Received: 8 January 2025 | Revised: 27 February 2025 | Accepted: 5 March 2025

DOI: 10.1111/dom.16336

ORIGINAL ARTICLE

WILEY

Efficacy and safety of imeglimin add-on to DPP-4 inhibitor therapy in Japanese patients with type 2 diabetes mellitus: An interim analysis of the randomised, double-blind FAMILIAR trial

Kohei Kaku MD[1] | Masashi Shimoda MD[1] | Takeshi Osonoi MD[2] | Masahiro Iwamoto MD[3] | Hideaki Kaneto MD[1]

[1]Department of Diabetes, Endocrinology and Metabolism, Kawasaki Medical School, Okayama, Japan

[2]Nakakinen Clinic, Ibaraki, Japan

[3]Iwamoto Naika Iin, Kagawa, Japan

Correspondence
Kohei Kaku, Department of Diabetes, Endocrinology and Metabolism, Kawasaki Medical School, 577 Matsushima, Kurashiki, Okayama 701-0192, Japan.
Email: kka@med.kawasaki-m.ac.jp

Funding information
Sumitomo Pharma Co., Ltd

Abstract

Aims: The ongoing FAMILIAR trial aims to provide evidence for clinical decision-making and offer a novel treatment paradigm in type 2 diabetes mellitus (T2DM) management. The interim findings of FAMILIAR through Week 24 are reported.

Materials and Methods: FAMILIAR is a multicentre, randomised, double-blind study comparing the efficacy and safety of imeglimin versus placebo in adult Japanese patients with T2DM and inadequate glycaemic control despite dipeptidyl peptidase-4 (DPP-4) inhibitor monotherapy, plus diet/exercise modifications. Patients entered a 24-week double-blind treatment phase (oral imeglimin 1000 mg or placebo twice daily) followed by an 80-week open-label phase (oral imeglimin 1000 mg twice daily). The primary end-point was change in glycated haemoglobin (HbA1c) level from baseline at Week 24. Safety was also monitored.

Results: Overall, 117 patients were randomised (imeglimin, $n = 58$; placebo, $n = 54$; excluded, $n = 5$). The least squares mean (standard error) changes in HbA1c level (baseline to Week 24) for the imeglimin and placebo groups, respectively, were −0.65% (0.11%) and 0.38% (0.11%) in the overall population (group-difference −1.02% [95% confidence interval −1.33%, −0.72%]; $p < 0.001$); −0.47% (0.17%) and 0.32% (0.18%) in patients aged <65 years (−0.79% [−1.29%, −0.29%]; $p = 0.003$); and −0.80% (0.14%) and 0.42% (0.14%) in patients aged ≥65 years (−1.22% [−1.61%, −0.82%]; $p < 0.001$). One patient in the imeglimin group had mild hypoglycaemia; the safety profile was favourable.

Conclusions: Imeglimin represents a potential new treatment option for patients with T2DM and inadequate glycaemic control with DPP-4 inhibitors, including those aged ≥65 years.

Clinical Trial Registration: jRCTs061210082.

KEYWORDS
antidiabetic drug, clinical trial, DPP-IV inhibitor, elderly, type 2 diabetes

1 | INTRODUCTION

Diabetes mellitus, representing a group of metabolic disorders primarily characterised by hyperglycaemia, poses a significant global health challenge.[1] In Japan, the prevalence of type 2 diabetes mellitus (T2DM) has risen dramatically because of rapid socio-economic changes and lifestyle shifts. Recent Japanese epidemiological data suggest that approximately 10 million individuals have T2DM, with an equal number at risk, underscoring the urgency of addressing this growing epidemic.[2]

Achieving and maintaining optimal glycaemic control in patients with T2DM often necessitate long-term pharmacological intervention. However, even patients who initially respond well to monotherapy frequently experience progressive deterioration of glycaemic control over time.[3–6] Current clinical practice guidelines recommend adjusting medication dosages, transitioning to more potent glucose-lowering agents or implementing combination therapies when glycaemic targets are not met.[7] Nevertheless, the evidence base for these strategies remains inadequate, particularly in the Japanese context where standardised protocols for combination therapy have yet to be established. This gap in clinical guidance has intensified interest in novel glucose-lowering agents that might complement or enhance existing treatments.

Imeglimin, a first-in-class oral antidiabetic agent containing tetrahydrotriazine, represents a promising therapeutic advancement with its unique mitochondria-targeted mechanism of action.[8,9] Preclinical investigations have elucidated multifaceted effects of imeglimin, including attenuation of excessive hepatic glucose production, enhancement of skeletal muscle glucose uptake and promotion of glucose-dependent insulin secretion.[9,10] Moreover, studies using rodent models of diabetes demonstrate that imeglimin inhibits β-cell apoptosis, suggesting a potential protective effect on pancreatic function.[11,12] Clinical trials conducted both in Japan and internationally have consistently shown imeglimin to be efficacious, safe and well tolerated in patients with T2DM.[13,14] Furthermore, in Western patients with T2DM, imeglimin has exhibited favourable outcomes in combination with established therapies such as metformin and sitagliptin,[15,16] highlighting its versatility in various treatment combinations for this patient population.

The Trials of Imeglimin for Efficacy and Safety (TIMES) programme, encompassing three pivotal phase 3 clinical trials, was designed to comprehensively evaluate imeglimin in the Japanese population. Of particular note, TIMES 2—a 52-week, open-label, parallel-group study in 714 patients with T2DM—assessed the long-term safety and efficacy of imeglimin (1000 mg twice daily) both as monotherapy and in combination with existing glucose-lowering medications.[17] Study findings indicated high tolerability and efficacy when imeglimin was combined with dipeptidyl peptidase-4 (DPP-4) inhibitors, a drug class known for its glucose-dependent insulin secretagogue effects.[18,19] However, the open-label design and lack of a placebo control in TIMES 2 mean that further investigation is needed to definitively establish the efficacy and safety profile of imeglimin as an add-on therapy to DPP-4 inhibitors.

The demographic shift towards an ageing society in Japan presents additional challenges in diabetes management, as the proportion of older patients with T2DM continues to rise.[20] Despite this trend, there remains a paucity of evidence specifically addressing the needs of older patients with T2DM. In Japan, DPP-4 inhibitors have emerged as one of the most frequently prescribed classes of oral glucose-lowering medications and are often the first-choice treatment for T2DM, owing to their high efficacy and safety in Asian populations and suitability for older patients.[21] Consequently, establishing the long-term efficacy and safety of imeglimin as an adjunct to DPP-4 inhibitor therapy could potentially expand the therapeutic armamentarium available to clinicians managing patients with T2DM and suboptimal glycaemic control. To address these knowledge gaps, the present study was designed to evaluate the efficacy and safety of imeglimin as an add-on therapy to DPP-4 inhibitors in patients with T2DM, with a particular focus on individuals aged ≥65 years who have inadequate glycaemic control despite adherence to recommended diet and exercise regimens and DPP-4 inhibitor monotherapy treatment. The ongoing multicentre FAMILIAR study (eFficacy and sAfety of iMeglimin add-on therapy to DPP-4 Inhibitor in patients with type 2 diabetes melLItus: A Randomized, double-blind, clinical trial) aims to provide robust evidence to inform clinical decision-making and potentially offer a novel treatment paradigm in T2DM management, particularly for the growing cohort of older patients in Japan's ageing population. Here, we report the interim findings of the FAMILIAR study through Week 24.

2 | MATERIALS AND METHODS

2.1 | Study design

This is an ongoing double-blind, placebo-controlled, randomised trial being conducted at 21 study sites in Japan. Patients were randomly assigned 1:1 to the imeglimin or placebo group using a minimization method and the following assignment factors: glycated haemoglobin (HbA1c) level (<8%/≥8% at eligibility testing), age (<65/≥ 65 years), body mass index (BMI; <25/≥25 kg/m^2) and history of oral hypoglycaemic agents (no history/oral hypoglycaemic agent washout). Details of randomisation and blinding are available in the Supplementary Text.

A study timeline illustrating the study phases (oral hypoglycaemic drug washout phase, double-blind phase and open-label phase), study treatments and study assessments is shown in Figure 1A. During the 24-week double-blind phase, patients received either oral imeglimin (1000 mg) or oral placebo twice daily in the morning and evening. During the 80-week open-label phase, all patients received oral imeglimin 1000 mg twice daily. Patient visits were every 4 weeks through Week 52, then every 8 weeks through Week 100, with a final visit during Week 104. HbA1c level was centrally measured by SRL, Inc. (Tokyo, Japan); all other blood tests and urinalysis were conducted at each study site (for a complete list see the Supplementary Text). Adverse events (AEs) and symptoms of hypoglycaemia were monitored throughout the study. Details of the Meal Tolerance Test (MTT)

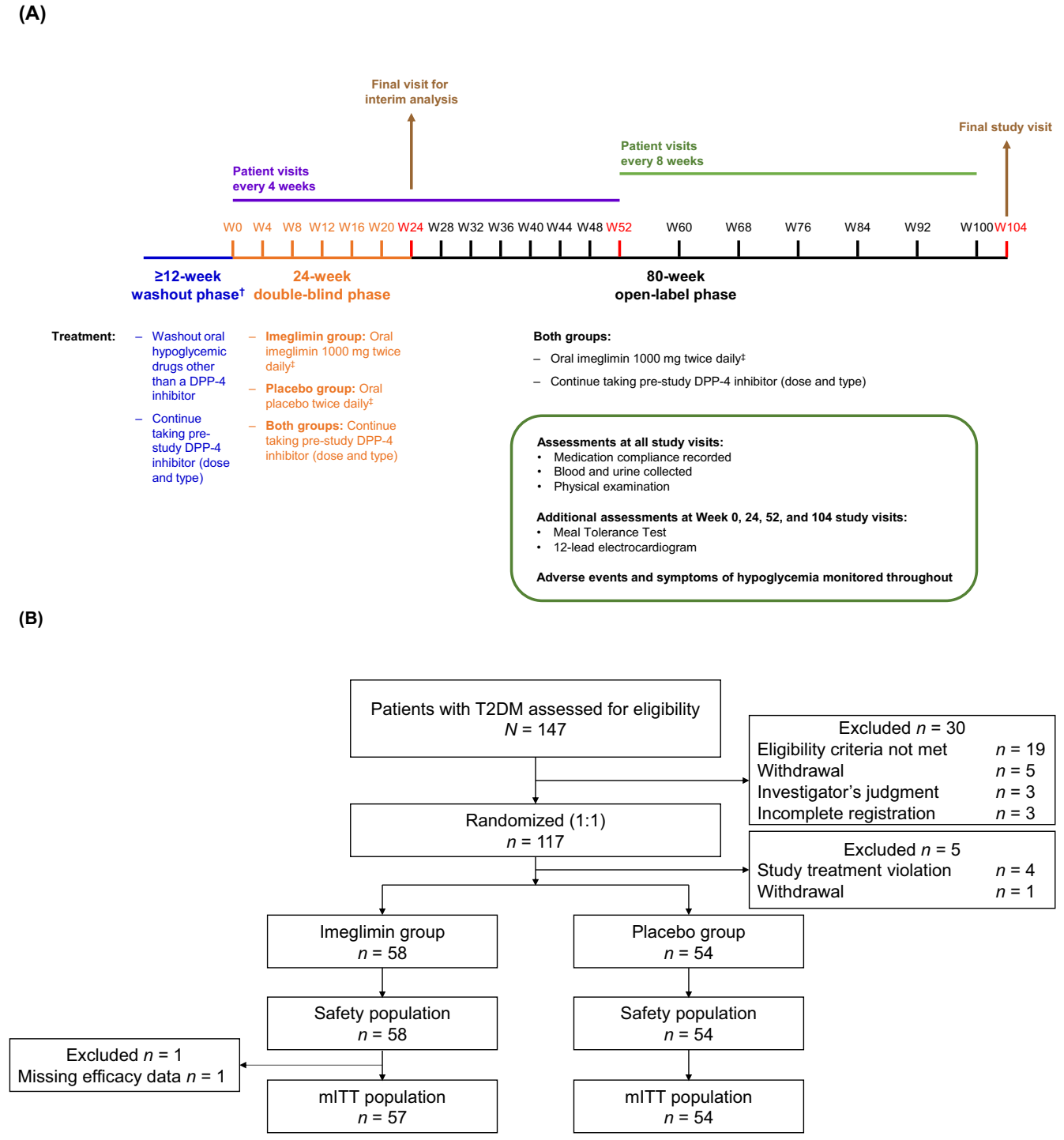

FIGURE 1 Timeline and recruitment of patients in the FAMILIAR study. (A) Study timeline. (B) Patient disposition. †Only patients who were taking an oral hypoglycaemic drug other than a DPP-4 inhibitor. ‡Administered once in the morning and once in the evening. DPP-4, dipeptidyl peptidase-4; FAMILIAR, eFficacy and sAfety of iMeglimin add-on therapy to DPP-4 Inhibitor in patients with type 2 diabetes melLItus: A Randomized, double-blind, clinical trial; mITT, modified intention-to-treat; T2DM, type 2 diabetes mellitus; W, week.

and hypoglycaemic monitoring are available in the Supplementary Text.

The study was conducted in accordance with the principles of the Declaration of Helsinki and the Clinical Trials Act in Japan. The study protocol was approved by the Kawasaki Medical School Clinical Research Review Board, Japan (CRB6200004; reference number, 21002-01). Written informed consent was obtained from all enrolled patients. The study was registered in the Japan Registry of Clinical Trials (jRCTs061210082) and the study protocol will be made available through this registry upon study completion.

2.2 | Study population

Eligible patients were aged ≥20 years, had a diagnosis of T2DM, had inadequate glycaemic control with an HbA1c level between 7.0% and 9.0% despite at least 12 weeks of treatment with a DPP-4 inhibitor as monotherapy and diet/exercise modification, and available HbA1c data collected between 10 and 4 weeks prior to and at the time of the eligibility test with values that fell within 10.0% of the HbA1c value at the eligibility test ([maximum value − minimum value]/maximum value) × 100. Key exclusion criteria were taking two or more oral hypoglycaemic agents other than DPP-4 inhibitors, taking oral hypoglycaemic agents other than DPP-4 inhibitors within the previous 12 weeks and a New York Heart Association functional classification of class III or IV within the year prior to the eligibility test.

2.3 | Study end-points

The primary end-point was the change in HbA1c level from baseline at Week 24 for the overall population and for the subpopulations of patients aged <65 years and ≥65 years. The secondary end-points were HbA1c, glycoalbumin and fasting blood glucose levels and their change from baseline at each study visit; the proportion of patients achieving the HbA1c target level (<7.0%); and the area under the curve (AUC) from 0 to 3 h during the MTT of blood glucose and serum insulin levels and their change from baseline. The safety end-point was the incidence of AEs; AE severity was determined by the investigators. AE information was systematically categorised and analysed based on the MedDRA (ver.26.1) System Organ Class and preferred term classification.

2.4 | Statistical analyses

Based on internal data from TIMES 1[22] and considering that the present study included patients with T2DM and inadequate glycaemic control despite DPP-4 inhibitor use, the difference in change from baseline at Week 24 in HbA1c level between the imeglimin and placebo groups was assumed to be 0.50% with a common SD of 1.00%. It was determined that 86 patients per group were needed to ensure 90% power (5% level of significance). Considering dropouts, the target number of patients was set at 100 per group (total 200 patients). The difference in change in HbA1c levels from baseline at Week 24 between the imeglimin and placebo groups was 0.90% (standard deviation [SD], 0.73%) and 0.75% (0.52%) for patients with T2DM aged <65 years and ≥65 years, respectively. Given the age-specific findings from TIMES 1 and the paucity of evidence for patients aged ≥65 years, this study included subgroup analyses by age (<65/≥65 years). Assuming that approximately half of all enrolled patients would fall into each age group and using a ratio of 1:1 between the imeglimin and placebo groups and the same SD as the primary analysis (1.00%) for both groups, a difference of 0.50% between the groups would be detectable at 71% power (5% level of significance) with 50 patients per group.

The modified intention-to-treat (mITT) population included patients who received the study treatment at least once after randomisation and had HbA1c values at baseline and at least one time point after receiving the study treatment. The safety population included all patients who were administered the study treatment at least once after randomisation.

Categorical variables are summarised using frequency and proportion, and continuous variables are summarised using descriptive statistics. The primary end-point was evaluated using the mITT population and a mixed-effects model for repeated measures with fixed effects for the assignment group, visit and interaction between group and visit. Baseline HbA1c value was used as the covariate. The least squares mean (LSM) difference in change from baseline at Week 24 in HbA1c value, its 95% confidence interval (CI) and the *p*-value for between-group comparisons (imeglimin versus placebo) were calculated using mixed-effects models for repeated measures. The superiority of imeglimin versus placebo was tested using a closed procedure in the following order: overall, subgroup aged ≥65 years, and subgroup aged <65 years. Logistic regression analysis with baseline HbA1c values as covariates was used to compare the percentage of patients in the imeglimin and placebo groups who achieved HbA1c targets of <7.0% at Week 24. Missing values were not imputed. Two-sided *p*-values <0.05 were considered statistically significant. Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

3.1 | Patients

Between 22 June 2022 and 1 August 2023, 117 patients were randomly assigned to either the imeglimin ($n = 58$) or placebo ($n = 54$) group (Figure 1B). The data cut-off for this interim analysis was when the last enrolled patient completed 24 weeks of observation (28 December 2023). In the imeglimin and placebo groups, 58 and 54 patients, respectively, were included in the safety population, and 57 and 54 patients, respectively, were included in the mITT population.

Baseline demographic and patient characteristics are shown in Table 1. Patient characteristics in the imeglimin and placebo groups were generally similar. The mean (standard deviation [SD]) age was 66.8 (11.3) years in the imeglimin group and 65.8 (10.2) years in the placebo group; respective mean (SD) body mass index was 23.8 (3.4) kg/m^2 and 23.5 (3.3) kg/m^2. There was a lower proportion of male patients in the imeglimin group (47.4%) compared with the placebo group (63.0%). The proportion of patients who underwent a washout period of oral glucose-lowering therapies was 26.3% and 20.4% in the imeglimin and placebo groups, respectively. The most common previously used glucose-lowering therapy besides DPP-4 inhibitors was a biguanide (imeglimin, 40.4%; placebo, 31.5%). Baseline mean (SD) HbA1c value was 7.35% (0.64%) for the imeglimin group and 7.38% (0.71%) for the placebo group; respective baseline fasting blood glucose levels were 153.7 (26.0) mg/dL and 151.2 (26.6) mg/dL (Table 2).

TABLE 1 Demographic and baseline characteristics in the modified intention-to-treat population.

	Imeglimin $N = 57$	Placebo $N = 54$
Age, years		
Mean (SD)	66.8 (11.3)	65.8 (10.2)
<65 years, *n* (%)	24 (42.1)	23 (42.6)
≥65 years, *n* (%)	33 (57.9)	31 (57.4)
Sex, *n* (%)		
Male	27 (47.4)	34 (63.0)
Female	30 (52.6)	20 (37.0)
Diabetes duration, years		
Mean (SD)	9.8 (6.9)	9.4 (7.2)
Body weight, kg		
Mean (SD)	61.2 (12.8)	63.0 (12.4)
BMI, kg/m^2		
Mean (SD)	23.8 (3.4)	23.5 (3.3)
<25 kg/m^2, *n* (%)	42 (73.7)	38 (70.4)
≥25 kg/m^2, *n* (%)	15 (26.3)	16 (29.6)
Washout of oral glucose-lowering therapies, *n* (%)	15 (26.3)	11 (20.4)
Previous glucose-lowering therapies, *n* (%)	57 (100.0)	54 (100.0)
α-glucosidase inhibitors	7 (12.3)	5 (9.3)
DPP-4 inhibitors	57 (100)	54 (100)
Rapid-acting insulin secretagogues	5 (8.8)	2 (3.7)
Biguanides	23 (40.4)	17 (31.5)
SGLT2 inhibitors	7 (12.3)	4 (7.4)
Sulfonylureas	1 (1.8)	1 (1.9)
Thiazolidinediones	0 (0)	1 (1.9)
GLP-1 receptor agonists	2 (3.5)	1 (1.9)
Insulin	1 (1.8)	2 (3.7)

Abbreviations: BMI, body mass index; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; SD, standard deviation; SGLT2, sodium-glucose cotransporter 2.

3.2 | Change in HbA1c

At Week 24, the LSM (standard error [SE]) change in HbA1c level from baseline demonstrated a reduction in the imeglimin group (−0.65% [0.11%]) and an increase in the placebo group (0.38% [0.11%]) (overall population) (Figure 2A). The LSM (95% CI) difference in HbA1c level for the imeglimin group versus placebo was −1.02% (−1.33%, −0.72%), which was significant ($p < 0.001$) (Figure 2A and Table 2). Regarding the LSM (SE) change in HbA1c level from baseline at Week 24 by age subgroups, there was a numerically greater decrease from baseline in patients aged ≥65 years than in those aged <65 years among those who received imeglimin double-blind treatment (−0.80% [0.14%]; $p < 0.001$ and −0.47% [0.17%]; $p = 0.009$, respectively), and a numerically greater increase among those who received placebo (0.42% [0.14%]; $p = 0.003$ and 0.32% [0.18%]; $p = 0.08$, respectively) (Figure 2A). The LSM (95% CI) difference in the HbA1c level for the imeglimin group versus the placebo group was −0.79% (−1.29%, −0.29%) among patients aged <65 years and −1.22% (−1.61%, −0.82%) among those aged ≥65 years; the difference was significant for both subgroups ($p = 0.003$ and $p < 0.001$, respectively) (Figure 2A and Table 2). In the overall population, the mean HbA1c level was reduced over time in the imeglimin group, but not in the placebo group (Figure 2B–D). Subgroup analysis demonstrated that differences in sex and BMI (<25 kg/m^2/≥25 kg/m^2) did not affect the results of the primary end-point (Table S1).

3.3 | Secondary end-points

During the MTT, the AUC of change in blood glucose (difference vs. placebo LSM change [95% CI] −131.75 mg h/dL [−182.38, −81.11]; $p < 0.001$) and of change in serum insulin (15.53 μIU h/mL [3.05, 28.00]; $p = 0.015$) were significantly different between the imeglimin and placebo groups (Table 2). The mean (SD) of AUC change from baseline at Week 24 in blood glucose was −75.59 (98.30) mg·h/dL and 56.24 (154.11) mg·h/dL for the imeglimin and placebo groups, respectively, and that of AUC change in serum insulin was a respective 9.55 (37.91) μIU·h/mL and − 5.84 (23.21) μIU·h/mL. The results of the subgroup analysis by age were generally similar to those in the overall population, with one exception (Table 2). LSM (95% CI) differences in the imeglimin group versus placebo at Week 24 were significant for patients aged ≥65 years (as in the overall population) but not for those aged <65 years for the secondary end-point of AUC change in serum insulin (≥65 years: 19.44 μIU h/mL [5.44, 33.43]; $p = 0.007$; <65 years: 9.38 μIU h/mL [−13.33, 32.08]; $p = 0.41$). Changes in blood glucose and serum insulin in the MTT are shown in Figures S1A–C and S2A–C, respectively.

At Week 24, the proportion of patients achieving an HbA1c level <7.0% in the imeglimin and placebo groups, respectively, was 64.0% (32/50) and 33.3% (17/51) among the overall population (odds ratio, 5.66; 95% CI, 2.03, 15.78; $p = 0.001$), 47.8% (11/23) and 31.8% (7/22) among those aged <65 years (odds ratio, 3.06; 95% CI, 0.62, 15.24; $p = 0.172$), and 77.8% (21/27) and 34.5% (10/29) among those aged ≥65 years (odds ratio, 12.59; 95% CI, 2.69, 58.95; $p = 0.001$).

In the overall population, LSM (95% CI) differences in the imeglimin versus placebo groups at Week 24 were significant for fasting blood glucose (−32.1 mg/dL [−47.2, −17.0]; $p < 0.001$) and glycoalbumin (−4.42% [−5.82%, −3.03%]; $p < 0.001$). Changes in secondary end-points are shown in Figure S3A–D. The mean (SD) fasting serum insulin (serum insulin at baseline of MTT) was 7.90 (4.90) μIU/mL and 7.17 (4.43) μIU/mL for the imeglimin and placebo groups, respectively, at Week 0 ($p = 0.41$), and 8.48 (6.15) μIU/mL and 6.34 (4.50) μIU/mL at Week 24 ($p = 0.06$).

3.4 | Safety

The most commonly reported AEs during the 24-week double-blind period are shown in Table 3. In the imeglimin group, all reported AEs were mild or moderate in severity, with the majority being mild. In the placebo

TABLE 2 Effects of imeglimin and placebo in combination with DPP-4 inhibitor on primary and key secondary efficacy end-points at Week 24.

	Overall		<65 years		≥65 years	
	Imeglimin	Placebo	Imeglimin	Placebo	Imeglimin	Placebo
	N = 57	*N* = 54	*n* = 24	*n* = 23	*n* = 33	*n* = 31
HbA1c, %						
n at Week 24	50	51	23	22	27	29
Baseline, mean (SD)	7.35 (0.64)	7.38 (0.71)	7.45 (0.63)	7.48 (0.87)	7.29 (0.64)	7.31 (0.57)
Week 24, mean (SD)	6.70 (0.57)	7.76 (1.21)	6.92 (0.60)	7.83 (1.31)	6.51 (0.47)	7.71 (1.15)
Change from baseline at Week 24, mean (SD)	−0.65 (0.57)	0.38 (0.94)	−0.47 (0.53)	0.32 (1.05)	−0.80 (0.56)	0.42 (0.87)
Difference versus placebo, LSM[a] (95% CI)	−1.02 (−1.33, −0.72)		−0.79 (−1.29, −0.29)		−1.22 (−1.61, −0.82)	
	$p < 0.001$		$p = 0.003$		$p < 0.001$	
AUC_{0-3h} in the MTT						
Blood glucose, mg·h/dL						
n at Week 24	46	44	21	18	25	26
Baseline, mean (SD)	697.19 (125.09)	661.92 (110.71)	692.17 (132.13)	652.03 (126.86)	700.85 (121.67)	669.25 (98.60)
Week 24, mean (SD)	627.20 (110.95)	723.02 (165.89)	623.01 (117.96)	684.78 (105.57)	630.72 (107.03)	749.50 (194.86)
Change from baseline at Week 24, mean (SD)	−75.59 (98.30)	56.24 (154.11)	−71.41 (114.41)	29.18 (103.88)	−79.11 (84.75)	74.98 (180.60)
Difference versus placebo, LSM[a] (95% CI)	−131.75 (−182.38, −81.11)		−98.27 (−163.52, −33.03)		−154.92 (−230.94, −78.89)	
	$p < 0.001$		$p = 0.004$		$p < 0.001$	
Serum insulin, μIU·h/mL						
n at Week 24	46	44	21	18	25	26
Baseline, mean (SD)	85.95 (40.89)	80.05 (46.35)	93.15 (46.01)	78.23 (53.77)	80.72 (36.56)	81.40 (40.87)
Week 24, mean (SD)	97.57 (54.12)	71.31 (43.34)	106.00 (63.74)	72.02 (58.51)	90.49 (44.64)	70.83 (30.04)
Change from baseline at Week 24, mean (SD)	9.55 (37.91)	−5.84 (23.21)	11.12 (46.57)	1.79 (23.20)	8.23 (29.73)	−11.12 (22.13)
Difference versus placebo, LSM[a] (95% CI)	15.53 (3.05, 28.00)		9.38 (−13.33, 32.08)		19.44 (5.44, 33.43)	
	$p = 0.015$		$p = 0.41$		$p = 0.007$	
Fasting blood glucose, mg/dL						
n at Week 24	47	45	21	19	26	26
Baseline, mean (SD)	153.7 (26.0)	151.2 (26.6)	155.3 (29.9)	150.7 (34.2)	152.6 (23.1)	151.5 (19.7)
Week 24, mean (SD)	136.2 (21.1)	166.4 (51.2)	140.5 (20.9)	167.8 (54.0)	132.7 (21.0)	165.4 (50.1)
Change from baseline at Week 24, mean (SD)	−16.9 (22.9)	15.3 (49.5)	−12.9 (25.7)	15.5 (51.5)	−20.2 (20.2)	15.1 (49.0)
Difference versus placebo, LSM[a] (95% CI)	−32.1 (−47.2, −17.0)		−28.3 (−52.3, −4.4)		−35.1 (−55.2, −15.1)	
	$p < 0.001$		$p = 0.022$		$p < 0.001$	

(Continues)

TABLE 2 (Continued)

	Overall		<65 years		≥65 years	
	Imeglimin	Placebo	Imeglimin	Placebo	Imeglimin	Placebo
	N = 57	*N* = 54	*n* = 24	*n* = 23	*n* = 33	*n* = 31
Glycoalbumin, %						
n at Week 24	50	50	23	22	27	28
Baseline, mean (SD)	20.33 (2.92)	19.93 (3.05)	20.03 (2.61)	19.93 (3.73)	20.55 (3.15)	19.93 (2.49)
Week 24, mean (SD)	17.54 (3.12)	21.61 (5.30)	17.92 (2.52)	21.53 (6.05)	17.21 (3.56)	21.67 (4.74)
Change from baseline at Week 24, mean (SD)	−2.83 (2.50)	1.59 (4.31)	−2.05 (1.74)	1.44 (5.24)	−3.50 (2.87)	1.71 (3.52)
Difference versus placebo, LSM[a] (95% CI)	−4.42 (−5.82, −3.03)		−3.48 (−5.81, −1.16)		−5.21 (−6.94, −3.48)	
	p < 0.001		*p* = 0.004		*p* < 0.001	

Abbreviations: AUC, area under the curve; CI, confidence interval; DPP-4, dipeptidyl peptidase 4; HbA1c, glycated haemoglobin; LSM, least squares mean; MTT, meal tolerance test; SD, standard deviation.
[a]Adjusted by assignment group, time of visit, assignment group × time of visit and baseline value.

group, all reported AEs were mild in severity. There were no major differences in the safety findings between the two age groups. Details of reported AEs in the overall population and patients aged <65 and ≥65 years are provided in Tables S2–S4. In the imeglimin group, hypoglycaemia was only reported in one patient, and it was considered mild.

4 | DISCUSSION

This interim analysis demonstrated significant improvements in glycaemic control after 24 weeks of treatment when imeglimin was added to DPP-4 inhibitor therapy in patients with T2DM who had inadequate glycaemic control. HbA1c levels were markedly reduced in the imeglimin group compared with the placebo group across all age groups, including older patients; the safety profile was favourable and similar between patients aged <65 years and ≥65 years.

Results from the FAMILIAR trial as well as other ongoing clinical trials of imeglimin are expected to further enhance the understanding of how imeglimin best fits into current treatment practice for patients with T2DM.[23] The present interim analysis highlights the potential utility of imeglimin as an add-on therapy for patients with T2DM and inadequate glycaemic control with DPP-4 inhibitors alone. The findings of this double-blind, placebo-controlled trial corroborate and validate the results of the open-label TIMES 2 study that reported a net reduction of 0.92% in the HbA1c level in adult patients who received DPP-4 inhibitor in combination with imeglemin.[17] While TIMES 2 included patients aged ≥20 years, it did not fully establish the efficacy of imeglimin specifically in older patients. The present study clearly demonstrates the effectiveness of imeglimin in older patients. Notably, for both the overall population and among patients aged ≥65 years, the achievement rate of an HbA1c level <7.0% was higher in the imeglimin group compared with the placebo group, suggesting that adding imeglimin to DPP-4 inhibitor therapy can safely achieve HbA1c levels <7.0%, even in older patients. The recent finding that imeglimin enhanced both glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide secretion is particularly interesting.[24] Given that DPP-4 inhibitors work by preventing the degradation of incretin hormones, this complementary mechanism may explain the robust glycaemic response observed with this combination therapy. The dual effect of imeglimin on incretin secretion and DPP-4 inhibitors on incretin degradation appears to create a synergistic effect that could explain the superior efficacy of this combination. The MTT results show that imeglimin is effective for improving postprandial glucose levels. While postprandial glucose control is generally considered important in diabetes management, its direct relationship with disease progression and vascular complications is complex and not fully established. Some studies suggest that postprandial hyperglycaemia may be an independent risk factor for cardiovascular disease,[25–28] but others indicate that overall glycaemic control, as measured by HbA1c level, might be a more reliable predictor of long-term outcomes. Further research is needed to fully elucidate the specific impact of improving postprandial glucose on preventing complications in T2DM. Nevertheless, the observed improvement in postprandial glucose levels with imeglimin may contribute to overall

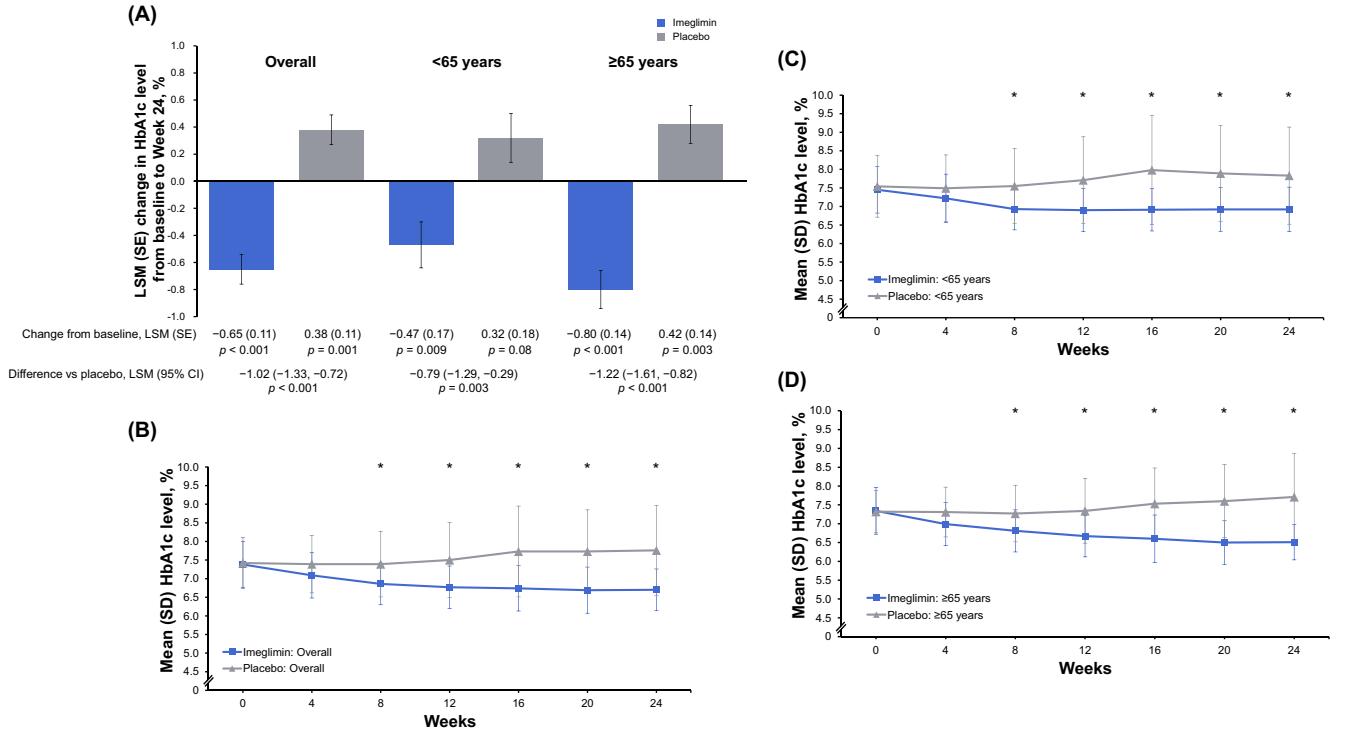

FIGURE 2 Change in HbA1c level. (A) Change from baseline at Week 24. (B) Change over time (baseline to Week 24), overall population. (C) Change over time (baseline to Week 24), population aged <65 years. (D) Change over time (baseline to Week 24), population aged ≥65 years. * indicates $p < 0.05$ for the intergroup comparison at each time point. CI, confidence interval; HbA1c, glycated haemoglobin; LSM, least squares mean; SD, standard deviation; SE, standard error.

TABLE 3 Overview of adverse events during the 24-week double-blind treatment period.

	Imeglimin			Placebo		
	Overall	<65 years	≥65 years	Overall	<65 years	≥65 years
	N = 58	*n* = 24	*n* = 34	*N* = 54	*n* = 23	*n* = 31
COVID-19	5 (8.6)	3 (12.5)	2 (5.9)	3 (5.6)	0	3 (9.7)
Nasopharyngitis	3 (5.2)	2 (8.3)	1 (2.9)	3 (5.6)	2 (8.7)	1 (3.2)
Abdominal discomfort	3 (5.2)	1 (4.2)	2 (5.9)	0	0	0
Loss of appetite	2 (3.4)	0	2 (5.9)	0	0	0
Insomnia	2 (3.4)	1 (4.2)	1 (2.9)	0	0	0
Nausea	2 (3.4)	1 (4.2)	1 (2.9)	2 (3.7)	0	2 (6.5)
Back pain	2 (3.4)	0	2 (5.9)	2 (3.7)	0	2 (6.5)
Ligament sprain	2 (3.4)	2 (8.3)	0	0	0	0
Dizziness	1 (1.7)	1 (4.2)	0	2 (3.7)	0	2 (6.5)
Headache	1 (1.7)	1 (4.2)	0	2 (3.7)	1 (4.3)	1 (3.2)
Constipation	1 (1.7)	0	1 (2.9)	2 (3.7)	1 (4.3)	1 (3.2)
Diarrhoea	1 (1.7)	0	1 (2.9)	2 (3.7)	0	2 (6.5)
Cystitis	0	0	0	4 (7.4)	1 (4.3)	3 (9.7)
Lymphadenitis	0	0	0	2 (3.7)	2 (8.7)	0
Dental caries	0	0	0	2 (3.7)	0	2 (6.5)
Hypoglycaemia	1 (1.7)	1 (4.2)	0	0	0	0

Note: The list of specific adverse events identifies those for which two or more occurrences were reported in either or both the imeglimin and placebo groups, and hypoglycaemia. Data are shown as the number of patients (%). Adverse event information was systematically categorised and analysed based on the MedDRA (ver.26.1) preferred term classification.
Abbreviation: COVID-19, coronavirus disease 2019.

glycaemic control, which is particularly relevant for older patients, who often exhibit postprandial hyperglycaemia.

Imeglimin has a novel mechanism of glucose-dependent insulin secretion different from that of DPP-4 inhibitors,[8] potentially providing complementary benefits when used in combination. Additionally, recent preclinical studies and a small clinical study have suggested the potential for imeglimin to exert extra-pancreatic effects that may contribute to glucose control. For example, in addition to enhancing glucose-induced insulin secretion and inhibiting β-cell apoptosis,[12,29] imeglimin is reported to reduce the oxygen consumption rate, activate AMP-activated protein kinase and upregulate genes encoding proteins involved in mitochondrial function in mouse primary hepatocytes.[30] A recent study by Awazawa et al. reported that imeglimin suppresses hepatic glucose production, inhibits the whitening of brown adipose tissue and improves gut microbiota composition in obese mice fed a high-fat diet.[10] Other publications have suggested that hepatic glucose production contributes to insulin sensitivity associated with adipocyte browning.[31] Sanada et al. recently reported that imeglimin had anti-atherosclerotic effects in ApoE knockout mice treated with streptozotocin, demonstrating reduced aortic plaque formation in mice treated with imeglimin versus controls.[32] Finally, a small study assessed endothelial function in 12 patients with T2DM.[33] The study reported improved postprandial flow-mediated dilation (an assessment of endothelial function) after 3 months of imeglimin treatment compared with baseline. While these studies provide promising evidence for extra-pancreatic effects for imeglimin, further clinical research is needed to fully elucidate the mechanisms.

This study has some limitations that should be considered when interpreting the findings. First, it was conducted in Japan, potentially limiting the generalizability of the findings to other populations. Second, the expected enrollment of 100 patients per group was not reached, with only approximately half of the expected number of patients being enrolled. The lower-than-expected enrollment was primarily due to overly stringent eligibility criteria and a lower prevalence of eligible patients than initially estimated. Despite extending the enrollment period, it was determined that reaching the target sample size within a reasonable timeframe was not feasible. Despite the lower-than-expected enrollment, statistically significant differences were observed between the imeglimin and placebo groups.

5 | CONCLUSIONS

Imeglimin combined with DPP-4 inhibitors significantly reduced HbA1c levels at 24 weeks compared with placebo in patients with T2DM with inadequate glycaemic control despite diet/exercise modifications and DPP-4 inhibitor medication. One possible reason for the observed reduction in HbA1c levels is that imeglimin stimulates postprandial serum insulin secretion and suppresses the increase in postprandial blood glucose levels normally seen in these patients. Imeglimin is a new potential treatment option for patients with T2DM as an add-on to DPP-4 inhibitors and was similarly effective in the overall population and in patients aged ≥65 years. Further studies are needed to clarify the effectiveness and safety of imeglimin in Japanese patients with T2DM, including elderly patients.

AUTHOR CONTRIBUTIONS

Kohei Kaku: Conceptualization; methodology; investigation; resources; writing—original draft; writing—review and editing; visualization; supervision; project administration; funding acquisition. **Masashi Shimoda**: Resources; writing—original draft; writing—review and editing; visualization; supervision; project administration; funding acquisition. **Takeshi Osonoi**: Resources; writing—review and editing. **Masahiro Iwamoto**: Resources; writing—review and editing. **Hideaki Kaneto**: Resources; writing—review and editing.

ACKNOWLEDGEMENTS

The authors thank Sarah Bubeck, PhD, of Edanz (www.edanz.com), for providing medical writing support, which was funded by Sumitomo Pharma Co., Ltd., in accordance with Good Publication Practice guidelines (https://www.ismpp.org/gpp-2022).

FUNDING INFORMATION

This study was funded by Sumitomo Pharma Co., Ltd. The company provided the investigational drug and was involved in the study and statistical analysis planning, but not in the data management, statistical analysis, monitoring or auditing of the study.

CONFLICT OF INTEREST STATEMENT

Kohei Kaku has received honoraria from Astellas Pharma Inc., Kowa Company, Ltd., Sanwa Kagaku Kenkyusho Co., Ltd., Sumitomo Pharma Co., Ltd., Novo Nordisk Pharma Ltd., Nippon Boehringer Ingelheim Co., Ltd., Eli Lilly Japan K.K., Taisho Pharmaceutical Holdings Co., Ltd., Mitsubishi Tanabe Pharma Corporation, and MSD K.K.; consulting fees from Sanwa Kagaku Kenkyusho Co., Ltd.; and scholarship donations from Nippon Boehringer Ingelheim Co., Ltd. and Taisho Pharmaceutical Holdings Co., Ltd. Masashi Shimoda has no conflicts of interest to disclose. Takeshi Osonoi has received honoraria and grants from Sumitomo Pharma Co., Ltd. Masahiro Iwamoto has received grants from Sumitomo Pharma Co., Ltd. and Eli Lilly Japan K.K. Hideaki Kaneto has received honoraria from Eli Lilly Japan K.K., Nippon Boehringer Ingelheim Co., Ltd., Sanofi K.K., Novo Nordisk Pharma Ltd., Sumitomo Pharma Co., Ltd., Daiichi Sankyo Company Limited, Mitsubishi Tanabe Pharma Corporation, MSD K.K. and Astellas Pharma Inc.; grants from Taisho Pharmaceutical Holdings Co., Ltd., Sumitomo Pharma Co., Ltd. and Nippon Boehringer Ingelheim Co., Ltd.; and scholarship donations from Eli Lilly Japan K.K., Nippon Boehringer Ingelheim Co., Ltd., Sanofi K.K., Novo Nordisk Pharma Ltd., Sumitomo Pharma Co., Ltd., Daiichi Sankyo Company Limited, Mitsubishi Tanabe Pharma Corporation, Kowa Co., Ltd., Takeda Pharmaceutical Co., Ltd., MSD K.K. and Abbott Japan LLC.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16336.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Kohei Kaku https://orcid.org/0000-0003-1574-0565
Masashi Shimoda https://orcid.org/0000-0002-4223-9613

REFERENCES

1. ElSayed NA, Aleppo G, Aroda VR, et al. 2. Classification and diagnosis of diabetes: standards of care in diabetes-2023. *Diabetes Care*. 2023; 46(Suppl 1):S19-S40.
2. Ministry of Health, Labour and Welfare. Results of the National Health and Nutrition Survey, 2016. Accessed October 8, 2024. https://www.mhlw.go.jp/stf/houdou/0000177189.html
3. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med*. 2006;355: 2427-2443.
4. Turner RC, Cull CA, Frighi V, Holman RR, UK Prospective Diabetes Study (UKPDS) Group. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). *Jama*. 1999;281: 2005-2012.
5. Wright A, Cull C, Holman R, et al. United Kingdom Prospective Diabetes Study 24: a 6-year, randomized, controlled trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. *Ann Intern Med*. 1998;128:165-175.
6. 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.
7. Araki E, Goto A, Kondo T, et al. Japanese clinical practice guideline for diabetes 2019. *J Diabetes Investig*. 2020;11:1020-1076.
8. 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.
9. 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.
10. Awazawa M, Matsushita M, Nomura I, et al. Imeglimin improves systemic metabolism by targeting brown adipose tissue and gut microbiota in obese model mice. *Metabolism*. 2024;153:155796.
11. Hallakou-Bozec S, Kergoat M, Moller DE, Bolze S. Imeglimin preserves islet beta-cell mass in type 2 diabetic ZDF rats. *Endocrinol Diabetes Metab*. 2021;4:e00193.
12. Sanada J, Obata A, Fushimi Y, et al. Imeglimin exerts favorable effects on pancreatic β-cells by improving morphology in mitochondria and increasing the number of insulin granules. *Sci Rep*. 2022;12: 13220.
13. Pirags V, Lebovitz H, Fouqueray P. Imeglimin, a novel glimin oral antidiabetic, exhibits a good efficacy and safety profile in type 2 diabetic patients. *Diabetes Obes Metab*. 2012;14:852-858.
14. 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.
15. 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.
16. 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.
17. Dubourg J, Fouqueray P, Quinslot D, Grouin JM, Kaku K. 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. *Diabetes Obes Metab*. 2022;24:609-619.
18. Aschner P, Kipnes MS, Lunceford JK, et al. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care*. 2006;29:2632-2637.
19. Charbonnel B, Karasik A, Liu J, Wu M, Meininger G, Sitagliptin Study 020 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. *Diabetes Care*. 2006;29:2638-2643.
20. Ministry of Health, Labour and Welfare. National Health and Nutrition Survey, 2016. Accessed September 18, 2024. https://www.mhlw.go.jp/file/04-Houdouhappyou-10904750-Kenkoukyoku-Gantaisakukenkouzoushinka/kekkagaiyou_7.pdf
21. Bouchi R, Sugiyama T, Goto A, et al. Retrospective nationwide study on the trends in first-line antidiabetic medication for patients with type 2 diabetes in Japan. *J Diabetes Investig*. 2022;13:280-291.
22. Dubourg J, Fouqueray P, Thang C, Grouin JM, Ueki K. 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. *Diabetes Care*. 2021;44:952-959.
23. Nomoto H, Takahashi A, Nakamura A, et al. Add-on imeglimin versus metformin dose escalation regarding glycemic control in patients with type 2 diabetes treated with a dipeptidyl peptidase-4 inhibitor plus low-dose metformin: study protocol for a multicenter, prospective, randomized, open-label, parallel-group comparison study (MEGMI study). *BMJ Open Diabetes Res Care*. 2022;10:e002988.
24. Usui R, Hamamoto Y, Imura M, et al. Differential effects of imeglimin and metformin on insulin and incretin secretion-an exploratory randomized controlled trial. *Diabetes Obes Metab*. 2025;27: 856-865.
25. DECODE Study Group, the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med*. 2001;161:397-405.
26. Cavalot F, Petrelli A, Traversa M, et al. Postprandial blood glucose is a stronger predictor of cardiovascular events than fasting blood glucose in type 2 diabetes mellitus, particularly in women: lessons from the San Luigi Gonzaga Diabetes Study. *J Clin Endocrinol Metab*. 2006;91: 813-819.
27. Node K, Inoue T. Postprandial hyperglycemia as an etiological factor in vascular failure. *Cardiovasc Diabetol*. 2009;8:23.
28. Kataoka Y, Yasuda S, Asaumi Y, et al. Long-term effects of lowering postprandial glucose level on cardiovascular outcomes in early-stage diabetic patients with coronary artery disease: 10-year post-trial follow-up analysis of the DIANA study. *J Diabetes Complications*. 2023;37:108469.
29. Fauzi M, Murakami T, Yabe D, Inagaki N. Current understanding of imeglimin action on pancreatic beta-cells: involvement of mitochondria and endoplasmic reticulum homeostasis. *J Diabetes Investig*. 2023;14:186-188.
30. Hozumi K, Sugawara K, Ishihara T, Ishihara N, Ogawa W. Effects of imeglimin on mitochondrial function, AMPK activity, and gene expression in hepatocytes. *Sci Rep*. 2023;13:746.
31. Casteras S, Abdul-Wahed A, Soty M, et al. The suppression of hepatic glucose production improves metabolism and insulin sensitivity in subcutaneous adipose tissue in mice. *Diabetologia*. 2016;59:2645-2653.

32. Sanada J, Kimura T, Shimoda M, et al. Protective effects of imeglimin on the development of atherosclerosis in ApoE KO mice treated with STZ. *Cardiovasc Diabetol*. 2024;23:105.
33. Uchida T, Ueno H, Konagata A, et al. Improving the effects of imeglimin on endothelial function: a prospective, single-center, observational study. *Diabetes Ther*. 2023;14:569-579.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Kaku K, Shimoda M, Osonoi T, Iwamoto M, Kaneto H. Efficacy and safety of imeglimin add-on to DPP-4 inhibitor therapy in Japanese patients with type 2 diabetes mellitus: An interim analysis of the randomised, double-blind FAMILIAR trial. *Diabetes Obes Metab*. 2025;27(6):3212-3222. doi:10.1111/dom.16336