





ORIGINAL ARTICLE

A randomized, placebo-controlled study to evaluate the efficacy and safety of adding omarigliptin to insulin therapy in Japanese patients with type 2 diabetes and inadequate glycaemic control

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Abstract

Aim: To evaluate the efficacy and safety of adding the once-weekly oral dipeptidyl peptidase-4 inhibitor omarigliptin to treatment of Japanese patients with type 2 diabetes and inadequate glycaemic control on insulin monotherapy.

Materials and Methods: In a 52-week clinical trial, Japanese patients on insulin monotherapy were randomized to once-weekly omarigliptin 25 mg ($N = 123$) or placebo ($N = 61$) for a 16-week, double-blind, placebo-controlled period. After Week 16, patients continued or switched to omarigliptin for a 36-week open-label period.

Results: From a mean baseline of approximately 8.8%, the Week 16 least squares mean changes in HbA1c were -0.61% (omarigliptin) and 0.29% (placebo); the between-group difference was -0.90% ($p < .001$). At Week 52, the mean change from baseline in HbA1c was -0.57% in both the group on omarigliptin for 52 weeks and the group on omarigliptin for 36 weeks (switched from placebo at Week 16). During the first 16 weeks of treatment, the incidences of adverse events (AEs), serious AEs, drug-related AEs and discontinuation from trial medication because of an AE were similar in both groups. A slight increase in incidence of symptomatic hypoglycaemia was observed in the omarigliptin group ($n = 13$ [10.6%]) compared with placebo ($n = 4$ [6.6%]). No severe hypoglycaemia was reported during the study. No new safety signals emerged with treatment beyond Week 16 through Week 52.

Conclusion: The addition of once-weekly omarigliptin to insulin therapy for up to 52 weeks was generally well tolerated and provided clinically meaningful improvement in glycaemic control throughout the trial period. ClinicalTrials.gov: NCT02906709

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KEYWORDS

dipeptidyl peptidase-4, incretins, insulin, MK-3102, once-weekly antihyperglycaemic agent, oral antihyperglycaemic agent

1 | INTRODUCTION

Treatment guidelines for type 2 diabetes (T2D)^{1,2} recommend initiating pharmacotherapy when diet and exercise are inadequate to control hyperglycaemia. International guidelines recommend metformin as the first oral hypoglycaemic agent (OHA) and selection of additional medication based on patient preference and clinical characteristics.¹ Japanese guidelines recommend an OHA and/or glucagon-like peptide-1 (GLP-1) receptor agonist or insulin therapy to be used as initial therapy, depending upon a patient's characteristics and pathophysiology. Japanese guidelines further indicate that when glycaemic control is inadequately maintained by initial therapy, up-titration of the initial OHA, co-administration of an OHA with a differing mechanism of action, or switch to or co-administration of a GLP-1 receptor agonist or insulin, can be considered.²

When glycaemic control is not achieved with insulin treatment, insulin intensification therapy can be considered. However, an increased risk of hypoglycaemia can be a barrier to insulin intensification. In addition, the requirement for more frequent injections increases the treatment burden on patients. As an alternative to insulin intensification, combining insulin with a dipeptidyl peptidase-4 (DPP-4) inhibitor has the potential to improve glycaemic control.³⁻⁹

Omarigliptin is a once-weekly (q.w.) DPP-4 inhibitor that was approved in Japan in 2015 for the treatment of patients with T2D. The efficacy, safety and tolerability of omarigliptin 25 mg once weekly was shown in two Japanese studies, both as monotherapy¹⁰ and as add-on therapy to five classes of OHA¹¹ in patients with T2D. In these studies, once-weekly dosing with omarigliptin was non-inferior to once-daily dosing of the DPP-4 inhibitor sitagliptin in reducing HbA1c, and the safety profile of omarigliptin was comparable with the daily DPP-4 inhibitor drug class.

In the phase IV, randomized, placebo-controlled, parallel-group, multisite, double-blind trial with open-label extension reported here, the efficacy and safety of the addition of omarigliptin was assessed in Japanese patients with T2D with inadequate glycaemic control on insulin monotherapy, a combination that was not studied prior to approval in Japan.

2 | METHODS

2.1 | Study population

At screening, eligible patients were Japanese, male or female, aged 20 years or older, with a body mass index (BMI) of more than 18 kg/m² and less than 40 kg/m², and T2D. Eligible patients were either on a stable regimen of insulin for 4 weeks or longer (8 to

40 units/day) in combination with a single OHA with an HbA1c of 7.0% or higher and 9.0% or less (group A), or on a stable regimen of insulin monotherapy for 10 weeks or longer (8 to 40 units/day) with an HbA1c of 7.5% or higher and 10.0% or less (group B). At screening, insulin monotherapy could be in the form of premixed/fixed ratio combination (if the content percentage of rapid-acting or ultra-rapid-acting insulin was $\leq 30\%$), intermediate-acting or long-acting insulin. At 2 weeks before randomization, eligible patients had been treated with diet and exercise therapy for 6 weeks or longer, a stable dose of insulin for 10 weeks or longer, no hypoglycaemic medication other than insulin for 8 weeks or longer, and had an HbA1c of 7.5% or higher and 10.0% or less, as well as fasting plasma glucose (FPG) of 126 mg/dL or more and 230 mg/dL or less.

Patients were excluded from the study if they had type 1 diabetes, a history of ketoacidosis, active liver disease, significant cardiovascular disease, a history of malignancy of 5 years or less prior to screening (excepting adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer) or haematological disorders, if they had been treated with a thiazolidinedione or a GLP-1 receptor agonist within 12 weeks prior to screening, or omarigliptin at any time, or had a history of severe hypoglycaemia resulting in coma, or loss of consciousness, or had recurrent (≥ 2 times per week) episodes of hypoglycaemia within 8 weeks prior to screening. Laboratory exclusion criteria included an estimated glomerular filtration rate (eGFR) of less than 35 mL/min/1.73m² (calculated with the three-variable Japanese equation for GFR estimation using serum creatinine level and age recommended by Matsuo et al.¹²), serum alanine aminotransferase or aspartate aminotransferase levels more than two times the upper limit of normal, haemoglobin of less than 110 g/L (male) or less than 100 g/L (female), triglycerides of more than 600 mg/dL, or thyroid-stimulating hormone outside the normal range.

2.2 | Study design

This was a randomized, placebo-controlled, parallel-group, multisite, double-blind trial with a subsequent open-label period (Figure 1). The study consisted of a screening period of up to 2 weeks, a pre-treatment period of 10 weeks (group A, to allow for OHA washout) or 2 weeks (group B) (in both groups this included a 2-week single-blind placebo run-in period), a 16-week double-blind treatment period (phase A) and a 36-week open-label period (phase B). After the placebo run-in period, participants were randomized centrally, using an interactive internet-based response system, in a 2:1 ratio to receive either omarigliptin 25 mg weekly or placebo-matching omarigliptin for 16 weeks. Randomization was stratified based on a participant's use of an OHA at screening (insulin + OHA or insulin monotherapy). In

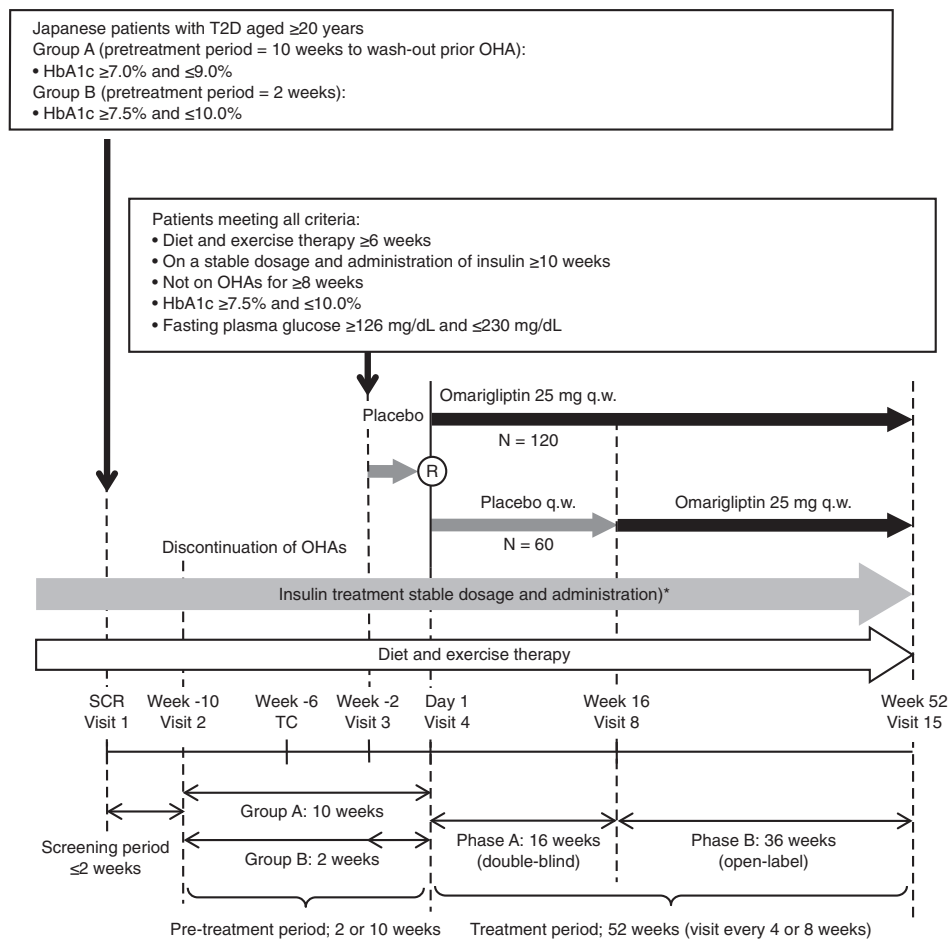


FIGURE 1 Study design. OHA, oral hypoglycaemic agent; q.w., once weekly; R, randomization; SCR, screening; TC, telephone contact; T2D, type 2 diabetes. *During phase B (open-label period), dosage adjustment of insulin was allowed as clinically appropriate to manage the patient's glycaemic control

phase B, participants taking placebo during phase A were switched to omargliptin.

During phase A (the double-blind period), the insulin type and dosage were to remain as used at screening unless a participant met the glycaemic rescue criteria for insulin uptitration, or the hypoglycaemia criteria for downtitration. During phase B (the open-label period), the investigator could modify the insulin dose as clinically required for appropriate glycaemic control, in addition to making an insulin dose adjustment based on the protocol-specified rescue/downtitration criteria. Rescue criteria: after Day 1 of treatment through Week 24, insulin was to be uptitrated as judged appropriate by the investigator if confirmed FPG reported by the central laboratory was more than 240 mg/dL; after Week 24, insulin was to be uptitrated if confirmed FPG was more than 200 mg/dL. Downtitration criteria: at any time during the study, if a participant had hypoglycaemic symptoms with a central laboratory FPG or self-monitored blood glucose (SMBG) value of 70 mg/dL or less, or had repeated (≥ 2) FPG or SMBG values of less than 80 mg/dL per week and was considered to be at a high risk of hypoglycaemia by the investigator, then the insulin dose could be adjusted as determined to be clinically appropriate by the investigator. There were no restrictions on the number of units by which the insulin dosage could be reduced.

The study (MK-3102-039; NCT02906709) was conducted in accordance with the principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. Informed consent was obtained from all study participants.

2.3 | Efficacy objectives

The primary study objectives were to assess the efficacy of omargliptin 25 mg once weekly compared with placebo based upon change from baseline in HbA1c at Week 16, and to assess the safety and tolerability of omargliptin through Week 16 and up to 52 weeks. The primary hypothesis was that omargliptin 25 mg once weekly provides greater reduction in HbA1c compared with placebo as assessed by change from baseline at Week 16.

The secondary objectives were to assess the efficacy of omargliptin 25 mg once weekly compared with placebo based on change from baseline in FPG at Week 16, the proportion of participants reaching an HbA1c goal of less than 7.0% or less than 6.5% at Week 16, and the change from baseline in 1, 5-anhydroglucitol (1, 5-AG) at Week 16. Changes from baseline in HbA1c and FPG,

and the proportion of participants reaching an HbA1c goal of less than 7.0% or less than 6.5%, were also assessed at 52 weeks of treatment.

The insulin dose and percentages of subjects with uptitration and downtitration of insulin dose at Week 16 and Week 52 were also efficacy endpoints.

2.4 | Safety evaluations

The primary safety endpoint was the percentage of participants experiencing one or more adverse event (AE) of symptomatic hypoglycaemia, regardless of glucose value. Other safety endpoints included AEs, percentages of subjects meeting predefined limits of change in laboratory variables (including blood chemistry and haematology) or ECG, and change (or % change) from baseline at Week 16 and Week 52 in laboratory variables, ECG, vital signs and body weight.

2.5 | Statistical analyses

The population for all efficacy endpoints included all randomized participants who received at least one dose of study medication and who had at least one measurement of the outcome variable (baseline or postrandomization). Safety analyses included all randomized participants who received at least one dose of study medication during the treatment period. To avoid the confounding influence of rescue therapy on treatment group comparisons at Week 16, efficacy data taken after the initiation of rescue therapy were treated as missing; most safety data taken after initiation of rescue therapy were also treated as missing, except for deaths, serious AEs and discontinuations because of AEs, which are presented, regardless of initiation of rescue therapy, to ensure a comprehensive assessment of these events.

For long-term efficacy and safety analyses (up to Week 52), all data were included in the analysis regardless of initiation of rescue therapy, because downtitration or uptitration of insulin dose during the extension period was allowed if clinically required.

For the analyses of change from baseline in HbA1c at Week 16, a longitudinal data analysis (LDA) model¹³ was used. The model included terms for treatment, prior OHA therapy status (yes/no), time and the interaction of time by treatment, time by prior OHA therapy status and time by treatment by prior OHA status, with a constraint that the true mean at baseline is common to all treatment groups (which is valid because of randomization). The same model was used to analyse Week 16 FPG and 1, 5-AG.

For the analysis of percentages of individuals at the HbA1c goals of less than 7.0% and less than 6.5% at Week 16, the LDA model used for the analysis of HbA1c was used to impute missing data. Participants were categorized as either a responder (satisfying the HbA1c specific goal of <7.0% or <6.5%) or a non-responder at Week 16 after imputations. Observed data were not imputed.

For long-term efficacy data up to Week 52, the mean change from baseline and the 95% confidence intervals (CIs) were calculated

for both treatment groups. Between-group comparison analyses were not performed.

Safety and tolerability were assessed through 21 days after treatment ended. For the AE summary, including any AE, drug-related AE, serious AE, serious drug-related AE or discontinuation because of an AE, and for specific AEs and laboratory tests exceeding predetermined limits of change with an incidence of four or more participants in either treatment group, between-group comparison point estimates with 95% CIs were calculated using the method of Miettinen and Nurminen¹⁴; for AEs of symptomatic hypoglycaemia, between-group comparison point estimates, 95% CIs and *p*-values were calculated. Descriptive statistics were calculated for all other safety endpoints.

To evaluate the long-term safety of omarigliptin, the incidence rates (%) of AEs were calculated for Weeks 1–52 for the group receiving omarigliptin during the entire duration of the study and for Weeks 16–52 for the group initiating omarigliptin at Week 16. Between-group comparisons and/or estimations of between-group differences were not performed for the open-label period.

A sample size of 180 subjects in a 2:1 ratio (i.e. 120 and 60 subjects for omarigliptin and placebo, respectively) was estimated to provide 97% power to detect a treatment difference of 0.5% in HbA1c reduction from baseline at Week 16 ($\alpha = .05$, two-sided test) based on the conditional standard deviation of 0.82%. This sample size was also estimated to provide 100 or more subjects exposed for 1 year (omarigliptin group only), assuming a 15% discontinuation rate for 52 weeks.

In both phases of this study, any potential case of pancreatitis was evaluated in a blinded manner by external clinical adjudication committees.

3 | RESULTS

3.1 | Patient disposition and characteristics

Of 301 patients screened, 184 were randomized (123 to omarigliptin and 61 to placebo) at 37 sites in Japan (Table S1). The most common reasons for patients not being randomized were meeting laboratory exclusion criteria and/or not meeting inclusion criteria related to OHA treatment and HbA1c levels. Study recruitment began with the first visit of the first patient on 18 October 2016 and follow-up ended with the last visit of the last patient on 21 August 2018. Of the randomized participants, 99.2% ($n = 122$) of those treated with omarigliptin, and 95.1% ($n = 58$) of those treated with placebo, completed the double-blind portion of the study (through Week 16); one participant in the group randomized to omarigliptin and three randomized to placebo discontinued study medication because of an AE (Figure S1). Of those randomized to placebo who discontinued because of an AE, one died. During the open-label period, five more participants discontinued from the group that had been randomized to omarigliptin (three because of an AE and two because of withdrawal by subject). All participants randomized to placebo who

TABLE 1 Baseline demographic and anthropometric characteristics of entire study population

Characteristic	Omarigliptin n = 123	Placebo n = 61
Age, years	61.1 ± 11.0	60.9 ± 11.7
Male, n (%)	86 (69.9)	47 (77.0)
Race, n (%)	123 (100.0)	61 (100.0)
Asian		
Body weight, kg	67.5 ± 11.6	69.1 ± 13.0
BMI, kg/m ²	25.1 ± 3.6	25.5 ± 3.4
eGFR, mL/min/1.73m ²	83.3 ± 21.4	86.1 ± 20.6
HbA1c, %	8.8 ± 0.7	8.8 ± 0.8
FPG, mg/dL	159.1 ± 31.9	152.2 ± 26.0
1, 5-AG, mg/L	3.6 ± 2.7	3.4 ± 2.1
Daily insulin dose, IU	19.2 ± 9.6	20.6 ± 9.1
Duration of T2D, years	12.6 ± 9.0	13.8 ± 7.8
Prior OHA use, yes, n (%)	43 (35.0)	22 (36.1)
Insulin type, n (%)		
Premixed ^a	43 (35.0)	15 (24.6)
Long-acting	71 (57.7)	41 (67.2)
Intermediate	0 (0.0)	3 (4.9)
Fixed ratio combination ^b	9 (7.3)	2 (3.3)

Abbreviations: AG, anhydroglucitol; BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; IU, international units; OHA, oral hypoglycaemic agent; T2D, type 2 diabetes. Data are expressed as mean ± standard deviation unless noted otherwise.

^aPremixed insulin type refers to combination products that contain Neutral Protamine Hagedorn insulin.

^bFixed ratio combination insulin refers to other combination insulin products.

initiated omarigliptin at Week 16 completed the study. During the double-blind period, no participants met the glycaemic rescue criteria; however, insulin was uptitrated or added for three participants by investigator decision. These participants were considered to have been rescued and, as described in the Methods section, data collected after insulin uptitration/addition were treated as missing because of rescue.

The omarigliptin and placebo treatment groups had similar baseline anthropometric and disease characteristics (Table 1). Study participants had a mean age of approximately 61 years and approximately 72% were male. Participants had an approximate mean BMI of 25 kg/m², HbA1c of 8.8%, FPG of 157 mg/dL and duration of T2D of 13 years.

3.2 | Efficacy

3.2.1 | Double-blind placebo-controlled period (Day 1 to Week 16)

From mean baseline HbA1c levels of 8.8% ± 0.7% (omariagliptin) and 8.8% ± 0.8% (placebo), 16 weeks of treatment resulted in a least

TABLE 2 Efficacy endpoints at Weeks 16 and 52

Variable	Omarigliptin 0 to 16 weeks n = 123	Placebo 0 to 16 weeks n = 61
HbA1c, %		
Baseline	8.8 ± 0.7	8.8 ± 0.8
Week 16	8.2 ± 1.0	9.0 ± 1.0
Change from baseline ^a	−0.61 (−0.75, −0.47)	0.29 (0.09, 0.49)
Change versus placebo ^b	−0.90 (−1.15, −0.66) ^c	–
FPG, mg/dL		
Baseline	159.1 ± 31.9	152.2 ± 26.0
Week 16	146.4 ± 30.3	157.5 ± 36.0
Change from baseline ^a	−11.6 (−17.5, −5.7)	3.4 (−4.7, 11.5)
Change versus placebo ^b	−15.0 (−24.5, −5.4) ^d	–
1, 5-AG, mg/L		
Baseline	3.6 ± 2.7	3.4 ± 2.1
Week 16	6.6 ± 5.2	3.5 ± 2.3
Change from baseline ^a	2.9 (2.4, 3.4)	−0.2 (−0.9, 0.5)
Change versus placebo ^b	3.1 (2.3, 4.0) ^c	–
	Omarigliptin/ omariagliptin 0 to 52 weeks n = 123	Placebo/ omariagliptin 16 to 52 weeks n = 58
HbA1c, %		
Baseline ^e	8.8 ± 0.7	8.8 ± 0.7
Week 52	8.3 ± 1.0	8.2 ± 1.1
Change from baseline	−0.57 (−0.73, −0.42)	−0.57 (−0.81, −0.32)
FPG, mg/dL		
Baseline ^e	159.1 ± 31.9	151.5 ± 25.8
Week 52	146.8 ± 35.1	146.2 ± 35.6
Change from baseline	−11.5 (−18.6, −4.5)	−5.3 (−14.1, −3.6)

Abbreviations: AG, anhydroglucitol; FPG, fasting plasma glucose. Values are mean ± standard deviation unless otherwise noted.

^aLeast squares mean (95% confidence interval) based on a model described in the Methods section.

^bDifference in LS means.

^c*p* < .001.

^d*p* = .002.

^eBaseline is Week 0 for the omarigliptin/omariagliptin group and for the placebo/omariagliptin group.

squares (LS) mean (95% CI) reduction of 0.61% (0.75%, 0.47%) in the omarigliptin group and an increase of 0.29% (0.09%, 0.49%) in the placebo group, resulting in a between-group difference in LS means (95% CI) of −0.90% (−1.15%, −0.66%), *p* < .001 (Table 2). A between-group difference in HbA1c was observed by Week 4, the first measurement taken after randomization (Figure 2A). In general, across subgroups defined by baseline HbA1c levels (</≥8.0%), age

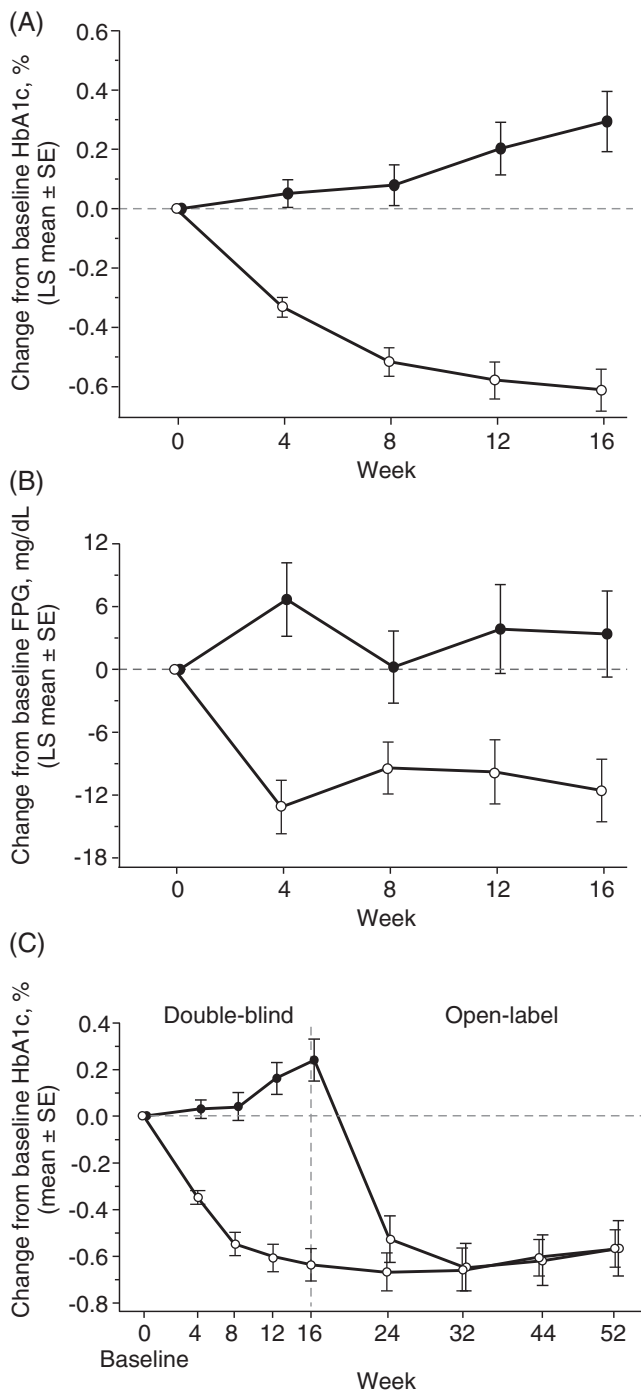


FIGURE 2 Change from baseline in HbA1c and fasting plasma glucose (FPG): A, least squares (LS) mean change in HbA1c through Week 16; B, LS mean change in FPG through Week 16; and C, mean change in HbA1c through Week 52. Open circles = omarigliptin, closed circles = placebo

(</ \geq 65 years), sex, OHA treatment at screening (yes/no), baseline BMI (</ \geq 25 kg/m²), duration of T2D (\leq / $>$ 10 years) and insulin type used (premixed/long-acting/intermediate or fixed ratio combination), changes from baseline HbA1c were consistent with the primary analysis and there were no notable between-subgroup differences (i.e. the 95% CIs for the between-group differences overlapped for each variable; Figure S2); the subgroup using an

intermediate or fixed ratio combination insulin was too small to provide an accurate assessment ($n = 14$).

The estimated percentages (95% CI) of patients achieving an HbA1c of less than 7.0% at Week 16 were 5.8% (2.8%, 11.5%) and 0.0% (0.0%, 6.2%) in the omarigliptin and placebo groups, respectively, and of those achieving an HbA1c of less than 6.5% (95% CI) at Week 16 were 1.7% (0.4%, 5.9%) and 0.0% (0.0%, 6.2%). In neither case was the between-group difference significant.

After 16 weeks of treatment, the placebo-subtracted LS mean (95% CI) change from baseline FPG in the omarigliptin group was -15.0 (-24.5 , -5.4) mg/dL, $p = .002$ (Table 2). The reduction from baseline FPG after omarigliptin treatment was maximal by the first post-baseline measurement (treatment Week 4) and was similar at subsequent measurements (Figure 2B). Treatment with omarigliptin raised LS mean 1, 5-AG levels ($p < .001$) compared with placebo (Table 2).

The mean changes from baseline in insulin dose at Week 16 were small in both the omarigliptin and placebo groups (Table S2). In the omarigliptin group, one patient (0.8%) uptitrated and four (3.3%) downtitrated insulin. In the placebo group, one patient uptitrated (1.6%) and one downtitrated (1.6%) insulin.

3.2.2 | Open-label period (up to 52 weeks)

After 52 weeks, the mean (95% CI) change from baseline in HbA1c levels in the omarigliptin/omariogliptin group was -0.57% (-0.73% , -0.42%). After switching from placebo to omarigliptin at Week 16, HbA1c in the placebo/omariogliptin group was similar to that in the omarigliptin/omariogliptin group by Week 32, and remained similar through Week 52 (Figure 2C and Table 2).

The estimated percentages (95% CI) of patients achieving an HbA1c of less than 7.0% at Week 52 were 7.3% (3.9%, 13.3%) and 8.6% (3.7%, 18.6%) in the omarigliptin/omariogliptin and placebo/omariogliptin groups, respectively, and of those achieving an HbA1c of less than 6.5% (95% CI) were 1.6% (0.4%, 5.7%) and 0.0% (NA).

At Week 52, the mean (95% CI) change from baseline in FPG levels in the omarigliptin/omariogliptin group was -11.5 (-18.6 , -4.5) mg/dL and in the placebo/omariogliptin group it was -5.3 (-14.1 , -3.6) mg/dL (Table 2).

The mean changes from baseline in insulin dose at Week 52 were small in both treatment groups (Table S2). In the omarigliptin/omariogliptin group, 31 patients (25.2%) uptitrated and nine (7.3%) downtitrated insulin. In the placebo/omariogliptin group, 10 uptitrated (17.2%) and two downtitrated (3.4%) insulin.

3.3 | Safety and tolerability

3.3.1 | Double-blind placebo-controlled period (Day 1 to Week 16)

During the double-blind period (Weeks 0 through 16), the overall incidences of AEs, including those assessed by the investigator as drug-

TABLE 3 Adverse events (AEs) summary, Weeks 0–16

Participants, n (%)	Omarigliptin N = 123	Placebo N = 61	Difference ^a
With one or more			
AEs	63 (51.2)	27 (44.3)	7.0 (–8.4, 21.8)
Drug-related ^b AEs	7 (5.7)	3 (4.9)	0.8 (–8.3, 7.4)
Serious AEs	5 (4.1)	2 (3.3)	0.8 (–7.5, 6.6)
Serious drug-related ^b AEs	0 (0.0)	0 (0.0)	0.0 (–6.0, 3.0)
Who died	0 (0.0)	1 (1.6)	–1.6 (–8.7, 1.4)
Who discontinued study medication because of			
An AE	1 (0.8)	3 (4.9)	–4.1 (–12.8, 0.4)
A drug-related ^b AE	0 (0.0)	0 (0.0)	0.0 (–6.0, 3.0)
A serious AE	0 (0.0)	1 (1.6)	–1.6 (–8.7, 1.4)
A serious drug-related ^b AE	0 (0.0)	0 (0.0)	0.0 (–6.0, 3.0)
With specific AEs with incidence ≥ 4 in ≥ 1 treatment group, by SOC ^c			
Gastrointestinal disorders			
Constipation	4 (3.3)	1 (1.6)	1.6 (–5.7, 6.7)
Infections and infestations			
Gastroenteritis	4 (3.3)	1 (1.6)	1.6 (–5.7, 6.7)
Nasopharyngitis	12 (9.8)	5 (8.2)	1.6 (–8.9, 9.8)
Metabolism and nutrition disorders			
Hypoglycaemia	18 (14.6)	5 (8.2)	6.4 (–4.4, 15.4)
With one or more episodes of hypoglycaemia	18 (14.6)	5 (8.2)	6.4 (–4.4, 15.4)
Symptomatic ^d	13 (10.6)	4 (6.6)	4.0 (–6.0, 12.0)
Severe ^e	0 (0.0)	0 (0.0)	
Asymptomatic ^f	6 (4.9)	1 (1.6)	3.2 (–4.2, 8.9)

^aDifference in % (95% CI) versus placebo.

^bAssessed by the investigator as related to study drug.

^cSystem organ class (SOC) defined by the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 classification system.

^dSymptomatic hypoglycaemia: episode with clinical symptoms attributed to hypoglycaemia, without regard to glucose level.

^eSevere hypoglycaemia: episode that required assistance, either medical or non-medical. Episodes with a markedly depressed level of consciousness, a loss of consciousness, or seizure were classified as having required medical assistance, whether or not medical assistance was obtained.

^fAsymptomatic hypoglycaemia: glucose values of ≤ 70 mg/dL without symptoms of hypoglycaemia.

related, were generally comparable between the treatment groups (Table 3). One death was reported in the placebo group; the cause of death was suspected myocardial ischaemia. There were no clinically meaningful differences in specific AEs by system organ class between treatment groups; the 95% CIs for all between-group difference estimates included zero (Table 3). There were no investigator-reported cases or adjudication-confirmed cases of acute or chronic pancreatitis.

Numerically higher incidences of symptomatic hypoglycaemia and all hypoglycaemia (including asymptomatic) were observed in the omarigliptin group compared with the placebo group; no severe hypoglycaemia was reported in either treatment group (Table 3).

There were no clinically meaningful findings related to laboratory safety measures or vital signs in either treatment group. At Week 16, LS mean (95% CI) changes from baseline in body weight were 0.6 (0.3, 0.8) kg (omarigliptin) and –0.3 (–0.8, 0.1) kg (placebo). The between-group difference was 0.9 (0.4, 1.4) kg.

3.3.2 | Open-label period (up to 52 weeks)

The safety results for long-term omarigliptin treatment (>16 weeks) include data collected over different lengths of time (Tables S3 and S4): 52 weeks for the omarigliptin/omarigliptin group and 36 weeks for the placebo/omarigliptin group. Therefore, there are no between-group comparisons of AEs in these two treatment groups.

In the omarigliptin/omarigliptin group (Weeks 0 to 52), 9.8% of patients (12/123) experienced serious AEs; 3.3% (4/123) discontinued the study drug because of an AE (none assessed by the investigator as drug-related); and no events led to death. The incidences of symptomatic and all hypoglycaemia were 15.4% (19/123) and 24.4% (30/123), respectively.

In the placebo/omarigliptin group (Weeks 16 to 52), 1.7% of patients (1/58) experienced serious AEs (none assessed by the investigator as drug-related); no patients discontinued because of an AE; and

no events led to death. The incidences of symptomatic hypoglycaemia and all hypoglycaemia were 6.9% (4/58) and 13.8% (8/58), respectively.

No AEs of hypoglycaemia led to discontinuation of study medication in either treatment group and no events of severe hypoglycaemia were reported.

There were no investigator-reported cases or adjudication-confirmed cases of acute or chronic pancreatitis. There was a slight increase of body weight after treatment with omarigliptin in both groups: the mean \pm SD changes from baseline (Week 0) at Week 52 in the omarigliptin/omariogliptin and the placebo/omariogliptin groups were 0.8 ± 1.8 and 0.8 ± 2.2 kg, respectively.

4 | DISCUSSION

This study showed the efficacy, safety and tolerability of once-weekly omarigliptin 25 mg in Japanese subjects with T2D who had inadequate glycaemic control on insulin monotherapy and diet and exercise therapy. The efficacy and safety profiles observed during the study were consistent with those from a similarly designed study in which once-daily sitagliptin was added to insulin in Japanese patients with T2D.¹⁵ The results reported here for omarigliptin are also generally consistent with data reported for trelagliptin, another once-weekly DPP-4 inhibitor, when added on to insulin treatment.¹⁶

In the current study, at the end of the 16-week double-blind period, addition of omarigliptin q.w. provided statistically significant and clinically meaningful reductions in HbA1c and FPG compared with placebo. Throughout the study (i.e. for up to 52 weeks), the glucose-lowering effects continued. Additionally, improvements were observed in 1, 5-AG. This may indicate improvement of postprandial hyperglycaemia,^{17,18} consistent with the mechanism of action of omarigliptin as a DPP-4 inhibitor stabilizing the incretins GLP-1 and glucose-dependent insulinotropic peptide,¹⁹ although the possibility of a contribution to this effect from improvement in overall glucose control cannot be excluded. The low percentages of participants achieving glycaemic goals of an HbA1c of less than 7.0% or less than 6.5% in both groups are probably attributable to the comparatively high baseline HbA1c of the study population; the baseline HbA1c range inclusion criterion for this study was higher compared with that of other omarigliptin studies.

Except for hypoglycaemia, which is an AE commonly observed with insulin use, no specific AEs representing a safety signal were observed during either treatment period.

Although not statistically significant, during the initial 16 weeks of the study, the incidence of hypoglycaemia in the omarigliptin group was greater than in the placebo group. This observation is consistent with previously observed higher incidences of hypoglycaemia when OHAs (including DPP-4 inhibitors), which by themselves are not associated with an increased risk of hypoglycaemia, are added to a stable dose of insulin.^{7,15,20,21} However, in studies that evaluated the uptitration of insulin to a target FPG level, it was observed that the use of a DPP-4 inhibitor during insulin therapy can significantly improve glycaemic

control without increasing hypoglycaemia.^{8,9} A similar effect may occur if titration of insulin to an FPG goal is allowed during omarigliptin use.

In recent years, a patient-centred approach has been recommended for the treatment of T2D,¹ and patient preference is being recognized as an important element of shared decision-making when choosing a medication. In keeping with these considerations, omarigliptin, with an efficacy and safety profile comparable with daily DPP-4 inhibitors, could be considered as appropriate for patients preferring a once-weekly dosing regimen. With the introduction of once-weekly DPP-4 inhibitors in Japan, several studies have been conducted to assess patient preference for a once-weekly DPP-4 inhibitor; once-weekly omarigliptin and trelagliptin were compared with once-daily sitagliptin and alogliptin, respectively.^{22,23} Reported preference varied significantly. One study found that approximately 90% of patients on sitagliptin, when asked, requested a change in treatment to weekly omarigliptin.²² The other study, conducted with a two-way crossover design, found that more patients preferred once-daily alogliptin (51.7%) compared with weekly trelagliptin (30.0%).²³ Although those studies did not elucidate why some patients preferred a weekly DPP-4 inhibitor, it should be recognized that there are a substantial number who do. Physician engagement directed at understanding individual patient preferences and the barriers that may prevent a patient from achieving optimal glycaemic control may help to identify patients for whom a weekly DPP-4 inhibitor is appropriate.

The primary limitation of this study is that it was conducted only in Japanese patients and the results may not apply to other populations. Another limitation is that, while in clinical practice insulin treatment is a flexible regimen (i.e. insulin type and dose are adjustable), this study restricted insulin type and limited dose adjustment.

In conclusion, omarigliptin added once-weekly to ongoing insulin monotherapy effectively improved glycaemic control and was generally well tolerated in Japanese patients with inadequate glycaemic control. The addition of once-weekly omarigliptin to insulin therapy may be an appropriate therapeutic option to consider for some patients, including those who prefer reduced oral dosing frequency for glycaemic control.

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CONFLICT OF INTEREST

TK has received contract research funds from AstraZeneca and Takeda; joint research funds from Daiichi Sankyo; grants from Astellas, Daiichi Sankyo, Eli Lilly, Kissei, Mitsubishi Tanabe, MSD, Novo Nordisk, Ono, Sanofi, Sumitomo Dainippon, Taisho and Takeda; fees of consulting and/or lectures from Abbott, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Cosmic, Daiichi Sankyo, Eli Lilly, Fujifilm, Johnson & Johnson, Kissei, Kowa, Kyowa Hakko Kirin, Medical Review, Medical View, Medscape Education, Medtronic Sofamor

Danek, Mitsubishi Tanabe, MSD, Musashino Foods, Nipro, Novartis, Novo Nordisk, Ono, Sanofi, Sanwa Kagaku, Sumitomo Dainippon, Taisho, Takeda and Terumo; and has been in an endowed chair from Asahi Mutual Life Insurance, Boehringer Ingelheim, Kowa, Mitsubishi Tanabe, MSD, Novo Nordisk, Ono and Takeda. YS has received contracted/collaborative research funds from Bayer, Boehringer Ingelheim and Terumo; scholarship grants from Arklay, Novo Nordisk, Ono, Sumitomo Dainippon and Taisho Toyama; and fees of consulting and/or lectures from Becton Dickinson, Boehringer Ingelheim, Kao, MSD, Novo Nordisk, Taisho, Taisho Toyama and Takeda. KK has received scholarship grants from Boehringer Ingelheim, Daiichi Sankyo and Mitsubishi Tanabe; and fees of consulting and/or lectures from Astellas, AstraZeneca, Boehringer Ingelheim, Fujifilm, Kissei, Kowa, Mitsubishi Tanabe, MSD, Novartis, Novo Nordisk, Sanofi, Sanwa Kagaku, Sumitomo Dainippon, Taisho Toyama and Takeda. TO, MK, AS, TH, NO, IG, EAO'N and SSE are current employees of MSD K.K., Tokyo, Japan, or Merck Sharp & Dohme Corp., subsidiaries of Merck & Co., Inc., Kenilworth, NJ, USA, and may own stock/stock options in Merck & Co., Inc., Kenilworth, NJ, USA. No other potential conflicts of interest relevant to this article are reported.

AUTHOR CONTRIBUTIONS

TK, YS and KK contributed to finalization of the study protocol with provision of substantive suggestions for the study design, interpreted the results and critically reviewed and/or revised the manuscript for important intellectual content. TO and IG conceived, designed and planned the study, interpreted the results, wrote sections of the initial draft, and critically reviewed and/or revised the manuscript for important intellectual content. MK, AS, TH and SSE conceived, designed and planned the study, interpreted the results, and critically reviewed and/or revised the manuscript for important intellectual content. NO analysed the data and critically reviewed the manuscript for important intellectual content. EAO'N interpreted the results, wrote sections of the initial draft, and critically reviewed and/or revised the manuscript for important intellectual content. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA's data sharing policy, including restrictions, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

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SUPPORTING INFORMATION

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

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