

ORIGINAL ARTICLE

Efficacy and safety of imeglimin add-on to insulin monotherapy in Japanese patients with type 2 diabetes (TIMES 3): A randomized, double-blind, placebo-controlled phase 3 trial with a 36-week open-label extension period

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Abstract

Aims: To evaluate the efficacy and safety of imeglimin for up to 52 weeks as combination therapy with insulin in Japanese patients with type 2 diabetes.

Materials and Methods: This double-blind, randomized, parallel-group phase 3 trial was performed at 35 sites in Japan. Eligible patients were individuals aged ≥ 20 years with type 2 diabetes and inadequate glycaemic control with insulin. Patients were randomly assigned (1:1) to either imeglimin (1000 mg twice daily) or matched placebo, in combination with insulin, for 16 weeks. In a subsequent 36-week, open-label extension period, all patients received imeglimin 1000 mg twice daily. The primary endpoint was change in mean glycosylated haemoglobin (HbA1c) from baseline to week 16.

Results: In all, 108 and 107 patients were randomly assigned to treatment with imeglimin 1000 mg twice daily or placebo, respectively. Compared with placebo, the adjusted mean difference in change from baseline HbA1c at Week 16 was -0.60% (95% confidence interval [CI] -0.80 to -0.40 ; $P < 0.0001$). This decrease was sustained up to 52 weeks with a mean decrease of -0.64% (95% CI -0.82 to -0.46) versus baseline. The incidence of patients experiencing adverse events and serious adverse events was similar in the two treatment groups. The number of patients experiencing hypoglycaemia was similar in the two treatment groups. In patients receiving imeglimin, all hypoglycaemic events were mild in severity; no episodes required assistance.

Conclusions: Imegl原因 significantly improved HbA1c in Japanese patients with insufficiently controlled type 2 diabetes by insulin and had a similar safety profile to placebo. The efficacy of imeglimin on top of insulin was sustained for 52 weeks. Imegl原因 represents a potential new treatment option for this population as add-on to insulin therapy.

Caroline Reilhac and Julie Dubourg contributed equally to the manuscript.

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1 | INTRODUCTION

The number of patients with type 2 diabetes mellitus is now estimated to exceed 500 million worldwide.¹ Insulin therapy is necessary for a substantial subset of these patients; however, its use in type 2 diabetes may vary depending on the geographic area. The proportion of patients using insulin may reach 7.4% to 15.5% worldwide in 2030.² In Japan, where approximately 7.6% of people aged 20 to 79 years have the disease,³ the consensus-based guidelines provided by the Japan Diabetes Society recommend that patients with type 2 diabetes mellitus initiate treatment with an oral hypoglycaemic agent or an injectable agent when lifestyle and diet modifications are inadequate to maintain glycaemic control⁴ and emphasize the importance of individualized, patient-centred care. In this context, the use of insulin has become quite prevalent, with potentially more than 10% of type 2 diabetes patients receiving insulin either as a monotherapy or in combination with other oral antidiabetes drugs.⁵ Importantly, insulin use in Japanese patients with type 2 diabetes is more frequent among older individuals, in those diagnosed at an earlier age, and with longer disease duration.⁵ Although combination therapies improve glycaemic control, they may increase the risk of side effects, particularly in the elderly population and in patients with diabetes complications, who are often burdened with additional therapies for treatment of comorbidities. Consequently, new alternative antidiabetic medicines that can be used in combination with insulin to achieve sustained efficacy and a good safety/tolerability profile are still needed as treatment options.

Imeglimin is a novel and promising pharmacological agent for the treatment of type 2 diabetes mellitus.^{6,7} Its mode of action is distinct from all other antihyperglycaemic classes⁸; imeglimin's underlying mechanism involves targeting of mitochondrial bioenergetics⁹ and improving mitochondrial function.⁶ Imeglimin has been shown to amplify glucose-stimulated insulin secretion by improving β -cell glucose responsiveness in patients with type 2 diabetes⁷ and to improve insulin sensitivity in a rodent model of diabetes, allowing the normalization of glucose tolerance.⁶ Imeglimin has also been shown to prevent the death of human endothelial cells by inhibiting opening of the mitochondrial permeability transition pore,¹⁰ suggesting the potential for end organ protection. Efficacy of imeglimin as monotherapy and add-on therapy was first demonstrated in patients with type 2 diabetes during phase 1 and phase 2 clinical trials with a favourable safety/tolerability profile^{9,11-14}; these findings were recently confirmed in monotherapy or combination therapy at the dose of 1000 mg twice daily in two previously reported pivotal phase 3 studies: the Trial for Imeglimin Efficacy and Safety (TIMES 1)¹⁵ and TIMES 2.¹⁶ Imeglimin has recently received a marketing authorization in Japan, following the completion of the phase 3 TIMES programme.

This article reports the findings of the third pivotal trial, TIMES 3, which assessed imeglimin 1000 mg twice daily as an add-on to insulin monotherapy. The trial was designed to confirm efficacy, safety and tolerability of imeglimin compared to placebo in Japanese patients with type 2 diabetes inadequately treated with insulin.

2 | RESEARCH DESIGN AND METHODS

2.1 | Study design

This was a phase 3, randomized, double-blind (DB), parallel-group, multicentre trial (TIMES 3) conducted at 35 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 (GCP), the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No 28, March 27, 1997), and the Helsinki Declaration of 1964, as revised in 2013. Written informed consent was obtained from all patients before the beginning of any study-related activities. This trial was registered on JAPIC (Japic CTI-183846).

Eligible patients were Japanese adults aged 20 years or older with type 2 diabetes and inadequate glycaemic control on a regimen of insulin monotherapy or insulin in combination with a stable dose of a single oral antidiabetic agent for at least 12 weeks prior to screening. Only basal insulin or premixed insulin were allowed. Only patients with a glycated haemoglobin (HbA1c) level of 7.5% to 11.0% and a total insulin daily dose of 8 to 40 IU/d, unchanged by >10% during the 12 weeks prior to randomization visit, were eligible. Key exclusion criteria included frequent severe hypoglycaemic events on insulin therapy that may complicate adequate study procedures, any injectable glucose-lowering drugs (except insulin) in the 30 days before screening, estimated glomerular filtration rate (eGFR; estimated with the Japanese Modification of Diet in Renal Disease equation) of less than 60 mL/min/1.73m² and 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 | Randomization and masking

Eligible patients were randomly assigned in a 1:1 ratio to receive either oral imeglimin (1000 mg twice daily) or matched placebo. Patients were allocated to treatment groups using an interactive web response system and stratified by HbA1c measured 1 week before randomization (<8% and \geq 8%) and previous treatment status (patients on insulin monotherapy vs. patients on insulin in combination with a single oral antidiabetic agent). The whole study team, including investigators, patients and sponsor, remained blinded throughout the DB portion of the trial.

2.3 | Procedures

After a screening period, all patients received oral placebo on top of insulin during a 4-week run-in period. Patients treated with insulin in addition to a single oral hypoglycaemic agent had an additional 8-week washout period (for full discontinuation of the oral hypoglycaemic agent) before the start of the run-in period. After

randomization, patients received imeglimin 1000 mg twice daily or matched placebo in combination with insulin for a 16-week DB treatment period. In a subsequent 36-week, open-label (OL) extension period, all patients received imeglimin 1000 mg twice daily on top of insulin (Supplemental Figure 1 in Appendix S1).

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

A rescue therapy could have been initiated by the investigator in case of unacceptable hyperglycaemia, that is, any fasting plasma glucose (FPG) value more than 13.9 mmol/L (250 mg/dL) at Week 4 and Week 8; and/or any HbA1c value of at least 11.0% from Week 12 to Week 52. The initiation, choice and dose of rescue medication used were at the discretion of the investigator, according to local prescribing information. In cases requiring rescue medication, patients discontinued study treatment prematurely but continued in the study.

2.4 | Insulin dosing

During the 16-week DB treatment period, the insulin therapy was to remain at a stable dose regimen (within $\pm 10\%$ of the baseline total daily dose). However, decreases in insulin dose were allowed in cases where patients experienced hypoglycaemia as defined either by repeated hypoglycaemic symptoms associated with self-monitoring of blood glucose (SMBG) concentrations of < 3.9 mmol/L (70 mg/dL) with major changes in lifestyle activities or two consecutive FPG values < 3.9 mmol/L (70 mg/dL), or hypoglycaemia that was determined to be clinically significant by the investigator.

2.5 | Outcomes

The primary efficacy endpoint was change from baseline in HbA1c at Week 16 with imeglimin versus placebo in combination with insulin, assessed at a central laboratory.

Key secondary endpoints were percentage of responders based on two different definitions: (1) the percentage of patients reaching a target HbA1c below 7.0% at Week 16 and (2) the percentage of patients with a relative decrease of at least 7% from baseline HbA1c at Week 16.

Other endpoints included change from baseline in HbA1c at Week 52 with imeglimin, percentage of patients requiring rescue therapy, and change from baseline to Weeks 16 and 52 in FPG, lipid variables (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol and triglycerides) and in mean insulin daily dose.

Change from baseline in HbA1c at Week 16 was also analysed in subgroups of patients according to baseline age (< 65 years and ≥ 65 years) and baseline chronic kidney disease (CKD) stage (CKD stage 1 and 2).

Safety endpoints included physical examination, vital signs, 12-lead electrocardiogram, clinical laboratory variables, and adverse events (AEs) including hypoglycaemia (preferred terms coded using

the Medical Dictionary for Drug Regulatory Activities [MedDRA] version 20.1). Patients were asked to check their glucose levels, using SMBG devices, at least three times a day. Events of hypoglycaemia were categorized according to the American Diabetes Association and the Endocrine Society guidance.¹⁷

2.6 | Statistical analysis

The sample size required to ensure a 90% power was 106 patients per randomized treatment group for an expected 0.5% treatment difference in mean changes of HbA1c between the imeglimin and placebo groups at the two-sided 0.05 alpha level, assuming a standard deviation 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 endpoint was significant at the two-sided nominal level of 0.05, then the first key secondary endpoint was tested at the same two-sided nominal level of 0.05, and only if this was also significant, the second key secondary endpoint was tested at the same two-sided nominal level of 0.05.

Efficacy analyses were primarily performed using a modified intention-to-treat approach, with the analyses comprising all randomized patients who were exposed to at least one dose of DB study medication and who had at least one post-baseline HbA1c value. The change in HbA1c (%) from baseline to Week 16 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 HbA1c as a continuous covariate. Measurements after treatment discontinuation were censored at the time of investigational medicinal product discontinuation. Least squares means of change from baseline for each treatment group and the differences in least squares means between imeglimin and placebo were estimated in this model along with 95% confidence intervals (CIs) and the comparison *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 at least one dose of study drug and was descriptive in nature. AEs reported included those which occurred between first drug intake (at randomization) and 7 days after cessation of drug administration, or which started before drug intake and worsened during the DB treatment period.

Analyses were performed using SAS version 9.4.

3 | RESULTS

The TIMES 3 trial was conducted between February 24, 2018 and September 26, 2019. A total of 334 patients were screened and 215 were randomized (108 imeglimin, 107 placebo) (Figure 1). Of these, 214 patients received at least one dose of study medication,

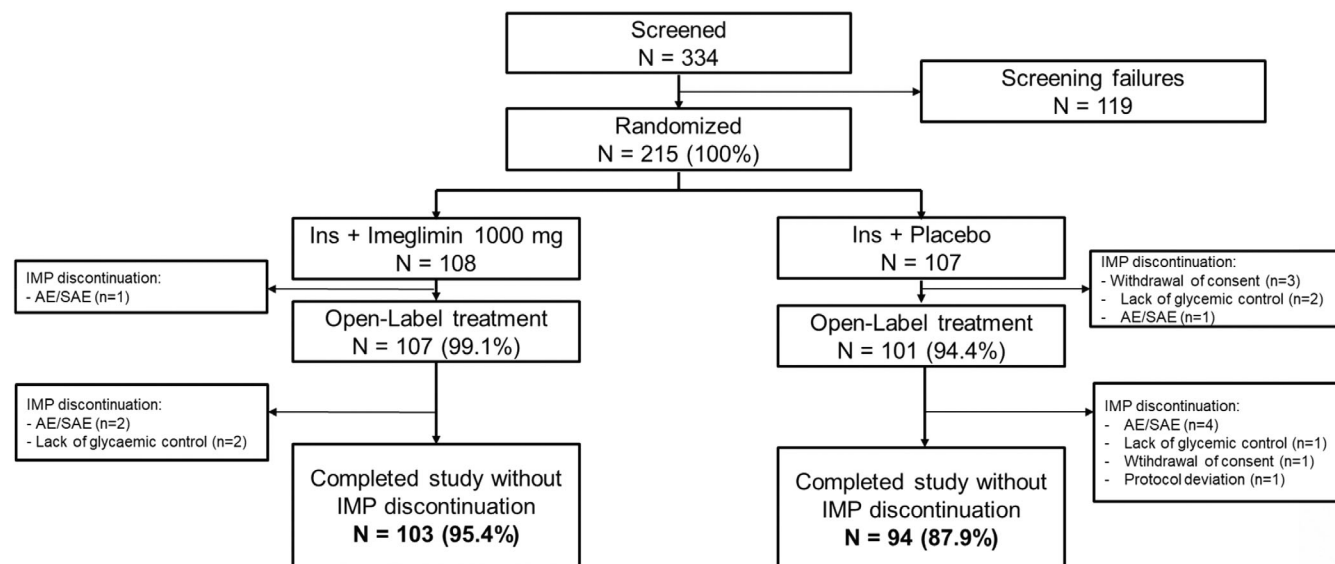


FIGURE 1 Trial profile. AE, adverse event; IMP, investigational medicinal product; Ins, insulin; SAE, serious adverse event

had at least one post-baseline HbA1c value, and were included in the modified intention-to-treat analysis. Of these patients, 208 (96.7%; 107 imeglimin, 101 placebo) completed the 16-week DB period, and 197 (91.6%; 103 imeglimin, 94 placebo) completed the 36-week OL extension period. Five patients (4.6%) in the imeglimin group during the DB period and imeglimin in the OL period (IME/IME) and 13 patients (12.1%) in the placebo group during the DB period and imeglimin in the OL period (PLA/IME) prematurely discontinued treatment mainly due to the occurrence of an AE or SAE (Figure 1).

Baseline characteristics were similar between treatment groups (Table 1) with respect to mean age, sex, HbA1c, insulin regimen and total daily dose, body mass index and eGFR. Mean (SD) age was 58.4 years (10.3), with 71 (33%) elderly patients (≥ 65 years), and mean eGFR was 77.2 mL/min/1.73m² (SD 13.0), with 30 (14%) CKD stage 1 patients and 185 (86%) CKD stage 2 patients. Mean HbA1c was 8.79% (SD 0.77). Patients were mainly receiving a basal insulin regimen (70%) and were previously treated mainly with insulin monotherapy (80.5%). In the imeglimin group, 37.0% and 47.2% of patients were receiving medication for hypertension and dyslipidaemia, respectively, and, in the placebo group, the corresponding values were 36.4% and 46.7%.

3.1 | Efficacy/DB period

Baseline HbA1c was 8.74% (SD 0.72) and 8.82% (SD 0.81) for the imeglimin and placebo groups, respectively. At Week 16, HbA1c had significantly decreased by 0.63% (95% CI -0.78 to -0.49) with imeglimin versus a decrease of 0.03% (95% CI -0.18 to 0.12) with placebo: estimated treatment difference versus placebo -0.60% (95% CI -0.80 to -0.40 ; $P < 0.0001$ [Figure 2, Table 2]).

An HbA1c concentration $< 7.0\%$ was achieved by significantly more patients ($P = 0.045$) in the imeglimin group (eight patients, 7.4%)

compared with the placebo group (one patient, 0.9%). A relative HbA1c decrease of at least 7% from baseline HbA1c was also achieved by significantly more patients ($P < 0.0001$) in the imeglimin group (59 patients, 54.6%) versus the placebo group (22 patients, 20.8%).

A clinically meaningful HbA1c decrease versus placebo was evident across all age subgroups with a reduction of 0.46% (95% CI -0.71 to -0.22) in patients younger than 65 years and a reduction of 0.77% (95% CI -1.08 to -0.46) in patients aged 65 years or older at Week 16 for patients in the imeglimin group. The HbA1c decrease was also consistent across CKD stage groups. At Week 16, HbA1c decreased by 0.53% (95% CI -1.00 to -0.07) in CKD stage 1 patients and by 0.62% (95% CI -0.84 to -0.40) in CKD stage 2 patients (Table 2).

At Week 16, a reduction in FPG by 0.63 mmol/L (95% CI -1.08 to -0.19) in the imeglimin group and 0.15 mmol/L (95% CI -6.61 to 0.30) in the placebo group was observed, with an estimated treatment difference versus placebo close to statistical significance: -0.48 mmol/L (95% CI -0.965 , 0.005; $P = 0.0522$ [Table 2]).

There were no meaningful changes in standard measures of serum lipids, including total triglycerides, total cholesterol, LDL cholesterol and HDL cholesterol (Table 2). None of the patients in the imeglimin group had an increase in insulin dose at Week 16 compared to one patient (0.9%) in the placebo group; decreases in insulin dose occurred in six (5.6%) of the imeglimin-treated patients compared to four (3.8%) in the placebo group. The threshold defined for indicating an increase or decrease was set at 10%, but the reported overall change in daily dose was less than 0.3 IU/d.

3.2 | Efficacy/OL extension period

The HbA1c decrease was sustained through to Week 52 for patients in the IME/IME group (change from baseline to Week 52: -0.64% ,

TABLE 1 Demographic and baseline characteristics

	Placebo (N = 107)	Imeglimin 1000 mg twice daily (N = 108)	Overall (N = 215)
Sex, n (%)			
Female	38 (35.5)	42 (38.9)	80 (37.2)
Male	69 (64.5)	66 (61.1)	135 (62.8)
Age, years	57.6 (10.10)	59.3 (10.49)	58.4 (10.31)
Age group, n (%)			
<65 years	76 (71.0)	68 (63.0)	144 (67.0)
≥65 years	31 (29.0)	40 (37.0)	71 (33.0)
Weight, kg	67.54 (11.816)	67.13 (12.266)	67.33 (12.018)
Body mass index, kg/m ²	24.887 (3.5104)	25.244 (3.6302)	25.066 (3.5673)
Diabetes duration, years	13.4 (7.4)	13.3 (8.2)	13.3 (7.8)
HbA1c, %	8.83 (0.814)	8.74 (0.721)	8.79 (0.768)
FPG, mmol/L	8.15 (2.106)	8.49 (2.092)	8.32 (2.101)
eGFR, mL/min/1.73 m ²	77.4 (13.73)	77.1 (12.31)	77.2 (13.01)
CKD stage, n (%)			
CKD stage 1	14 (13.1)	16 (14.8)	30 (14.0)
CKD stage 2	93 (86.9)	92 (85.2)	185 (86.0)
Insulin type, n (%)			
Basal	78 (72.9)	73 (67.6)	151 (70.2)
Premix	29 (27.1)	35 (32.4)	64 (29.8)
Previous diabetes therapy			
Insulin monotherapy	86 (80.4)	87 (80.6)	173 (80.5)
Insulin in combination with one OHA	21 (19.6)	21 (19.4)	42 (19.5)
BIG	11 (10.3)	9 (8.3)	20 (9.3)
DPP-4 inhibitor	6 (5.6)	4 (3.7)	10 (4.7)
SGLT2 inhibitor	1 (0.9)	6 (5.6)	7 (3.3)
GLIN	2 (1.9)	2 (1.9)	4 (1.9)
SU	1 (0.9)	0	1 (0.5)
Insulin daily dose, IU/d	22.21 (9.763)	20.49 (10.000)	21.35 (9.897)

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

Abbreviations: BIG, biguanide; CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; GLIN, glinide; HbA1c, glycated haemoglobin; OHA, oral hypoglycaemic drug; SGLT2, sodium-glucose cotransporter-2; SU, sulphonylurea.

95% CI -0.82 to -0.46 [Figure 3]). Switching from placebo to imeglimin at Week 16 was also associated with a reduction of 0.54% (95% CI -0.71 to -0.38) in HbA1c (PLA/IME group) after 36 weeks of added imeglimin treatment (Figure 3). At Week 52, nine patients (8.3%) in the IME/IME group and one patient (1.0%) in the PLA/IME group achieved an HbA1c $\leq 7.0\%$. A relative decrease of at least 7% from baseline HbA1c was achieved by 63 patients (58.3%) in the IME/IME group and 46 (45.5%) in the PLA/IME group. The number of patients whose insulin dose was increased by more than 10% was 28 (25.9%) in IME/IME compared to 24 (23.8%) in the PLA/IME group, and 10 patients (9.3%) had their insulin dose decreased by more than 10% in the IME/IME compared to 11 (10.9%) in the PLA/IME group. The overall insulin daily dose increased by 1.2 IU/d

(95% CI 0.3 to 2.0) in the IME/IME group and by 0.92 IU/d (95% CI -0.03 to 1.88) in the PLA/IME group.

3.3 | Safety/DB period

During the 16-week DB treatment period, the proportion of patients reporting any AEs was similar in the two groups (57 patients [52.8%] vs. 51 patients [47.7%] in the imeglimin and placebo groups, respectively; Supplemental Table 1 in Appendix S1). Most reported AEs were mild in severity and only two patients in the placebo group experienced one AE of severe intensity. One patient (0.9%) in the imeglimin group and three patients (2.8%) in the placebo group experienced at

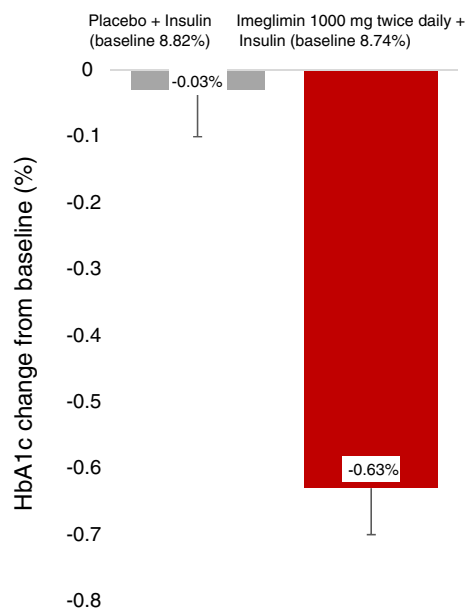


FIGURE 2 Mean glycated haemoglobin (HbA1c) reduction after 16 weeks (imeglimin and placebo on top of insulin)

least one serious AE. One patient (0.9%) in the imeglimin group and four patients (3.7%) in the placebo group discontinued treatment prematurely because of AEs (Supplemental Table 1 in Appendix S1). All patients requiring rescue therapy were in the placebo group (two patients, 1.9%).

Gastrointestinal disorders were reported in 9.3% of patients in the imeglimin group and 6.5% in the placebo group (Supplemental Table 3 in Appendix S1). These events were mostly mild in intensity. Constipation, nausea and gastroesophageal reflux disease were the most frequent gastrointestinal events experienced.

The number of patients experiencing hypoglycaemia was similar in the two groups (23 patients [21.3%] in the imeglimin group vs. 17 patients [15.9%] in the placebo group). All hypoglycaemia events were mild in severity except for one case of probable symptomatic hypoglycaemia in a placebo group which was considered moderate in severity. Most of the hypoglycaemia events were asymptomatic.

Hypoglycaemia and nasopharyngitis, which were experienced by 5% or more patients in both treatment groups, were the most frequent AEs.

TABLE 2 Effects of imeglimin and placebo in combination with insulin therapy on primary and secondary efficacy endpoints at week 16

		Placebo	Imeglimin 1000 mg twice daily
HbA1c	<i>n</i>	106	108
Baseline, %	Mean (SD)	8.82 (0.813)	8.74 (0.721)
Change from baseline, %	LS mean (SE)	-0.03 (0.07)	-0.63 (0.07)
Difference vs. placebo, %	LS mean (95% CI)		-0.60 (-0.802, -0.404)
	<i>P</i> value		<0.0001
HbA1c: patients < 65 years	<i>n</i>	73	68
Baseline, %	Mean (SD)	8.90 (0.811)	8.77 (0.710)
Change from baseline, %	LS mean (SE)	0.04 (0.09)	-0.42 (0.09)
Difference vs. placebo, %	LS mean (95% CI)		-0.46 (-0.705, -0.223)
	<i>P</i> value		0.0002
HbA1c: patients ≥65 years	<i>n</i>	39	29
Baseline, %	Mean (SD)	8.65 (0.805)	8.69 (0.745)
Change from baseline, %	LS mean (SE)	-0.22 (0.12)	-0.99 (0.10)
Difference vs. placebo, %	LS mean (95% CI)		-0.77 (-1.083, -0.464)
	<i>P</i> value		<0.0001
HbA1c: patients with CKD stage 1	<i>n</i>	14	15
Baseline, %	Mean (SD)	9.04 (0.941)	8.77 (0.525)
Change from baseline, %	LS mean (SE)	-0.19 (0.20)	-0.72 (0.19)
Difference vs. placebo, %	LS mean (95% CI)		-0.53 (-0.996, -0.067)
	<i>P</i> value		0.0266
HbA1c: patients with CKD stage 2	<i>n</i>	88	92
Baseline, %	Mean (SD)	8.79 (0.792)	8.74 (0.752)
Change from baseline, %	LS mean (SE)	-0.02 (0.08)	-0.64 (0.08)
Difference vs. placebo, %	LS mean (95% CI)		-0.62 (-0.837, -0.396)

(Continues)

TABLE 2 (Continued)

		Placebo	Imeglimin 1000 mg twice daily
	P value		<.0001
FPG	n	102	107
Baseline, mmol/L	Mean (SD)	8.15 (2.106)	8.49 (2.092)
Change from baseline, mmol/L	LS mean (SE)	-0.15 (0.23)	-0.63 (0.23)
Difference vs. placebo, mmol/L	LS mean (95% CI)		-0.48 (-0.965, 0.005)
	P value		0.0522
Mean insulin daily dose	n	102	107
Baseline, IU/d	Mean (SD)	22.16 (9.758)	20.56 (10.034)
Change from baseline, IU/d	LS mean (SE)	-0.20 (0.13)	-0.27 (0.13)
Difference vs. placebo, IU/d	LS mean (95% CI)		-0.08 (-0.42, 0.26)
	P value		0.6485
Percent change in total cholesterol	n	102	107
Baseline, mmol/L	Mean (SD)	4.90 (0.846)	4.83 (0.894)
Change from baseline, %	LS mean (SE)	6.09 (1.76)	6.92 (1.72)
Difference vs. placebo, %	LS mean (95% CI)		0.83 (-2.464, 4.114)
	P value		0.6216
Percent change in LDL cholesterol	n	102	107
Baseline, mmol/L	Mean (SD)	2.85 (0.662)	2.72 (0.779)
Change from baseline, %	LS mean (SE)	8.77 (3.17)	11.08 (3.10)
Difference vs. placebo, %	LS mean (95% CI)		2.31 (-3.610, 8.232)
	P value		0.4424
Percent change in HDL cholesterol	n	102	107
Baseline, mmol/L	Mean (SD)	1.41 (0.374)	1.41 (0.398)
Change from baseline, %	LS mean (SE)	5.22 (1.90)	3.15 (1.87)
Difference vs. placebo, %	LS mean (95% CI)		-2.07 (-5.587, 1.452)
	P value		0.2481
Percent change in triglycerides	n	102	107
Baseline, mmol/L	Mean (SD)	1.46 (1.161)	1.45 (0.773)
Change from baseline, %	LS mean (SE)	3.65 (5.95)	4.30 (5.85)
Difference vs. placebo, %	LS mean (95% CI)		0.65 (-10.371, 11.670)
	P value		0.9076

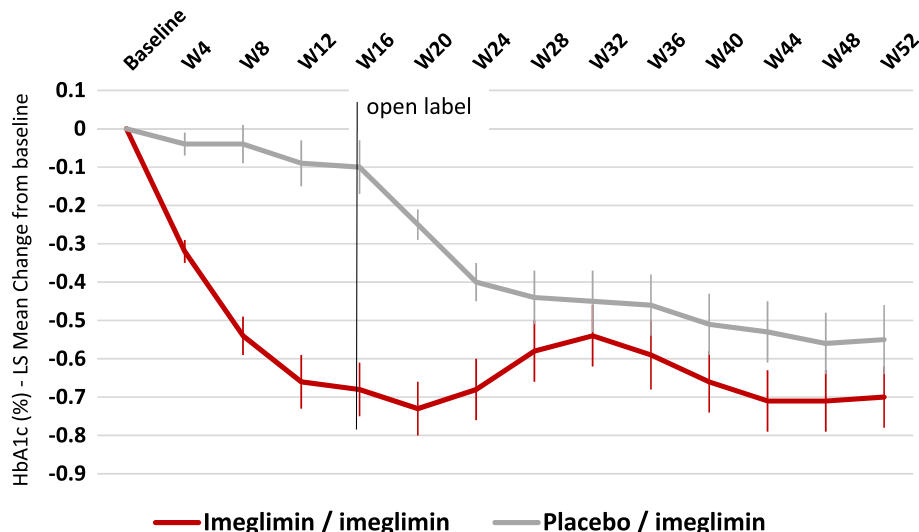
Abbreviations: CI, confidence interval; CKD, chronic kidney disease; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LS, least squares.

3.4 | Safety/OL extension period

Regarding the OL treatment extension period (PLA/IME; 36 weeks of treatment) / whole study (IME/IME; 52 weeks of treatment), most AEs were also mild in intensity and only one patient (0.9%) in the IME/IME group and three patients (3.0%) in the PLA/IME group experienced at least one AE of severe intensity. Six patients (5.6%) in the IME/IME group and six patients (5.9%) in the PLA/IME group experienced at least one serious AE (including severe AEs), which were all considered unrelated to study drug by the investigator. Five patients (4.6%) in the IME/IME group versus three patients (3.0%) in the PLA/IME group discontinued the study drug due to an AE (Supplemental Table 2 in Appendix S1). One death (serious AE of

sudden death, unrelated) was reported in the PLA/IME group. Two patients (1.9%) in the IME/IME group and one patient (1.0%) in the PLA/IME group required rescue therapy. Hypoglycaemia was reported in 39 patients (36.1%) in the IME/IME group and 36 patients (35.6%) in the PLA/IME group. Hypoglycaemia and nasopharyngitis were experienced by 5% or more patients in both treatment groups, as well as back pain and constipation in the IME/IME group and bronchitis in the PLA/IME group (Supplemental Table 4 in Appendix S1). None of the hypoglycaemic events led to discontinuation of imeglimin. Overall, body weight and blood pressure values did not change over time following 16 and 52 weeks of treatment (Supplemental Table 5 in Appendix S1). Finally, no additional clinically relevant changes over time were noted in safety laboratory

FIGURE 3 Time course of glycated haemoglobin (HbA1c) over the 52-week study period according to treatment groups. LS, least squares; W, week



assessments, physical examination, or electrocardiograms regardless of treatment group.

4 | DISCUSSION

Imeglimin has been previously reported to lower HbA1c when used alone and in combination therapy with existing antidiabetic medicines.^{11,12,15,18,19} However, its utility when combined with insulin has not been previously reported. In the present phase 3 trial, a similar glycaemic-lowering effect was observed when imeglimin was used in combination with insulin. Imeglimin is therefore expected to exert clinically meaningful blood glucose-lowering effects regardless of the class of medicine it could be combined with. One potential exception is combination use with injectable glucagon-like peptide-1 (GLP-1) receptor agonists where only modest additive efficacy was observed in the TIMES 2 pivotal trial.¹⁶ In the TIMES 3 trial, imeglimin 1000 mg twice daily produced a significant and clinically meaningful HbA1c reduction (-0.60%) compared with placebo in Japanese patients with type 2 diabetes responding inadequately to insulin. In addition, a consistent and durable HbA1c-lowering effect was observed up to Week 52 with continued imeglimin administration, demonstrating the long-term efficacy potential of imeglimin in combination with insulin.

Type 2 diabetes is a progressive disease, characterized by increasing deterioration of pancreatic β -cell function.²⁰ Compared with previous studies with imeglimin as monotherapy or in combination with oral antidiabetic agents,^{14,15} the insulin-using patients included in the present study had longer disease duration (13.3 years in the present study vs. ~ 6 years in the Japan phase 2b, ~ 8 years in TIMES 1 and ~ 5.9 to 10.7 years according to background therapy in TIMES 2) and higher HbA1c levels, suggesting a greater degree of impaired β -cell function at study initiation. Despite the advanced disease profile of these patients, imeglimin improved HbA1c control in a durable fashion for 52 weeks. As imeglimin's mode of action includes a prominent effect to ameliorate β -cell function (even in extreme animal

models with markedly reduced β -cell mass),⁸ we speculate that patients in the present study may have residual β -cell mass and could have benefited from a small degree of enhanced glucose-stimulated insulin secretion.

As type 2 diabetes is a progressive disease, patients who require insulin will frequently need intensification of their insulin regimen in order to maintain adequate glycaemic control, either via an increase in basal insulin dose(s) and/or with the addition of prandial rapid insulin doses.²¹⁻²³ It is therefore notable that the combination of imeglimin and insulin in this study allowed improved glycaemic control without increases in insulin daily doses. The mean change in daily dose of insulin from baseline during the DB period was very small (<0.3 IU/d). This may be explained by the protocol requirements of the study; the insulin dose was fixed during the DB treatment period except when increases or decreases in insulin dose were considered necessary by the investigator for a safety reason. In addition, after the DB period, the overall insulin daily dose adjustments implemented by investigators (while this was allowed) were only of 0.92 to 1.2 IU/L; this is consistent with a sustained effect of imeglimin as judged by the investigators.

As noted above, previous reports demonstrated the effects of imeglimin on β cells to amplify glucose-stimulated insulin release.^{7,8} The underlying mechanism is distinct from GLP-1 receptor activation and involves an increase in the cellular NAD⁺ pool along with augmentation of glucose-induced ATP levels. This is of particular interest in the Japanese population as it is now widely recognized that Japanese patients with type 2 diabetes have a different profile from White patients.²⁴⁻²⁸ Type 2 diabetes in the East Asian population is reported to be primarily characterized by prominent β -cell dysfunction with less adiposity and less insulin resistance compared to White populations. Thus, body mass index is less well correlated with an increase in the prevalence of type 2 diabetes in East Asian populations compared to the US population.²⁹ Accordingly, two recent meta-analyses^{30,31} have demonstrated the superiority of drugs that promote β -cell function in the Asian population compared to the non-Asian population.

This study showed a trend towards also decreasing FPG, but this result was not statistically significant. This is not consistent with previous studies.^{14,15} This inconsistency may be explained by the relatively low baseline FPG values in this study (8.49 mmol/L vs. 8.15 mmol/L in the imeglimin group and placebo group, respectively) in comparison to the previous studies (9.07 mmol/L, 9.09 mmol/L and 9.06 mmol/L in imeglimin groups for phase 2b,¹⁴ TIMES 1¹⁵ and TIMES 2 studies, respectively). In addition, a majority of patients were on basal insulin at screening (67.6% of patients in the imeglimin group and 72.9% of patients in the placebo group), which may have accounted for relatively low baseline FPG values because basal insulin therapy is designed to facilitate glucose control coverage between meals and overnight.³² It therefore appears likely that imeglimin may exert a complementary role on top of basal insulin by preferentially decreasing glucose excursions in the postprandial state. Unfortunately, postprandial glucose values were not specifically assessed in the present study. However, this concept is consistent with the well-described effect of imeglimin to substantially augment glucose-mediated insulin release, which was demonstrated both *in vitro* with primary cultured pancreatic islets and *in vivo* in animals and humans,^{7,8,33} while improving the overall insulin sensitivity.⁸

No unexpected safety concerns were raised in this study and imeglimin was well tolerated when used as add-on to insulin. A similar safety/tolerability profile was observed between the treatment groups, which is consistent with previous observations in clinical trials with imeglimin.^{15,18} No weight gain nor any clear increase in gastrointestinal disorders were observed during the study. Gastrointestinal events have been previously reported at imeglimin doses of 1500 mg twice daily or higher,^{9,18} but no increase in such events relative to placebo was observed in the monotherapy pivotal Japanese study (TIMES 1) at the dose of 1000 mg twice daily.¹⁵ In addition, no events of lactic acidosis nor any increase in mean lactate levels versus placebo were evident.

Hypoglycaemia was the most frequently reported treatment-emergent AE in both treatment groups, but no severe events were described. The number of patients experiencing hypoglycaemia was similar in the imeglimin and placebo groups but remained higher than in previous studies. An increased risk of hypoglycaemia has been reported in patients with type 2 diabetes mellitus receiving combination treatment involving insulin, such as oral hypoglycaemic agent(s) administration as an add-on to insulin therapy.³⁴ The prevalent finding of hypoglycaemia in both treatment groups in the present study is explained by the insulin background therapy; importantly, imeglimin was not shown to increase this risk. This is consistent with previous studies suggesting that imeglimin is not expected to increase incidence of hypoglycaemia or severe hypoglycaemia.^{9,11,12,18,19} This result also aligns with the mechanism of action of imeglimin, where increased insulin secretion occurs only in response to glucose.^{7,35}

In this study, 33.0% of the patients were elderly (≥ 65 years), while the majority also already had mild renal dysfunction (86.0% CKD stage 2 vs. 14.0% CKD stage 1), as indicated by the baseline eGFR measurements. However, the efficacy profile, defined by a significant HbA1c decrease, was consistent across subgroup analyses, suggesting that

imeglimin is a new and safe treatment option in the elderly population. The addition of imeglimin to insulin therapy in patients with poor glycaemic control could therefore provide benefits to elderly patients who are known to have functional limitations (eg, difficulty in accurately injecting insulin), comorbidities or insufficient social support.^{5,36}

Some limitations need to be addressed regarding the present study. First, our results may not be generalizable to patients in other countries or to White populations.³⁷ Secondly, the use of self-measured glucose profiles in this study has certain limitations, including variability resulting from day-to-day differences, not only in collection time and eating patterns in individual patients, but also in terms of number of glycaemic measurements taken per day per patient. Therefore, additional studies using continuous glucose monitoring in well-defined populations would be of interest in order to better assess hypoglycaemia events as well as to define the relative effects of imeglimin on postprandial hyperglycaemia in the context of basal insulin use.

In conclusion, imeglimin 1000 mg twice daily as add-on to insulin therapy for 52 weeks was well tolerated and was associated with clinically meaningful and sustained reductions in HbA1c. The results further suggest that imeglimin could potentially be used to augment basal insulin use by enhancing glycaemic control during and after meals. The net efficacy and safety profile of imeglimin when used in conjunction with insulin in patients with advancing age and renal dysfunction also appears to be favourable. Therefore, imeglimin has been characterized as a new and safe treatment option in combination with insulin for Japanese patients with type 2 diabetes.

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P.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

CONFLICTS OF INTEREST

C.R., C.T. and P.F. are employees of Poxel. J.D. is a former employee of Poxel. J.M.G. is a consultant for Poxel. H.W. has received honoraria for lectures for Mitsubishi Tanabe Pharma, Dainippon Sumitomo Pharma, Sanwa Kagaku, Takeda, Sanofi, Kowa, Merck Sharp & Dohme, Boehringer Ingelheim, Eli Lilly and Novo Nordisk, and research activities for Takeda, Boehringer Ingelheim, Kissei Pharma, Novo Nordisk, Mitsubishi Tanabe Pharma, Lifescan Japan, Dainippon Sumitomo Pharma, Poxel, Kyowa Kirin and Merck Sharp & Dohme.

AUTHOR CONTRIBUTIONS

Julie Dubourg and Caroline Reilhac contributed to the study design, interpretation of data, drafted and edited the report. Carole Thang, Pascale Fouqueray and Jean-Marie Grouin contributed to the study design, interpretation of data and reviewed the report. Hirotaka Watada contributed to the study design, interpretation of data and reviewed the report. All authors read the manuscript critically and approved the submitted version.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

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

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