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A randomised, double-blind, trial of the safety and efficacy of omarigliptin (a once-weekly DPP-4 inhibitor) in subjects with type 2 diabetes and renal impairment

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Summary

Aims: To assess the safety and efficacy of omarigliptin in subjects with type 2 diabetes mellitus (T2DM) and chronic renal impairment (RI).

Methods: Patients with T2DM with moderate RI (estimated glomerular filtration rate [eGFR] ≥30 to <60 mL/min/1.73 m^2) (N=114), severe RI (eGFR <30 mL/min/1.73 m^2) (N=55) or end-stage renal disease on dialysis (N=44), who were either not on an antihyperglycaemic agent therapy for at least 12 weeks at screening, washed-off of oral antihyperglycaemic agent monotherapy or low-dose dual combination therapy, or on insulin monotherapy, with baseline glycated haemoglobin (HbA1c) of 6.5%-10.0% were randomised to omarigliptin or to placebo for 24 weeks (primary end-point) followed by a 30-week period with subjects on placebo switched to blinded glipizide (if not on insulin).

Results: After 24 weeks, from a mean baseline HbA1c of 8.4% in the omarigliptin group and 8.3% in the placebo group, the least squares mean (95% CI) change from baseline in HbA1c in the overall population (all renal strata combined) was −0.77% (−1.00 to −0.54) in the omarigliptin group and −0.44% (−0.67 to −0.21) in the placebo group; between-group difference of −0.33% (−0.63 to −0.02); *P*=0.035. After 24 weeks, the incidences of subjects with symptomatic hypoglycaemia, one or more adverse event (AE), drug-related AE, serious AE and discontinuation due to an AE were similar in the omarigliptin and placebo groups.

Conclusions: In this study in subjects with T2DM and RI, relative to placebo, omarigliptin provided clinically meaningful reductions in HbA1c, had a similar incidence of symptomatic hypoglycaemia and was generally well tolerated.

1 | INTRODUCTION

Among patients with type 2 diabetes mellitus (T2DM), the prevalence with renal impairment (defined as an estimated glomerular filtration [eGFR] rate less than 60 mL/min/1.73 m^2) is approximately 22%.[1] Definitions of renal impairment that include the presence of albuminuria in addition to reduced eGFR yield estimates as high as 35%.[2] T2DM is a leading cause of kidney failure accounting for nearly 44% of new cases.[3] Moreover, having both T2DM and kidney disease is associated with increased mortality compared with having T2DM alone.[4] Because of safety and tolerability issues, antihyperglycaemic treatment options for patients with T2DM who have chronic renal

impairment (RI), especially those with an eGFR <45 mL/min/1.73 m^2 or end-stage renal disease (ESRD) on dialysis, is more restricted than for patients with T2DM with normal renal function or mild RI, despite recent recommendations that broaden the use of metformin in this population.[5-7] Over the past decade, dipeptidyl peptidase-4 (DPP-4) inhibitors have become an established therapy for the treatment T2DM[8,9] and are among the treatment options available for patients with T2DM and chronic RI.[5]

Omarigliptin (MK-3102) is a selective, oral DPP-4 inhibitor with a half-life that enables once-weekly dosing that is primarily eliminated by renal excretion.[10] A once-weekly oral antihyperglycaemic agent (AHA) has the potential to provide patients with T2DM an additional option for managing their glycaemic control as part of a patient-centred approach. Omarigliptin has previously been demonstrated to have efficacy comparable to sitagliptin, a marketed daily DPP-4 inhibitor,[11,12] and is approved in Japan.

Herein, we report the results of a global, double-blind, randomised, parallel-group Phase 3 clinical trial, which assessed the efficacy and safety of omarigliptin administered once-weekly (q.w.) in subjects with moderate and severe RI and ESRD on dialysis.

What's known

- Omarigliptin is a once-weekly DPP-4 inhibitor that is primarily eliminated by renal excretion, which has been demonstrated to have efficacy comparable to sitagliptin, a daily DPP-4 inhibitor.

What's new

- This article presents the results of a trial conducted in subjects with type 2 diabetes with renal impairment that support the efficacy and safety of the 25 mg dose of omarigliptin in subjects with moderate renal impairment, and the 12.5 mg dose of omarigliptin in subjects with severe RI and end-stage renal disease on dialysis.

2 | MATERIALS AND METHODS

2.1 | Subjects

Eligible patients for the study were male or female ≥30 years of age with T2DM and moderate RI (eGFR ≥30 to <60 mL/min/1.73 m^2) or severe RI (eGFR <30 mL/min/1.73 m^2), as determined by the modification of diet in renal disease (MDRD) formula,[13] or ESRD on dialysis for at least 6 months. Eligible patients were either (1) not on an AHA (naïve or off therapy for ≥12 weeks) with glycated haemoglobin (HbA1c) ≥7.0% and ≤10.0%; (2) on a single oral AHA or low-dose dual oral combination AHA (ie, at ≤50% of maximum labelled dose of each agent) with an HbA1c of ≥6.5% and ≤9.0%; or (3) on a stable insulin regimen, at a dose of at least 15 U/d, for ≥10 weeks, with no oral AHA and HbA1c ≥7.5% and ≤10.0% and fasting plasma glucose (FPG) >7.22 mmol/L. Subjects on oral AHA therapy had their medication discontinued ("washed-off"). Subjects had a fasting finger-stick glucose >7.22 mmol/L and <14.43 mmol/L at randomisation. Subjects who entered the trial on insulin monotherapy at screening were to remain on a stable dose of insulin throughout the remainder of the trial unless glycaemic rescue criteria were met (see below). A stable insulin regimen was defined as all daily insulin doses within ±10% of the subject's usual administered daily dose. Subjects could be receiving premixed, intermediate-acting or long-acting insulin (premeal short-acting or rapid-acting insulins were not allowed).

Patients were excluded from the study if they had type 1 diabetes, a history of ketoacidosis, a C-peptide level <0.7 ng/mL, active liver disease, significant cardiovascular disease, a haematological disorder or a history of malignancy, or had been treated with any incretin mimetic or thiazolidinedione within the prior 12 weeks of screening, or with omarigliptin at any time prior to signing informed consent.

Laboratory exclusion criteria included alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 times the upper limit of normal (ULN), triglycerides >600 mg/dL or thyroid-stimulating hormone outside the central laboratory normal range.

2.2 | Study design

This was a randomised, placebo-controlled, parallel-group, double-blind, multicentre study (Figure S1) conducted at 109 centres in Australia (4), Canada (3), Croatia (6), Czech Republic (5), Georgia (6), Hong Kong (5), Hungary (6), Israel (4), Malaysia (9), Philippines (3), Poland (7), Russia (5), Serbia (3), South Africa (4), Spain (8), the United Kingdom (4) and the United States (27). Study duration was up to 69 weeks, including a 1-week screening period, an 8-week "wash-off" period (for patients on oral AHA at screening), a 2-week single-blind placebo run-in period, a 54-week double-blind treatment period consisting of a 24-week placebo-controlled period (Phase A) and a 30-week active-controlled period (Phase B) and a post-trial phone follow-up 28 days after final dose.

Subjects were randomised to omarigliptin or matching placebo in a 1:1 ratio. Randomisation was stratified based on renal status, medical history of cardiovascular disease or heart failure and treatment with insulin at screening. Subjects with moderate RI received omarigliptin 25 mg or matching placebo q.w. Subjects with severe RI or with ESRD on dialysis received omarigliptin 12.5 mg or matching placebo q.w.

During Phase B, subjects receiving placebo during Phase A continued to receive omarigliptin placebo; those who were *not* on insulin were treated with blinded glipizide at a starting dose of 2.5 mg once daily and electively titrated, based on glycaemic control, up to a maximum of 20 mg/d. During Phase B, subjects receiving either omarigliptin or placebo and who were on insulin during Phase A continued to receive omarigliptin or placebo and did not receive blinded glipizide/glipizide-matching placebo. Subjects receiving omarigliptin who were not on insulin during Phase A received glipizide-matching placebo.

Subjects not meeting progressively stricter prespecified glycaemic control criteria postrandomisation were rescued (see Figure S1). In Phase A, subjects not on insulin were rescued with open-label

glipizide, while subjects on insulin were rescued by up-titrating insulin. In Phase B, subjects on open-label glipizide or blinded glipizide/glipizide-matching placebo who needed rescue after maximum up-titration of glipizide had open-label glipizide or blinded glipizide/glipizide-matching placebo discontinued, and were rescued with insulin glargine. In Phase B, subjects on insulin who needed rescue had their insulin up-titrated or insulin regimen changed. Randomisation was done centrally using an interactive voice response system.

The study (MK-3102-019, NCT01698775) was conducted in accordance with the principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies.

2.3 | Study evaluations

The primary objectives of Phase A of this study were assessment of the efficacy, safety and tolerability of omarigliptin compared with placebo through 24 weeks of treatment. The primary study hypothesis was that 24 weeks of treatment with omarigliptin provides greater reduction from baseline in HbA1c than treatment with placebo. Secondary objectives of Phase A were to assess the effect of omarigliptin compared with placebo on change from baseline FPG and eGFR after 24 weeks of treatment. The objectives of Phase B were to assess the effect of omarigliptin on change from baseline of HbA1c, FPG and eGFR after 54 weeks of treatment.

2.4 | Efficacy end-points

Efficacy end-points were changes from baseline in HbA1c and FPG and percentages of subjects at HbA1c goal of <7.0%.

2.5 | Safety end-points

Safety assessment included collection of AEs, physical examination (including vital signs), laboratory blood chemistry (including ALT, AST, total bilirubin, creatine kinase and alkaline phosphatase), lipid panel, haematology, urinalysis and electrocardiogram. In addition, at the request of several European countries, measurements of serum amylase and lipase were instituted after the study was initiated; therefore, not all subjects had baseline values. Renal function was assessed by measuring eGFR (MDRD formula[13]). A standard questionnaire was provided to subjects to collect hypoglycaemia information.

Potential patients with pancreatitis (events assessed by the investigator as possibly being pancreatitis or events meeting prespecified event terms suggestive of pancreatitis) and prespecified hypersensitivity AEs (anaphylactic reaction, angiooedema, asthma-bronchospasm, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms) were evaluated in a blinded manner by external clinical adjudication committees.

2.6 | Population pharmacokinetics

Population pharmacokinetics (PK) sampling was performed at Day 1 (predose), Visit 5/Week 6 (planned time point 2 hours postdose), Visit 6/Week 12 (nominal planned time point 1-2 days postdose), Visit 7/Week 18 (planned time point predose trough) and Visit 9/Week 30 (planned time point 3-5 days postdose).

2.7 | Statistical methods

For efficacy analyses, the primary population included all randomised subjects who received at least one dose of study treatment and had a baseline or a postrandomisation measurement. Data acquired after the initiation of rescue therapy was treated as missing to avoid the confounding influence of rescue therapy.

Analysis of the primary efficacy end-point (change from baseline in HbA1c) used a longitudinal data analysis (LDA) model[14] including terms for treatment, RI stratum, baseline treatment with insulin stratum, time, the interaction of time by treatment, the interaction of time by RI stratum and the interaction of time by baseline treatment with insulin stratum, with a constraint that true mean at baseline is common to all treatment groups (which is valid as a result of randomisation). The primary hypothesis regarding the superiority of omarigliptin compared with placebo in decreasing HbA1c was assessed using the estimated treatment difference from the LDA model. Change from baseline in FPG was analysed using the same LDA model, substituting the appropriate baseline efficacy measurement for HbA1c.

For the analysis of percentages of individuals at the HbA1c goal of <7.0% at Week 24, the LDA model described above was used to impute missing HbA1c data. Ten sets of imputations of each missing value were constructed from the LDA model. Observed data were not imputed. After imputations, all subjects were categorised as at or not at the goal at Week 24. The estimated proportions of subjects at the goal from the 10 imputed datasets were combined using standard multiple imputation techniques proposed by Rubin[15] to yield an overall estimate of response rate and associated variance for each group.

The estimated response rates and adjusted effective sample sizes were used to obtain the confidence interval (CI) for between-group rate difference by the method of Miettinen and Nurminen[16] stratified by RI stratum and baseline treatment with insulin stratum.

Efficacy end-points at Week 54 were summarised. No between-group comparisons were prespecified or intended for Week 54, since treatments were not concurrently initiated, and the placebo group switched to glipizide was no longer the intact group randomised at the beginning of the trial. Statistical models and analysis populations for Week 54 were analogous to those at Week 24.

For safety analyses, the population of all randomised subjects who received at least one dose of study treatment was used. All safety end-points were analysed for the time frame consisting of the Treatment Period +28 days. The primary safety analysis excluded data after rescue to avoid the confounding effect of rescue medication. AEs of symptomatic hypoglycaemia were prespecified as events of interest and point estimates with *P*-values and 95% CI for between-treatment differences in the percentages of subjects with symptomatic hypoglycaemia events were calculated using the method of Miettinen and Nurminen,[16] with RI stratum and baseline insulin stratum as stratification factors. For body weight and eGFR, change from baseline was

analysed using the LDA method described above for HbA1c, substituting the appropriate baseline value for the HbA1c.

The trial targeted the enrolment of 100 subjects (50 subjects/arm) with moderate RI; 60 subjects (30 subjects/arm) with severe RI; and 50 subjects (25 subjects/arm) with ESRD on dialysis. Subjects with moderate RI were to be enrolled so that at least 50% of subjects had an eGFR from ≥30 to ≤45 mL/min/1.73 m^2. Using a standard deviation (SD) of 1.0% and factoring for expected missing data, 105 randomised subjects per treatment group was calculated to provide 90% power to detect a true difference of 0.47% in the mean change from baseline in HbA1c (2-sided test, α=0.05).

For the assessment of safety, two treatment periods are described below: the placebo-controlled period (Phase A) and the combined 54-week treatment period (Phase A and B).

3 | RESULTS

3.1 | Patient disposition and characteristics

A total of 644 patients were screened and 431 were excluded during screening (Figure S2). The most common reason for not being randomised was screen failure (404 patients). Screen failure most commonly occurred because of not meeting the antihyperglycaemic therapy and HbA1c requirements or meeting exclusionary laboratory values. The trial was initiated on 5 October 2012, the last subject visit during Phase A of the study occurred on 22 June 2015 and the last subject visit during Phase B was on 19 January 2016.

Of the 213 subjects randomised (107 in the omarigliptin group and 106 in the placebo group), 195 (91.5%) completed study Phase A on study medication and 170 (79.8%) completed Phase B (Figure S2). Baseline demographics and efficacy parameters were generally balanced between the randomised treatment groups (Table 1). The mean age was 65.2 years, approximately 62% were male; the mean body mass index was 30.1 kg/m^2, and mean duration of diabetes was 15 years.

TABLE 1 Baseline demographic, anthropometric and disease characteristics of study treatment groups

	Omarigliptin N=107	Placebo N=106
Age, years	65.9±9.4	64.5±9.7
Male, n (%)	68 (63.6)	63 (59.4)
Race, n (%)		
White	59 (55.1)	63 (59.4)
Asian	37 (34.6)	38 (35.8)
Black	7 (6.5)	4 (3.8)
Multi-racial	4 (3.7)	0 (0.0)
Native Hawaiian or other Pacific Islander	0 (0.0)	1 (0.9)
Ethnicity, n (%)		
Not Hispanic or Latino	95 (88.8)	96 (90.6)
Hispanic or Latino	10 (9.3)	8 (7.5)
Unknown	2 (1.9)	2 (1.9)
Body weight, kg	80.0±16.3	84.2±20.4
BMI, kg/m^2	29.5±4.5	30.7±6.8
HbA1c, %	8.3±0.8	8.3±0.8
FPG, mmol/L	9.5±2.8	9.5±2.3
Duration of T2DM, years	14.9±8.2	15.1±8.7

Values are mean±SD unless otherwise noted. BMI, body mass index; FPG, fasting plasma glucose; T2DM, type 2 diabetes mellitus.

3.2 | Efficacy results

3.2.1 | Phase A (24-week placebo-controlled period)

From a mean baseline in HbA1c of 8.4% in the omarigliptin group and 8.3% in the placebo group, the LS mean (95% CI) for the change from baseline at Week 24 in HbA1c was −0.77% (−1.00 to −0.54) in the omarigliptin group and −0.44% (−0.67 to −0.21) in the placebo group with a between-group difference of −0.33% (−0.63 to −0.02); *P*=0.035 (Table 2). The reduction in HbA1c from baseline in the omarigliptin group was generally consistent across subgroups (baseline HbA1c, age, sex, BMI, race, ethnicity, duration of diabetes, geographical region, renal stratum and insulin at screening, data not shown). However, there was a smaller between-group difference in HbA1c in subjects using insulin (Table S1).

Treatment with omarigliptin led to comparable reductions in HbA1c from baseline across renal strata, but the between-group differences across strata were affected by unusually large placebo reductions in the severe RI and ESRD strata (Table 2).

The estimated percentage (95% CI) of subjects at the HbA1c target of <7.0% was 27.2% (19.1 to 37.1) in the omarigliptin group and 19.2% (12.2 to 28.8) in the placebo group; *P*=0.305.

The LS mean (95% CI) change from baseline at Week 24 in FPG was −1.4 mmol/L (−2.0 to −0.8) in the omarigliptin group and −1.1 mmol/L (−1.8 to −0.5) in the placebo group with a between-group difference of −0.2 mmol/L (−0.9 to 0.5); nominal *P*=0.540 (Table 2).

A post hoc analysis was performed in the moderate RI stratum, subdividing it into two subgroups: eGFR ≥45-<60 mL/min/1.73 m^2 and eGFR ≥30-<45 mL/min/1.73 m^2 (Table S2). Although the number of subjects in these subgroups was limited, there was no attenuation of efficacy observed in the omarigliptin group in these two subgroups. From a mean baseline HbA1c of 8.6% in the eGFR ≥45-<60 mL/min/1.73 m^2 subgroup, the mean change from baseline in HbA1c was −0.68% (n=18) and from a mean baseline HbA1c of 8.2% in the eGFR ≥30-<45 mL/min/1.73 m^2 subgroup, the mean change from baseline in HbA1C was −0.72% (n=35).

3.2.2 | Phase A and Phase B (54-week treatment period)

The LS means (95% CIs) for the changes from baseline at Week 54 in HbA1c in the omarigliptin group and placebo/glipizide group were −0.79% (−1.10 to −0.47) and −0.83% (−1.16 to −0.49), respectively

TABLE 2 Efficacy end-points at Week 24

Parameter	Omarigliptin N=106[a]	Placebo N=106
HbA1c, %		
Full analysis set		
Baseline	8.4±0.8	8.3±0.8
Week 24	7.5±1.1	7.9±1.1
Change from baseline[b]	−0.77 (−1.00 to −0.54)	−0.44 (−0.67 to −0.21)
Change vs. placebo[c]	−0.33 (−0.63 to −0.02)[d]	—
Moderate renal impairment, not on dialysis		
(eGFR ≥30 to <60 mL/min/1.73 m^2)	n=53	n=61
Baseline	8.3±0.8	8.4±0.8
Week 24	7.6±0.8	8.1±1.1
Change from baseline[b]	−0.68 (−0.95 to −0.42)	−0.06 (−0.31 to 0.18)
Change vs. placebo[c]	−0.62 (−0.97 to −0.26)	—
Severe renal impairment, not on dialysis		
(eGFR <30 mL/min/1.73 m^2)	n=32	n=22
Baseline	8.5±0.8	8.3±0.7
Week 24	7.5±1.4	7.4±1.1
Change from baseline[b]	−0.80 (−1.33 to −0.27)	−0.88 (−1.50 to −0.27)
Change vs. placebo[c]	0.09 (−0.7 to 0.87)	—
ESRD on dialysis	n=21	n=23
Baseline	8.2±0.9	8.3±0.8
Week 24	7.4±1.3	7.6±1.0
Change from baseline[b]	−0.75 (−1.31 to −0.20)	−0.64 (−1.16 to −0.13)
Change vs. placebo[c]	−0.11 (−0.86 to 0.64)	—
FPG, mmol/L		
Full analysis set		
Baseline	9.4±2.8	9.5±2.3
Week 24	7.9±2.4	8.1±2.3
Change from baseline[b]	−1.4 (−2.0 to −0.8)	−1.1 (−1.8 to −0.5)
Change vs. placebo[c]	−0.2 (−0.9 to 0.5)	—

Values are mean±SD unless otherwise noted. To convert mmol/L to mg/dL multiply by 18. [a]One subject in the omarigliptin arm discontinued study medication before taking the first dose and is therefore not included in any analysis population. [b]Least squares (LS) mean (95% CI). [c]Difference in LS means (95% CI). [d]P=0.035.
eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; FPG, fasting plasma glucose.

(Table S3). The profile of change in HbA1c over time is shown in Figure 1A. Twenty-four of the 97 subjects in the placebo/glipizide group who entered Phase B were treated with blinded glipizide; the other subjects in the placebo/glipizide group were on insulin and per protocol did not receive blinded glipizide. The average daily dose of blinded glipizide was 3.85 mg/d. A subgroup analysis showed that treatment with omarigliptin led to reductions in HbA1c from baseline at Week 54 in all renal strata in subjects who were or were not on insulin at screening (Table S3).

The LS means and the 95% CIs for the change from baseline at Week 54 in FPG in the omarigliptin group and placebo/glipizide group were −1.1 mmol/L (−2.0 to −0.1) and −0.9 mmol/L (−1.9 to 0.1), respectively. Change from baseline in FPG over time is shown in Figure 1B.

The approximate percentage (95% CI) of subjects with HbA1c <7.0% at Week 54 was 31.1% (22.2 to 41.8) in the omarigliptin group and 34.2% (24.8 to 45.1) in the placebo/glipizide group.

3.3 | Safety results

3.3.1 | Phase A (24-week placebo-controlled period)

During the first 24 weeks (Phase A) of the trial, the incidences of subjects with one or more AEs, drug-related AEs, serious AEs (SAEs) and discontinuations due to AEs were similar in the omarigliptin and placebo groups (Table 3). One subject died in each treatment group (one fatal SAE of acute cardiac failure in the omarigliptin group and one fatal SAE of cardiorespiratory arrest in the placebo group). There

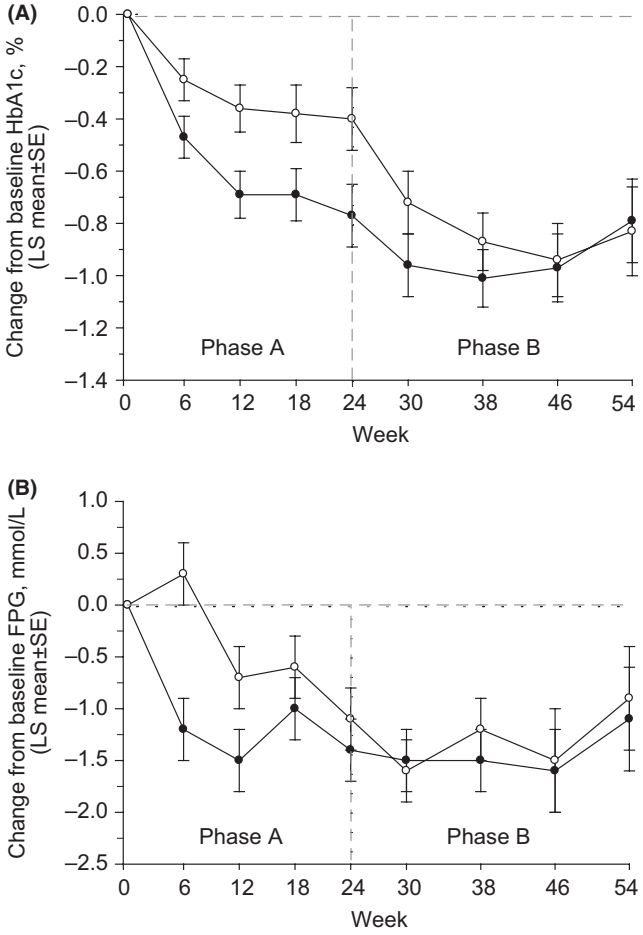

FIGURE 1 Efficacy measures through Week 54; A) change from baseline HbA1c (%); B) change from baseline fasting plasma glucose (mmol/L); ● omarigliptin; ○ placebo; based on a model with terms for treatment, chronic renal impairment (RI) stratum, baseline treatment with insulin stratum, time, the interaction of time by treatment, the interaction of time by RI stratum, and the interaction of time by baseline treatment with insulin stratum with the restriction of a common baseline mean across treatment groups

were no clinically meaningful between-group differences in specific AEs in any System Organ Class (SOC, based on Medical Dictionary for Regulatory Activities Version 17.1[17]; data not shown).

The percentage of subjects reporting one or more AEs of symptomatic hypoglycaemia was 17.0% (18/106) in the omarigliptin and 15.1% (16/106) in the placebo groups; *P*=0.709. All subjects experiencing an AE of symptomatic hypoglycaemia were on insulin therapy at screening (Table 4). The incidences of severe hypoglycaemia (any episode of symptomatic hypoglycaemia that required medical or non-medical assistance) were 5.7% (6/106) in the omarigliptin and 7.5% (8/106) in the placebo groups; 1.9% of subjects (2/106) in the omarigliptin and 2.8% of subjects (3/106) in the placebo groups required medical assistance.

The LS mean (95% CI) change from baseline in eGFR was −0.5 mL/min/1.73 m^2 (−2.1 to 1.2) in the omarigliptin group and −0.0 mL/min/1.73 m^2 (−1.8 to 1.7) in the placebo group (between-group difference of −0.4 mL/min/1.73 m^2 [−2.7 to 1.9]; *P*=0.720). During Phase A, 3.8% of subjects (4/106) in the omarigliptin group and 5.7% of subjects (6/106) in the placebo group in the moderate RI stratum had worsening of renal function defined as two consecutive eGFR values <30 mL/min/1.73 m^2 on different days during the treatment period.

The LS mean (95% CI) change from baseline in body weight was −0.1 kg (−0.6 to 0.5) in the omarigliptin group and −0.3 kg (−0.8 to 0.2) in the placebo group; *P*=0.477.

3.3.2 | Phase A and Phase B (54-week treatment period)

Over the 54-week treatment period (Phase A and Phase B), there were no notable differences between the omarigliptin and placebo/glipizide groups in summary AE measures, including the percentage of subjects with one or more AEs, drug-related AEs, SAEs, and discontinuations due to AEs (Table 3). There were no clinically meaningful differences in overall AEs by SOC or of any specific AE within an SOC (data not shown). In the renal disorders SOC, none of the AEs in the omarigliptin group led to the discontinuation of study medication or were considered by the investigator to be related to study drug.

The percentage of subjects reporting one or more AEs of symptomatic hypoglycaemia was 22.6% (24/106) in the omarigliptin and 20.8% (22/106) in the placebo/glipizide group; *P*=0.915. In those on insulin, the incidence of symptomatic hypoglycaemia was 32.9% in the omarigliptin group and 30.2% in the placebo/glipizide group (Table 4). One of the subjects with an AE of symptomatic hypoglycaemia in the omarigliptin group was not on insulin (2.8%), while three subjects not on insulin in the placebo/glipizide group had at least one AE of symptomatic hypoglycaemia (7.0%), one of which was severe.

The LS mean (95% CI) change from baseline in eGFR was −2.0 mL/min/1.73 m^2 (−4.0 to −0.1) in the omarigliptin group and −2.3 mL/min/1.73 m^2 (−4.3 to −0.2) in the placebo group. During Phase A and Phase B, 11.3% of subjects (6/53) in the omarigliptin group and 14.8% of subjects (9/61) in the placebo/glipizide group in the moderate renal stratum had worsening renal function.

Both at the 24-week time point (placebo-controlled period) and over 54 weeks, omarigliptin treatment did not result in any clinically meaningful changes from baseline in safety laboratory measures or between-group differences in percentage of subjects who met predefined limits of change for safety laboratory measures, including liver tests and lipids. Similarly, there were no clinically meaningful changes from baseline in blood pressure, pulse rate or ECG parameters.

The LS mean (95% CI) change from baseline in body weight was −0.6 kg (−2.1 to 0.8) in the omarigliptin group and −1.5 kg (−2.9 to −0.0) in the placebo group.

Small increases from baseline in mean serum amylase were observed in the overall population (combined strata) at Week 24 and Week 54 in both treatment groups; the mean change was slightly greater in the omarigliptin group at Week 24 but not at Week 54. Mean baseline, Week 24 and Week 54 serum amylase levels were within normal laboratory range in both treatment groups (Table S4). Small increases from baseline in mean serum lipase were observed in the overall population (combined strata) in the omarigliptin group at Week 24 and Week 54. Mean baseline and Week 54 values of serum

TABLE 3 Adverse events summary

	Phase A		Phase A + B	
Subjects, n (%)	Omarigliptin N=106[b]	Placebo N=106	Omarigliptin N=106	Placebo/glipizide N=106
With one or more				
AEs	70 (66.0)	74 (69.8)	82 (77.4)	83 (78.3)
Drug-related[a] AEs	10 (9.4)	9 (8.5)	13 (12.3)	10 (9.4)
Serious AEs	9 (8.5)	13 (12.3)	21 (19.8)	20 (18.9)
Serious drug-related[a] AEs	1 (0.9)	0 (0.0)	1 (0.9)	0 (0.0)
Who died	1 (0.9)	1 (0.9)	2 (1.9)	3 (2.8)
Who discontinued due to				
An AE	3 (2.8)	1 (0.9)	7 (6.6)	4 (3.8)
A drug-related[a] AE	1 (0.9)	1 (0.9)	2 (1.9)	1 (0.9)
A serious AE	1 (0.9)	0 (0.0)	3 (2.8)	3 (2.8)
A serious drug-related[a] AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a]Assessed by the investigator to be related to the drug. [b]One subject in the omarigliptin arm discontinued study medication before taking the first dose and is therefore not included in any analysis population.

lipase were slightly above the laboratory upper limit of normal for both treatment groups (Table S4).

There were no adjudication-confirmed patients of prespecified hypersensitivity or pancreatitis (acute or chronic) during Phase A or Phase B of the trial.

3.4 | Population pharmacokinetics

Sparse PK data from this study were pooled with the PK data from other Phase 1, Phase 2 and Phase 3 trials for an integrated population PK analysis. The details of this analysis will be the subject of a separate publication. The population PK analysis, including PK data from this study, demonstrated that the 25 mg dose in subjects with moderate renal impairment and 12.5 mg dose in subjects with severe renal impairment and ESRD achieved omarigliptin plasma drug exposures which were within 1.5 -fold the exposure of 25 mg dose in a normal renal function. The results of the pooled PK analysis showed that plasma exposures with omarigliptin 12.5 mg and 25 mg were consistent with those predicted from an earlier clinical pharmacology trial.[18]

4 | DISCUSSION

Omarigliptin has a long half-life that supports once-weekly dosing. The long half-life of omarigliptin is because of its limited metabolism and low renal clearance. Because omarigliptin is eliminated primarily

TABLE 4 Adverse events of hypoglycaemia

	Phase A		Phase A + B	
Subjects, n (%)	Omarigliptin N=106	Placebo N=106	Omarigliptin N=106	Placebo/glipizide N=106
On insulin	n=70	n=63	n=70	n=63
With one or more AE of hypoglycaemia	22 (31.4)	19 (30.2)	28 (40.0)	22 (34.9)
Symptomatic[a]	18 (25.7)	16 (25.4)	23 (32.9)	19 (30.2)
Severe[b]	6 (8.6)	8 (12.7)	7 (10.0)	8 (12.7)
Asymptomatic[c]	11 (15.7)	6 (9.5)	14 (20.0)	12 (19.0)
Not on insulin	n=36	n=43	n=36	n=43
With one or more AE of hypoglycaemia	0 (0.0)	0 (0.0)	1 (2.8)	3 (7.0)
Symptomatic[a]	0 (0.0)	0 (0.0)	1 (2.8)	3 (7.0)
Severe[b]	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)
Asymptomatic[c]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a]Symptomatic hypoglycaemia: episode with clinical symptoms attributed to hypoglycaemia, without regard to glucose level. [b]Severe 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. [c]Asymptomatic hypoglycaemia: glucose values ≤3.9 mmol/L without symptoms.

by the kidney, the assessment of efficacy and safety of omarigliptin in subjects with renal impairment is of particular interest.

In this study, in the overall population of subjects with renal impairment, treatment with omarigliptin once weekly for 24 weeks achieved a clinically meaningful reduction in HbA1c from baseline compared with placebo and the prespecified primary efficacy hypothesis for HbA1c in the placebo-controlled portion of the trial (Phase A) was met. The proportion of subjects achieving HbA1c goals of <7.0% were numerically higher in the omarigliptin group than the placebo group, although the difference between the treatment groups was not significant. Treatment for 24 weeks with omarigliptin compared with placebo did not result in a significant reduction in FPG, the secondary glycaemic end-point. The lack of a between-group difference in FPG may be attributed to a decrease in FPG over 24 weeks observed in the placebo group. Notably, the initial (at Week 6) between-group difference in FPG was substantial, but subsequently FPG in the placebo group decreased from baseline, narrowing the difference between groups. The decrease in the placebo group was unexpected, and could reflect a trial effect in that group, with greater compliance to diet and medication (eg, insulin).

In subgroups based on degree of RI, similar reductions from baseline in HbA1c were observed across all renal strata in the omarigliptin group; however, because of varying degrees of reductions in HbA1c in the placebo group, smaller between-group differences in the severe RI and ESRD on dialysis subgroups were observed compared with the moderate RI subgroup. Subgroup results, which contain smaller numbers of subjects, should be viewed with caution since the study was not designed to have precision to examine subgroup effects.

Improvements in glycaemic control in subjects on placebo have been attributed to better adherence to diet and exercise associated with participation in a clinical trial, although this explanation is unlikely to completely account for the magnitude of effect observed in this study in some subgroups. Overall, 63% of subjects in the study were on insulin therapy. The change from baseline with placebo was more prominent in subjects on insulin than those not on insulin, which raises the possibility that the trial effect reflected not only better adherence to diet and exercise, but also better adherence to (or adjustment of) insulin therapy. Because subjects on insulin routinely monitor their finger-stick glucose, adherence to insulin, diet and exercise may be influenced by knowledge of glucose measurements, leading to unequal trial effects in the two treatment arms.

It is unlikely that omarigliptin has a different therapeutic effect in subjects with severe RI and ESRD compared with those with moderate RI. Based on the properties of omarigliptin, there is no reason to expect a different efficacy profile between omarigliptin and other DPP-4 inhibitors. DPP-4 inhibitors are effective in patients with chronic renal impairment including in patients with varying degrees of RI, providing strong evidence that DPP-4 inhibition is maintained irrespective of renal status.

There were no prespecified comparisons of the omarigliptin group with the placebo/glipizide group in Phase B, since the treatments (omarigliptin and glipizide) were not concurrently initiated and subjects in the placebo/glipizide group at entry into Phase B were no longer the intact group randomised at the beginning of Phase A. The reason for the use of glipizide in Phase B was to provide subjects who were randomised to placebo in Phase A and who were not on insulin with an oral AHA treatment under blinded conditions to avoid inadequate glycaemic control during Phase B.

Treatment with omarigliptin once weekly resulted in reductions in HbA1c and FPG from baseline throughout the 54-week treatment period in the overall study population (combined renal strata). A subgroup analysis by renal stratum and insulin use at baseline showed that reductions were observed in all renal strata regardless of insulin use at baseline. Given the known efficacy of glipizide in patients with RI,[19,20] the observation of similar reductions in HbA1c at Week 54 in both treatment groups supports the efficacy of omarigliptin at Week 54 in this study population.

No notable between-group differences occurred in any SOC including the renal disorders SOC. Small mean decreases in eGFR were observed in both treatment groups. The percentage of subjects with worsening of renal function in both Phase A and B was similar between treatment groups. The small changes in these renal parameters are consistent with progression of renal disease that might be anticipated in the study population.[21] Thus, there were no findings to suggest that omarigliptin treatment increases the risk of worsening renal dysfunction in this study population with RI.

The hypoglycaemia profile is an important feature of any AHA. In this study, there were no notable between-group differences in the incidences of symptomatic, asymptomatic or severe hypoglycaemia. Consistent with the recognised increase in hypoglycaemia when DPP-4 inhibitors are used with agents that are associated with hypoglycaemia (such as sulfonylureas and insulin) almost all of the subjects experiencing hypoglycaemia in this study were using insulin concomitantly, while only one subject in the omarigliptin group and three in the placebo/glipizide group not on insulin had an AE of symptomatic hypoglycaemia.

The small changes from baseline in mean serum amylase and lipase did not appear to be clinically meaningful. There were no patients of adjudication-confirmed pancreatitis in either treatment group.

The results of PK analysis were consistent with previous predictions that were used to support the selection of doses for this trial[18] and lend further support for the use of 25 mg once weekly in subjects with moderate RI and the use of 12.5 mg once weekly in subjects with severe RI and ESRD to maintain exposures of omarigliptin similar to those observed in patients with normal renal function. Omarigliptin is highly membrane permeable and not secreted by renal transporters [unpublished data]. These properties account for the reabsorption of a large fraction of the filtered omarigliptin in the kidney, which is demonstrated by the observation that the unbound renal clearance of omarigliptin at steady state is substantially below the average glomerular filtration rate. It is postulated that the reabsorption of omarigliptin in the tubules occurs passively along with sodium and water reabsorption.[22]

The present trial conducted in subjects with T2DM and varying degrees of RI, extends our understanding of omarigliptin efficacy and safety in this patient population. The safety profile of omarigliptin observed in this trial is consistent with the safety profile of presently

marketed daily DPP-4 inhibitors. The results of this trial support the safety of omarigliptin with long-term use in subjects with RI (moderate and severe RI and ESRD on dialysis).

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CONFLICT OF INTEREST

Ira Gantz, Geraldine Mendizabal, Lucila Durlach, Edward A. O'Neill, Zachary Zimmer, Shailaja Suryawanshi, Samuel S. Engel and Eseng Lai are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, who may own stock and/or hold stock options in the Company. Antonio Chacra lists no conflict of interest.

AUTHOR CONTRIBUTIONS

Antonio Chacra, Ira Gantz, Geraldine Mendizabal, Lucila Durlach, Edward A. O'Neill, Zachary Zimmer, Shailaja Suryawanshi, Samuel S. Engel and Eseng Lai are responsible for the work described in this paper. All authors were involved in at least one of the following: conception, design, acquisition, analysis, statistical analysis, and interpretation of data in addition to drafting the manuscript and/or revising/reviewing 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.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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