
BMI (kg/m^2)	25.66 (4.22)	25.31 (4.12)	25.49 (4.16)
eGFR (MDRD; mL/min/1.73 m^2)	72.49 (13.20)	70.14 (11.79)	71.31 (12.54)
CKD stage			
1	12 (11.3)	7 (6.5)	19 (8.9)
2	73 (68.9)	82 (76.6)	155 (72.8)
3	21 (19.8)	18 (16.8)	39 (18.3)

Data are reported as mean (SD) or n (%).

Hypoglycemia events were reported in three patients (2.8%) in the imeglimin group and one (0.9%) in the placebo group (Supplementary Table 2). Two events of documented hypoglycemia with SMBG values of 59 mg/dL (3.27 mmol/L) and 68 mg/dL (3.77 mmol/L) were reported in one patient in the imeglimin group. This patient already reported two events of documented symptomatic hypoglycemia, with SMBG values of 64 (3.55 mmol/L) and 68 mg/dL (3.77 mmol/L), during the placebo run-in period. No episodes of severe hypoglycemia were reported.

No effect was observed on blood pressure or body weight. Total cholesterol level increased by 3.3% in the imeglimin group compared with the placebo group (P = 0.0439) and LDL cholesterol levels increased by 7.2% (P = 0.0051). These differences were not clinically relevant (Supplementary Table 3). No clinically relevant changes were noted in other safety laboratory assessments, physical examination, or electrocardiograms. In the imeglimin group, six patients (5.7%) had undetectable plasma imeglimin concentrations during the trial, indicating they had not routinely taken the drug.

CONCLUSIONS

In this trial, imeglimin, given at the dose of 1,000 mg twice daily orally for 24 weeks, significantly improved glycemic control in

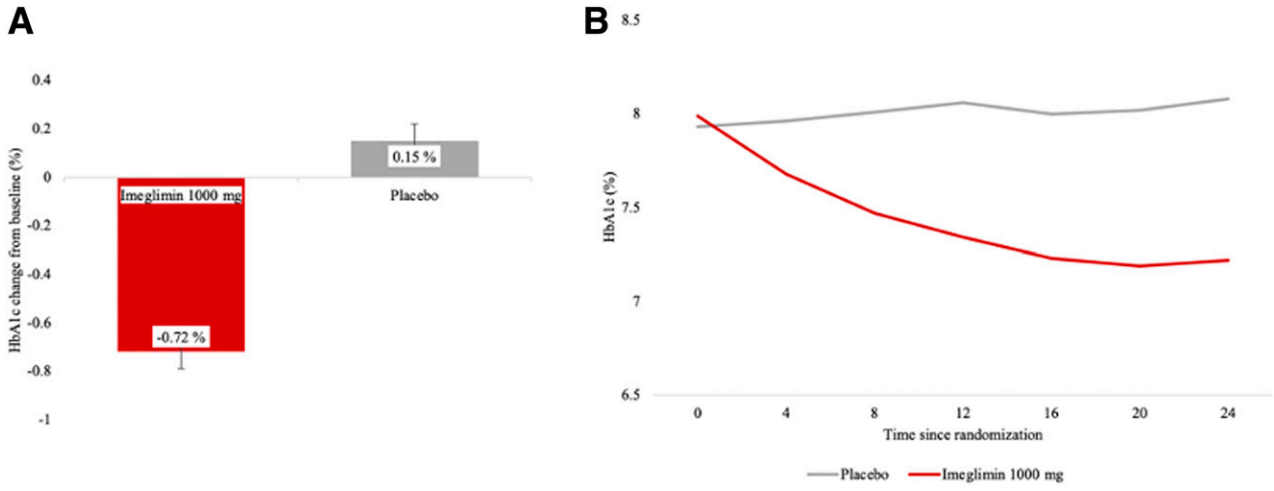

Figure 2—HbA_{1c} reduction with imeglimin compared with placebo. Mean HbA_{1c} after 24 weeks (*A*), change in mean HbA_{1c} by week (*B*).

Table 2—Effects of imeglimin versus placebo on primary and secondary efficacy end points

	Imeglimin	Placebo
HbA_{1c} (%), *n*	106	106
Baseline, mean (SD)	7.99 (0.764)	7.93 (0.684)
Change from baseline, LSM (SE)	−0.72 (0.07)	0.15 (0.07)
Difference vs. placebo, LSM (95% CI)	−0.87 (−1.041, −0.691)	
	$P < 0.0001$	
HbA_{1c} (mmol/mol), *n*	106	106
Baseline, mean (SD)	64 (8.4)	63 (7.5)
Change from baseline, LSM (SE)	−7.9 (0.8)	1.6 (0.8)
Difference vs. placebo, LSM (95% CI)	−9.5 (−11.4, −7.5)	
	$P < 0.0001$	
FPG (mmol/L), *n*	106	106
Baseline, mean (SD)	9.09 (1.587)	8.85 (1.370)
Change from baseline, LSM (SE)	−0.31 (0.16)	0.71 (0.16)
Difference vs. placebo, LSM (95% CI)	−1.03 (−1.357, −0.700)	
	$P < 0.0001$	
Fasting proinsulin-to-insulin ratio, *n*	106	106
Baseline, mean (SD)	0.1542 (0.08168)	0.1816 (0.10990)
Change from baseline, LSM (SE)	−0.0138 (0.0088)	0.0036 (0.0092)
Difference vs. placebo, LSM (95% CI)	−0.0173 (−0.03520, 0.00059)	
	$P = 0.0579$	
Fasting proinsulin-to-c-peptide ratio, *n*	106	106
Baseline, mean (SD)	0.0031 (0.00171)	0.0034 (0.00149)
Change from baseline, LSM (SE)	−0.0003 (0.0002)	0.0002 (0.0002)
Difference vs. placebo, LSM (95% CI)	−0.0005 (−0.00083, −0.00021)	
	$P = 0.0012$	
HOMA-IR, *n*	106	106
Baseline, mean (SD)	2.4700 (1.85368)	2.3298 (1.67803)
Change from baseline, LSM (SE)	0.1961 (0.1775)	0.1321 (0.1835)
Difference vs. placebo, LSM (95% CI)	0.0640 (−0.30471, 0.43268)	
	$P = 0.7325$	
QUICKI, *n*	106	106
Baseline, mean (SD)	0.3504 (0.03949)	0.3546 (0.04408)
Change from baseline, LSM (SE)	0.0017 (0.0033)	−0.0076 (0.0034)
Difference vs. placebo, LSM (95% CI)	0.0093 (0.00283, 0.01569)	
	$P = 0.0050$	
HOMA-β, *n*	106	106
Baseline, mean (SD)	21.4532 (13.30453)	22.4627 (15.89649)
Change from baseline, LSM (SE)	3.5276 (1.6059)	−2.7121 (1.6673)
Difference vs. placebo, LSM (95% CI)	6.2397 (2.96742, 9.51196)	
	$P = 0.0002$	

LSM, least square mean.

Japanese patients with type 2 diabetes. Imeglimin was associated with significant HbA_{1c} and FPG reduction compared with placebo. These findings are consistent with observations in an earlier phase 2, 24-week dose-finding study of imeglimin that included 299 Japanese patients with type 2 diabetes. During this dose-finding trial, the two top doses of imeglimin achieved an HbA_{1c} reduction of 0.94% from baseline versus placebo (95% CI −1.19 to −0.68 [10.3 mmol/mol, 95% CI −13.0 to −7.4]) and 1.00% (95% CI −1.26 to −0.75 [10.9 mmol/mol, 95% CI −13.8 to −8.2]) for the dose of 1,000 mg twice daily and 1,500 mg twice daily, respectively (13). Because a slight increase in the incidence of gastrointestinal adverse events was observed at the top dose of 1,500 mg twice daily (mild events of abdominal pain, nausea, vomiting, and diarrhea), the imeglimin dose of 1,000 mg twice daily was eventually selected for the phase 3 program in Japan.

In the present phase 3 monotherapy study, there was no clear difference between treatment-naive and previously treated patients with respect to placebo-adjusted HbA_{1c} changes. However, the absolute decrease from baseline in the treatment-naive group was greater than in previously treated patients. This suggests the possibility that in some patients who were treatment naive, imeglimin may achieve better efficacy because of its capacity to improve glucose-stimulated insulin secretion. However, we cannot exclude that the total washout period of 12 weeks may not have been sufficient for patients who were previously treated with other agents.

An increase in the proinsulin-to-insulin ratio reflects β-cell dysfunction associated with the onset and progression of type 2 diabetes (15,16). However, fasting insulin concentrations may be affected by both β-cell secretion and hepatic clearance of insulin (17). C-peptide is secreted with insulin at a ratio of 1:1. It has been suggested that the proinsulin-to-C-peptide ratio may be better indicator of distressed β-cells because C-peptide is not cleared by the liver and, therefore, concentrations are less affected by insulin resistance (17). In this study, both proinsulin-to-insulin and proinsulin-to-C-peptide ratios were decreased in the imeglimin group after 24 weeks of treatment compared with placebo, but the decrease was only significant for the proinsulin-to-C-peptide ratio. Furthermore, we observed a significant improvement in HOMA-β values in the imeglimin group, suggesting an improvement in pancreatic β-cell function. These results are consistent with those of previous studies, especially a hyperglycemic clamp study in which the effect of imeglimin on glucose-stimulated insulin secretion was assessed in 33 Caucasian patients with type 2 diabetes and showed an improvement in β-cell function (18).

Insulin sensitivity is another key abnormality underlying the development of type 2 diabetes. In this Japanese patient population with type 2 diabetes, the baseline HOMA-IR was <2.5. Fasting surrogate markers of insulin sensitivity (HOMA-IR and QUICKI) were analyzed in this trial. The QUICKI value was significantly decreased in the imeglimin group compared with the placebo group after 24 weeks of treatment, suggesting an improvement in insulin sensitivity.

In this study, the safety and tolerability profile of imeglimin was similar to the profile observed in the placebo group

and was consistent with the safety profile observed in previous clinical studies. In previous clinical studies, gastrointestinal events have been reported, with a higher incidence at high doses. In the current study, gastrointestinal adverse events were mainly mild in intensity and included abdominal discomfort, diarrhea, and vomiting. There was no increase in the incidence of hypoglycemia, nor in reports of symptomatic hypoglycemia in patients treated with imeglimin. Importantly, although imeglimin potentiates β-cell function and insulin secretion, preclinical and clinical studies have consistently demonstrated that this compound only induces insulin secretion in response to glucose (8,19).

In this study, almost half the patients were elderly (≥65 years) and baseline eGFR measurements also indicated that the majority already had a slight impairment of renal function: 72.8% had stage 2 CKD and 18.3% had stage 3A CKD. However, the efficacy profile was consistent across analyses of subgroups. The patients with stage 1 CKD could not be considered, because the sample size of this subgroup was too small. However, the confidence interval is in the range of other subgroups, suggesting a similar effect in this specific subgroup. Because there is still an unmet medical need for elderly patients and for those with type 2 diabetes and CKD, imeglimin might represent a new and safe treatment option in these populations.

The findings from this study confirm the previously published data on monotherapy (13). Considering the efficacy and safety profile observed in this study, imeglimin is a new promising oral agent for the treatment of Japanese patients with type 2 diabetes, in particular in the elderly population, which represents >50% of the Japanese patients treated for type 2 diabetes (20).

This study had some limitations. It was conducted with Japanese patients only. Because there are differences in diet as well as type 2 diabetes pathophysiology between Japanese and Caucasian populations, the study results may not be readily extrapolated to other ethnic groups without consideration of these points. Indeed, in Japan, approximately half of all patients with diabetes have a genetic predisposition, and insulin secretion is frequently impaired in lean individuals with type 2 diabetes (21). Furthermore, this was a 24-week study, so the long-term safety and efficacy of imeglimin are still unknown and need to be further evaluated. The TIMES is a program including three pivotal studies: TIMES 1 (reported in this article); TIMES 2, assessing the long-term safety and efficacy of imeglimin for 1 year (in monotherapy and in add-on therapy to α-glucosidase inhibitor, biguanide, dipeptidyl peptidase-4 inhibitor, glinide, glucagon-like peptide 1 receptor agonist, SGLT2-I, sulphonylurea, and thiazolidinedione); and TIMES 3, assessing the long-term safety and efficacy of imeglimin as an add-on to insulin for 1 year. TIMES 2 and TIMES 3 will contribute additional information to the efficacy and safety profile of this new compound.

In conclusion, imeglimin monotherapy in Japanese individuals with type 2 diabetes was associated with substantial improvements in glycemic control that were superior to placebo. These results confirm the efficacy, safety, and tolerability of imeglimin monotherapy in Japanese patients with type 2 diabetes.

Duality of Interest. Sumitomo Dainippon Pharma funded the TIMES 1 trial. Poxel was responsible for trial design and data analysis. All authors had full access to all data, were responsible for data interpretation and report writing, and had final responsibility for the decision to submit the manuscript for publication.

J.D., P.F., and C.T. are employees of Poxel. J.-M.G. is a consultant for Poxel. K.U. has served on a scientific advisory board for Poxel and Dainippon Sumitomo Pharma. K.U. has received lecture fees from Takeda, Novo Nordisk, Nippon Boehringer Ingelheim, Mitsubishi Tanabe Pharma, AstraZeneca, MSD, Ono, Sumitomo Dainippon Pharma, Sanofi, and Astellas; research grants from Astellas, Novo Nordisk, Eli Lilly, Nippon Boehringer Ingelheim, Abbott Japan, and MSD; and endowments from Takeda, Astellas, Novo Nordisk, Sumitomo Dainippon Pharma, Sanofi, Kyowa Hakko Kirin, Mitsubishi Tanabe Pharma, Daiichi-Sankyo, and Ono. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. J.D., P.F., C.T., and J.-M.G. contributed to the study design and interpretation of data. J.D. drafted and edited the manuscript. P.F., C.T., and J.-M.G. reviewed the manuscript. K.U. contributed to interpretation of data and reviewed the manuscript. All authors read the manuscript critically and approved the submitted version. J.D. and P.F. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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