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A randomized, double-blind trial evaluating the efficacy and safety of monotherapy with the once-weekly dipeptidyl peptidase-4 inhibitor omarigliptin in people with type 2 diabetes

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ABSTRACT

Aims: To assess the efficacy and safety of once-weekly omarigliptin as monotherapy in people with type 2 diabetes mellitus (T2DM).

Methods: People with T2DM not on glucose-lowering medications, or who were washed off monotherapy or low-dose dual therapy, were randomized double-blind to omarigliptin 25 mg (n = 165) or matching omarigliptin placebo (n = 164) for 24 weeks, followed by a 30-week period to assess continuing efficacy and safety longer-term of omarigliptin during which metformin was added to the placebo group and metformin placebo to the omarigliptin group.

Results: From a mean baseline HbA1c of 8.0–8.1%, the least squares mean (95% CI) change from baseline in HbA1c at week 24 (primary endpoint) was −0.49% (−0.73, −0.24) in the omarigliptin group and −0.10% (−0.34, 0.14) in the placebo group, for a between-group difference of −0.39% (−0.59, −0.19) ($p < .001$). Protocol deviation in use of metformin by 38 of 252 (15%) people whose samples were available for evaluation probably attenuated glycemic efficacy results, as suggested by the LS mean difference −0.53% (−0.75, −0.32) after censoring of such participants. At 24 and 54 weeks, the incidences of adverse events (AEs) were similar in the omarigliptin and placebo groups. During 54 weeks there were no AEs of symptomatic hypoglycemia in the omarigliptin group and 5 AEs in the placebo group. Over 54 weeks, a majority of the omarigliptin treatment had a persistent reduction in HbA1c, remaining rescue-free.

Conclusions: In people with T2DM, omarigliptin monotherapy improved glycemic control over 54 weeks and was generally well tolerated with a low risk of hypoglycemia.

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1. Introduction

Omarigliptin (MK-3102) is a selective, oral dipeptidyl peptidase-4 (DPP-4) inhibitor with a half-life that enables once-weekly dosing [1] that is presently approved in Japan. In a phase 2 dose-range finding study [2], as monotherapy [3] and in combination with metformin [4], omarigliptin had comparable glucose-lowering efficacy to daily sitagliptin. Experience of oral weekly glucose-lowering therapies in type 2 diabetes (T2DM) is very limited, and raises issues of adherence and safety/tolerability.

We have therefore examined the efficacy and safety of omarigliptin in a phase 3 clinical trial, using standard double-blind, randomized, parallel group, placebo-controlled methodology, with an extension phase to provide additional exposure for safety purposes and to confirm maintenance of efficacy. Because the glycemic efficacy at the primary endpoint (week 24) was less robust than that observed in other omarigliptin trials, a series of investigations were undertaken that uncovered the off-protocol use of metformin by some trial participants. Metformin use was prohibited by protocol except as investigator prescribed rescue medication. Protocol violations in the use of metformin are likely to have affected the trial results. We note the potential for this to be an issue in other studies.

2. Methods

2.1. Study population

Eligible participants were men or women, ≥18 years of age with T2DM, who at screening were either not on an oral glucose-lowering drug (OGLD) for at least 12 weeks and had a screening visit HbA1c ≥7.0% (53 mmol/mol) and ≤10.0% (86 mmol/mol) on diet and exercise alone, or had HbA1c ≥6.5% (48 mmol/mol) and ≤9.0% (75 mmol/mol) on OGLD monotherapy or low-dose (≤50% of maximum label dose of each agent) dual oral therapy. Details of inclusion/exclusion criteria, including excluded medications, are given in the Supplementary Appendix.

2.2. Study design

This was a multicenter, double-blind, randomized, parallel-group trial. The duration of the trial was up to 65 weeks with 12 visits (Supplemental Fig. 1). This trial included a 1-week screening period; an 8-week diet/exercise and oral agent "wash-off" (for people using OGLDs) period; a 2-week single-blind placebo run-in period; a 24-week placebo-controlled, double-blind treatment period (phase A); and a 30-week active-controlled, double-blind treatment period (phase B). Use of other OGLDs was prohibited before the primary endpoint at the end of the 24-week treatment period, except for rescue therapy (see below). At or within 2 weeks prior to week −2, all eligible participants were required to have HbA1c ≥7.0% (53 mmol/mol) and ≤10.0% (86 mmol/mol), and all were required to have a fasting finger-capillary plasma glucose <14.4 mmol/L at the time of randomization. Randomization was to omarigliptin 25 mg once weekly (q.w.) or matching placebo for 24 weeks (phase A).

At the end of phase A (the primary time point), participants entered the 30-week extension period (phase B), in which those randomized to placebo and who were not previously rescued with open-label metformin had blinded metformin added to their treatment regimen to avoid prolonged 'treatment' with placebo alone. Metformin was started at 500 mg twice daily and up-titrated to 1000 mg twice daily. Omarigliptin was continued in those randomized to it, and blinded metformin placebo added unless metformin had already been begun as rescue therapy. Participants on open-label metformin rescue therapy remained in the trial throughout phase B.

During the trial, participants who did not meet progressively stricter protocol-specified glycemic thresholds were given rescue therapy (see Supplementary Table 1 for glycemic thresholds). Prior to week 24, participants were rescued by adding open-label metformin and after that time by adding open-label glimepiride.

A meal tolerance test (MTT) was conducted at randomization, before beginning trial medication, and at week 24 (or at rescue/discontinuation visit) up to 7 days after the last dose of omarigliptin, in participants from a subset of trial sites (see Supplemental Appendix).

The study (Merck protocol MK-3102-011) was conducted in accordance with Good Clinical Practice and the principles of the Declaration of Helsinki and was approved by the regulatory agencies and appropriate institutional review boards/ethics committees. Written informed consent was obtained from all study participants.

2.3. Study evaluations and endpoints

The primary objectives of this study were assessment of the efficacy, safety and tolerability of omarigliptin compared with placebo when used as monotherapy. The primary study hypothesis was that after 24 weeks of treatment, omarigliptin 25 mg once weekly would provide a greater reduction from baseline in HbA1c than treatment with placebo. Secondary objectives were to assess the effect of omarigliptin compared with placebo on FPG, on the proportion of participants achieving HbA1c of <7.0% (53 mmol/mol), and on 2-h post-meal plasma glucose (2-h PMG). Efficacy endpoints were change from baseline in HbA1c, FPG and 2-h PMG. Blood samples for omarigliptin population PK were collected at designated visits and time points (see Supplementary Appendix). Analytical methods are given in the Supplementary Appendix. Data will be reported in a separate publication.

Safety/tolerability assessment included collection of adverse events (AEs), physical examination and vital signs, blood chemistry, amylase, lipase, lipids, and hematology, urinalysis, body weight, and electrocardiogram (ECG). A questionnaire was provided to participants to collect data on hypoglycemia. Potential cases of 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, angioedema, asthma-bronchospasm, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms) were evaluated blind to randomized treatments by external clinical adjudication committees.

2.4. Statistical analyses

For efficacy analyses, the population of all randomized participants who received at least one dose of study treatment and had a baseline or a post-randomization measurement served as the primary population. For analyses of glycemic endpoints, a longitudinal data analysis (LDA) model [5], including terms for treatment, time, prior AHA therapy status, and the interaction of time by treatment, and time by prior AHA therapy status, with the restriction of a common baseline mean across treatment groups (valid through randomization), was used. Analysis of percentages of populations at the HbA1c goal of <7.0% (53 mmol/mol) at week 24 was based on estimated rates and confidence intervals for between-group rate differences computed using the Miettinen and Nurminen method [6]. Multiple imputations based on the LDA model used for the analysis of HbA1c were used to handle missing data [7].

For the analysis of safety data, the population of all randomized patients who received at least one dose of study treatment was used. Safety and tolerability were assessed during the treatment period and for 21 days after treatment ended. AEs of symptomatic hypoglycemia were prespecified as events of interest and p-values and 95% confidence intervals (CI) for between-treatment group comparisons of incidence were calculated. Change from baseline in body weight was analyzed using the LDA model described above.

The primary analyses for both efficacy and safety censored data acquired after beginning rescue therapy to avoid the confounding effects of rescue therapy. A secondary analysis was performed including data after rescue.

As defined in the statistical analysis plan, only observational comparisons of omarigliptin with metformin were made in phase B, since metformin treatment was expected to be imbalanced by the end of the primary phase due to asymmetric use of it as rescue therapy. In addition, the placebo group switched to metformin at entry into phase B was no longer the intact group randomized at the beginning of the base period.

Using a conditional standard deviation (SD) for HbA1c change over time of 1.0% (10.9 mmol/mol) in an analysis model with baseline as a covariate, an effective sample size of 135 subjects per treatment group at week 24 was calculated to provide 90% power to detect a true difference of 0.40% (4.4 mmol/mol) in the mean change from baseline between the two treatment groups (2-sided test, $\alpha = 0.05$).

3. Results

3.1. Participant disposition and characteristics

In total, 751 people were screened with 422 excluded. The most common reasons for screen failure were not meeting the glucose-lowering therapy and HbA1c requirements, or having exclusionary laboratory values. The remaining 329 people were randomized at 76 sites in 10 countries (Bulgaria [10], Germany [36], Hungary [44], Italy [13], Netherlands [17], Philippines [36], Romania [49], South Korea [12], Taiwan [40], and United States [72]). The trial was begun in December 2012 and the last participant visit at 54 weeks was in June 2015. Baseline characteristics were similar between the randomized treatment groups, including prior use of glucose-lowering therapies prior to wash-off (Table 1). Of the 329 people randomized, 56.2% (185 people) had been treated with metformin and 2.7% (9 people) had been treated with other OGLDs prior to enrollment in the study and required wash-off.

Of the 165 participants in the omarigliptin group, 89.1% (147/165) completed phase A on trial medication, 88.5% (146/165) entered phase B, 87.3% (144/165) completed the trial through 54 weeks, and 73.3% (121/165) completed on trial medication (Supplementary Table 2).

Of the 164 participants in the placebo group, 92.1% (151/164) completed phase A on trial medication and entered phase B; 83.5% (137/164) completed the trial through 54 weeks, and 77.4% (127/164) completed on trial medication.

Of the randomized population, in the omarigliptin group at 24 weeks, 10.9% (18/165) had initiated rescue therapy, the Kaplan-Meier estimate allowing for discontinuations being 11.9% (95%CI 7.7, 18.2). This compares to 15.2% (25/164) and 16.0% (95%CI 11.1, 22.8) for the placebo, not statistically significantly different from the omarigliptin group. At 54 weeks these figures were 32.7% (54/165) and 37.7% (95%CI 30.3, 46.3) for the omarigliptin group and 23.2% (38/164) and 25.3% (95%CI 19.1, 33.2) for the placebo/metformin group.

3.2. Efficacy

3.2.1. 24-week placebo-controlled period (phase A)

From a mean baseline HbA1c of 8.0% (64 mmol/mol) in the omarigliptin group and 8.1% (65 mmol/mol) in the placebo group, the between-group difference in least squares (LS) mean (95% CI) change from baseline in HbA1c at week 24 was −0.39% (−0.59, −0.19) (−4.3 mmol/mol [−6.4, −2.1]); p < .001 (Table 2). The estimated percentage (95% CI) of participants at the HbA1c target of <7.0% (53 mmol/mol) was 36.5% (29.3%, 44.5%) in the omarigliptin group, and 16.3% (11.3%, 22.5%) in the placebo group (p < .001 between groups).

The between-group difference in LS mean (95% CI) change from baseline at week 24 in FPG was −0.6 (−1.1, −0.0) mmol/L, p = .036 (Table 2). For 2-h PMG this was −0.6 (−1.6, 0.3) mmol/L (Table 2).

3.2.2. 54-week period (phases A + B)

The LS mean (95% CIs) changes from baseline at week 54 in HbA1c in the omarigliptin and placebo/metformin groups were −0.40% (−0.67, −0.13) (−4.4 mmol/mol [−7.3, −1.4]) and −0.80% (−1.07, −0.53) (−8.7 mmol/mol [−11.7, −5.8]), (Supplementary Table 3). The modeled profile of change in HbA1c over time is shown in Fig. 1A. The estimated percentage (95% CI) of people with HbA1c <7.0% (53 mmol/mol) in the omarigliptin and placebo/metformin groups were 33.8% (26.8%, 41.5%) and 43.8% (36.2%, 51.7%). The LS mean (95% CI) changes from baseline to week 54 in FPG in the omarigliptin and placebo/metformin groups were −0.5 (−1.1, 0.2) mmol/L and −1.2 (−1.8, −0.5) mmol/L (Supplementary Table 3). The profile of change from baseline in FPG over time is shown in Fig. 1B.

Table 1 – Baseline characteristics of the people with type 2 diabetes studied.

	Omarigliptin n = 165	Placebo n = 164
Age, years	57.4 ± 9.2	57.0 ± 9.7
Male, *n* (%)	95 (57.6)	97 (59.1)
Race, *n* (%)		
White	113 (68.5)	111 (67.7)
Asian	47 (28.5)	43 (26.2)
Black	4 (2.4)	9 (5.5)
Multi-racial	0 (0.0)	1 (0.6)
American Indian/Alaska Native	1 (0.6)	0 (0.0)
Ethnicity, *n* (%)		
Not Hispanic or Latino	162 (98.2)	162 (98.8)
Hispanic or Latino	3 (1.8)	2 (1.2)
Body weight, kg	87.6 ± 21.6	87.9 ± 23.2
BMI, kg/m^2	31.1 ± 6.1	30.8 ± 6.6
HbA1c		
%	8.0 ± 0.9	8.1 ± 1.0
mmol/mol	64 ± 10	65 ± 11
2-Hour PMG, mmol/L	14.2 ± 4.1	13.4 ± 3.8
FPG, mmol/L	9.6 ± 2.3	9.4 ± 2.4
Duration of diabetes, years	5.4 ± 3.8	5.7 ± 4.7
Prior OGLD therapy		
None	74 (44.8)	61 (37.2)
Metformin user	87 (52.7)	98 (59.8)
Not-metformin user	4 (2.4)	5 (3.0)

Values are Mean ± SD or n (%).
BMI, body mass index; PMG, post-meal plasma glucose; FPG, fasting plasma glucose; OGLD, oral glucose-lowering drug.
Glucose in mg/dL = mmol/L × 18.0.

3.3. *Safety and tolerability*

3.3.1. *24-week placebo-controlled period (primary phase A) and 54-week period (phase A + B)*

In both phase A and over the entire treatment period (phase A + B), the percentage of patients with one or more adverse event (AE), drug-related AE, serious AE, and who discontinued due to an AE were similar between treatment groups (Table 3). There were no clinically meaningful between-group differences in the incidences of AEs by Medical Dictionary for Regulatory Activities (MedDRA) system organ class or any specific AE in either treatment period, with the exception of the AE of hypoglycemia as described below.

During phase A, AEs of hypoglycemia (symptomatic or asymptomatic), excluding data after glycemic rescue, were reported for 1 person (0.6%) in the omarigliptin group and two (1.2%) in the placebo group (Table 3). The single AE of hypoglycemia in the omarigliptin group was asymptomatic (documented glucose level $\leq$3.9 mmol/L without symptoms); the AEs in the placebo group were documented symptomatic hypoglycemia. During phases A + B, the proportion of participants with the AE of symptomatic hypoglycemia was significantly lower in the omarigliptin group (none) compared with the placebo/metformin group (3.0% [5/164 people]; 4 of whom had documented hypoglycemia) (Table 3). No severe hypoglycemia was reported in the study.

During phases A + B, no participants in either treatment group had adjudication-confirmed pancreatitis (acute or chronic). No one in the omarigliptin group and 1 person in the placebo group had adjudication-confirmed asthma-bronchospasm. There were no other hypersensitivity reactions (see Methods). There were no clinically meaningful mean changes from baseline in laboratory measures (including electrolytes, liver function tests, renal function measures, serum lipids, and hematology, serum amylase or lipase), predefined limits of change for laboratory measures, vital signs, body weight (see Supplementary Table 4), or ECG parameters in either treatment group.

3.4. *Investigations into the attenuated glycemic efficacy*

Given that the glycemic efficacy observed in this study was attenuated compared with previous omarigliptin studies (see Discussion) a series of investigations were undertaken to determine if compliance with study medication, operational errors or other trial-related failings might have contributed to the results. Compliance with study medication (omarigliptin or matching omarigliptin placebo) was assessed at each visit by patient report. During the primary 24 week phase, mean compliance with study medication was 95.2% in the omarigliptin group and 94.7% in the placebo group. Over the 54-week treatment period, mean compliance with study medication was the same (95.3%) in the two the treatment groups.

No errors were identified in the distribution of study medication based on reviews of the allocation schedule, interactive voice recognition system (used to randomize subjects), drug dispensing logs or drug supply records. Measurement of omarigliptin concentrations, which were assessed in the PK samples of subjects in both the omarigliptin and placebo

Table 2 – Glycemic endpoints at week 24.

		Omarigliptin	Placebo
Full study population (randomized and treated)			
HbA1c (n = 165/164)			
Baseline	%	8.0 ± 0.9	8.1 ± 1.0
	mmol/mol	64 ± 10	65 ± 11
Week 24[a]	%	7.4 ± 1.1	7.8 ± 1.0
	mmol/mol	57 ± 12	61 ± 11
Change from baseline[b]	%	−0.49 (−0.73, −0.24)	−0.10 (−0.34, 0.14)
	mmol/mol	−5.3 [−8.0, −2.7]	−1.1 [−3.7, 1.6]
Change vs. placebo[c,d]	%	−0.39 (−0.59, −0.19)	–
	mmol/mol	−4.2 (−6.4, −2.1)	–
FPG (n = 165/164), mmol/l			
Baseline		9.6 ± 2.3	9.4 ± 2.4
Week 24[a]		8.5 ± 2.3	8.8 ± 2.3
Change from baseline[b]		−0.7 (−1.4, −0.0)	−0.1 (−0.8, 0.6)
Change vs. placebo[c,e]		−0.6 (−1.1, −0.0)	–
2-h PMG (n = 106/102), mmol/L			
Baseline		14.2 ± 4.1	13.4 ± 3.8
Week 24[a]		12.0 ± 3.8	11.9 ± 3.7
Change from baseline[b]		−1.4 (−3.1, 0.3)	−0.8 (−2.4, 0.9)
Change vs. placebo[c]		−0.6 (−1.6, 0.3)	–
Per protocol population excluding users of prohibited metformin			
HbA1c (n = 149/131),%			
Baseline	%	8.0 ± 0.9	8.0 ± 0.9
	mmol/mol	64 ± 9.8	64 ± 9.8
Week 24[a]	%	7.3 ± 1.1	7.8 ± 1.1
	mmol/mol	56 ± 12.0	62 ± 12
Change from baseline[b]	%	−0.54 (−0.68, −0.39)	−0.00 (−0.17, 0.16)
	mmol/mol	−5.9 (−7.4, −4.3)	−0.0 (−1.9, 1.7)
Change vs. placebo[c,d]	%	−0.53 (−0.75, −0.32)	–
	mmol/mol	−5.8 (−8.2, −3.5)	–
FPG (n = 149/131), mmol/L			
Baseline		9.7 ± 2.4	9.3 ± 2.3
Week 24[a]		8.4 ± 2.4	8.9 ± 2.4
Change from baseline[b]		−0.9 (−1.2, −0.5)	−0.1 (−0.6, 0.4)
Change vs. placebo[c,f]		−0.7 (−1.3, −0.2)	–
2-h PMG (n = 95/80), mmol/L			
Baseline		14.2 ± 4.1	13.3 ± 3.9
Week 24[a]		11.7 ± 4.0	11.6 ± 3.7
Change from baseline[b]		−2.2 (−3.0, −1.5)	−1.1 (−1.9, −0.3)
Change vs. placebo[c,g]		−1.1 (−2.2, −0.1)	–

Unless noted, values are Mean ± SD.
PMG, post-meal glucose; FPG, fasting plasma glucose.
Plasma glucose mg/dl = mmol/l × 18.0.
[a] Completers on randomized therapy.
[b] Least squares (LS) mean (95% CI).
[c] Difference in LS means (95% CI).
[d] $p < .001$
[e] $p = .036$
[f] $p = .014$
[g] $p = .031$

groups, showed that PK concentrations in subjects receiving omarigliptin were in the expected range, with 3.3% of samples having no measurable drug (suggesting the possibility of a missed dose).

Because off-protocol use of a prohibited medication, metformin, was found in another study in the omarigliptin phase 3 program [8], plasma samples drawn for the measurement of PK at week 18 were assayed for metformin. Two hundred-seventy of the trial participants had week 18 pharmacokinetic samples that were analyzable. Excluding the 18 people on metformin rescue therapy, measurable levels of metformin were found in 9.8% (12/123) of people in the omarigliptin group and 20.2% (26/129) of people in the placebo group. People found to have off-protocol metformin were from the following countries (n): Germany (6), Hungary (13), Netherlands (3), Philippines (3), Romania (6), Taiwan (5) and United States

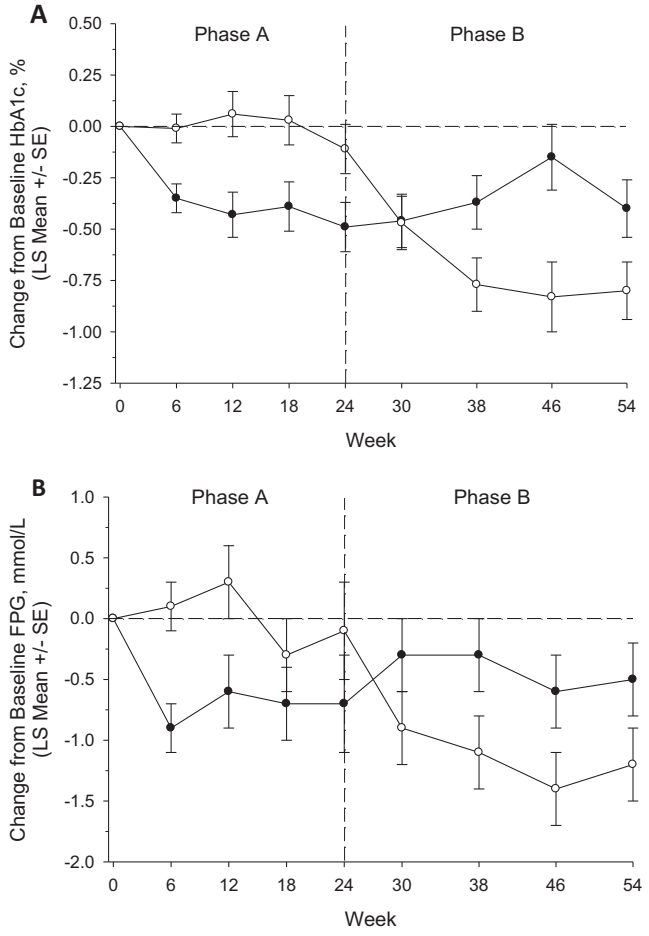

Fig. 1 – The trajectory of efficacy measures over the duration of the study. (A) Least squares (LS) mean change from baseline in HbA1c; (B) LS mean change from baseline in fasting plasma glucose (FPG). ● omarigliptin; ○ placebo/metformin. Data derived from a longitudinal data analysis model including terms for treatment, time, prior glucose-lowering (OGLD) therapy status, and the interaction of time by treatment, and time by prior OGLD therapy status, with the constraint that the mean baseline is the same for all treatment groups, and censoring for rescue. Baseline data and statistical comparisons are given in Table 2.

(2). A post hoc, per protocol analysis was performed excluding from the modified ITT population those taking prohibited metformin. Here the omarigliptin-placebo difference was larger for HbA1c than in the primary analysis, though with no change for other glucose measures (Table 2).

4. Discussion

This study was designed to assess the efficacy, and obtain safety data, for omarigliptin 25 mg once daily (q.w.) when used as monotherapy in people with T2DM with inadequate glycemic control on diet and exercise. Based on the prespecified primary and secondary analyses, the key trial hypotheses and objectives of demonstrating that use of omarigliptin for 24 weeks provided significantly greater reductions from baseline in HbA1c and FPG, compared with placebo, were met. However, glycemic efficacy from a baseline HbA1c of around 8.0% (64 mmol/mol) was less robust than anticipated compared with other omarigliptin trials [2–4] and that reported in the literature for daily DPP-4 inhibitors [9–17]. For example, the placebo-adjusted LS mean reduction from baseline in HbA1c at week 24, 0.39% (0.59, 0.19) (4.3 mmol/mol [6.4, 2.1]), compares to 0.71% (0.93, 0.50) (7.8 mmol/mol [10.2, 5.5]) at 12 weeks in the phase 2 dose-range finding trial from similar baseline levels [2]. It is also at the lower end of the range of changes in HbA1c reported from trials of once-daily DPP-4 inhibitors conducted in similar patient populations with similar mean baseline HbA1c, where findings ranged from 0.41% (4.5 mmol/mol) to 0.80% (8.7 mmol/mol) [9–14].

The situation was similar for reduction in 2-h PMG, being 1.4 (3.1, 0.3) mmol/l absolute, but only 0.6 (1.6, 0.3) placebo-adjusted at 24 weeks, from a mean baseline of 14.2 mmol/L, against the placebo-adjusted reduction of 2.5 (3.3, 1.7) mmol/l at 12 weeks in the phase 2 study [2]. The finding is also at variance with reductions reported for once daily DPP-4 inhibitors in the literature [9,11,14–16]. For fasting plasma glucose the situation is a little different but not completely inconsistent. Thus again the findings in the current study of a 0.6 (1.1, 0.0) mmol/L treatment difference are below those of 1.3 (1.8, 0.9) mmol/L from a mean baseline of 9.7 mmol/L in the phase 2 study [2]. However, the placebo-adjusted reduction in FPG observed in the current study is consistent with the reductions reported in the literature for daily DPP-4 inhibitors, where reductions in FPG from a mean baseline of around 9.4 mmol/L ranged from 0.2 to 1.3 mmol/L [9–13,17].

These glucose-lowering findings were also inconsistent with the results of a phase 3 head-to-head comparison trial of omarigliptin 25 mg q.w. and sitagliptin 100 mg once-daily, in which the HbA1c-lowering of omarigliptin was not only demonstrated to be non-inferior to sitagliptin, but the changes in profile over time of HbA1c and FPG for omarigliptin and sitagliptin were essentially overlapping [4].

Neither the statistical modeling nor population changes through drop-out or rescue therapy are likely explanations of these unexpected results in the current study. Both discontinuation from study and rescue before the primary endpoint (week 24) affected only a small proportion of the randomized population. The achieved HbA1c of the completer non-rescue population at 24 weeks is just 0.60% (6.6 mmol/mol) below the mean baseline level (Table 2). Similarly, although the reported adherence to study medication (approximately 95%) was slightly lower than that observed in other omarigliptin studies (98–99%), this is unlikely to result in a meaningful attenuation in efficacy. Furthermore, analyses indicated that the 'attenuated' efficacy was not due to operational aspects of the trial.

However, investigations into the use of prohibited metformin revealed that it was twofold more prevalent in the placebo group than the omarigliptin group, and to an extent that would be expected to bias the primary results against omarigliptin. Indeed, a post hoc analysis that excluded participants found to have prohibited metformin in a single plasma sample showed a greater treatment effect (Table 2). Thus,

Table 3 – Adverse events (AE) summary for omarigliptin and placebo groups to week 24, and omarigliptin and placebo/metformin groups thereafter.

Participants, *n* (%)	Phase A (to week 24)			Phase A + B (to week 54)		
	Omarigliptin n = 165	Placebo n = 164	Difference (%)[a]	Omarigliptin n = 165	Placebo/metformin n = 164	Difference (%)[a]
With one or more						
AEs	69 (41.8)	82 (50.0)	−8.2 (−18.8, 2.6)	90 (54.5)	99 (60.4)	−5.8 (−16.4, 4.9)
Drug-related AEs[b]	4 (2.4)	3 (1.8)	0.6 (−3.1, 4.5)	13 (7.9)	16 (9.8)	−1.9 (−8.3, 4.4)
Serious AEs	4 (2.4)	5 (3.0)	−0.6 (−4.8, 3.4)	5 (3.0)	8 (4.9)	−1.8 (−6.7, 2.7)
Serious drug-related AEs[b]	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–
Death[c]	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–
Who discontinued due to						
An AE	4 (2.4)	3 (1.8)	0.6 (−3.1, 4.5)	5 (3.0)	4 (2.4)	0.6 (−3.5, 4.8)
A drug-related AE[b]	1 (0.6)	1 (0.6)	–	2 (1.2)	2 (1.2)	–
A serious AE	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–
A serious drug-related AE[b]	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–
With ≥1 AE of hypoglycemia	1 (0.6)	2 (1.2)	–	1 (0.6)	5 (3.0)	−2.4 (−6.4, 0.6)
Symptomatic[d]	0 (0.0)	2 (1.2)	–	0 (0.0)	5 (3.0)	−3.0[g] (−6.9, −0.7)
Severe[e]	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–
Asymptomatic[f]	1 (0.6)	0 (0.0)	–	1 (0.6)	0 (0.0)	–

[a] Percent difference estimate (95% CI) was computed only if ≥4 participants had a relevant events in ≥1 treatment group.
[b] Assessed by the investigator to be related to the study drug.
[c] One person in the placebo group who died >21 days after their last documented dose of study medication is not included.
[d] Symptomatic hypoglycemia: episode with clinical symptoms attributed to hypoglycemia, without regard to glucose level.
[e] Severe hypoglycemia: episode that required assistance, either medical or non-medical.
[f] Asymptomatic hypoglycemia: self-measured glucose values ≤3.9 mmol/L without symptoms.
[g] p = 0.024

compared to the primary analysis, which showed a placebo-adjusted LS mean reduction from baseline in HbA1c of 0.39% (0.59, 0.19) (4.2 mmol/mol [6.4, 2.1]), the post hoc analysis showed a between-group difference of 0.53% (0.75, 0.32) (5.8 mmol/mol [8.2, 3.5]), which is consistent with the literature. However, this post hoc analysis is limited by the fact that the prohibited metformin was only measured at one time point, and it is unknown how long the participants took it, nor if others had also used it earlier. Prohibited OGLDs other than metformin were not assessed.

The randomized, double-blind, placebo-controlled clinical trial design is considered the gold standard to assess absolute drug efficacy, since the intrinsic safety and efficacy of any test compound is best compared to placebo. However, placebo-controlled approaches in people with T2DM have inherent design features that lend themselves to the excess use of prescribed, rescue, and prohibited additional glucose-lowering therapies. The majority of participants in the current study were washed off other glucose-lowering medications prior to randomization, and self-monitoring of finger capillary glucose was used to ensure that glucose levels remained safe in the short term. This potentially leads to loss of the benefit of concealed randomization, promoting the chances of rescue and prohibited use of other medications, particularly in the placebo group. Sources of the prohibited metformin might include previous prescriptions (56.2% of participants had been previously treated with metformin), a "drop-in" effect in which physicians other than the investigator prescribed metformin, medication from other family members, and, where available, over-the-counter metformin without prescription. We note our findings may be relevant to many other studies of new medications in diabetes, including some already published.

Our study continued out to 54 weeks. This was mainly for the purposes of gathering more safety and tolerability data. Because the randomization against placebo was lost by the addition of metformin to that arm (in those not on it as rescue therapy), the efficacy observations in the placebo/metformin treatment group cannot be directly compared to the omarigliptin treatment group. However, despite the change in the rescue threshold to an HbA1c of 8.0% (64 mmol/mol) at 30 weeks, only a further quarter of the population on omarigliptin was rescued between 24 and 54 weeks. The implication is that a majority of the omarigliptin-treated population achieved continuing efficacy.

In this trial, omarigliptin was generally well tolerated. There was a very low incidence of hypoglycemia, consistent with the glucose-dependent mechanism of action of DPP-4 inhibitors [18], and no severe hypoglycemia. There was also no clinically relevant increase in body weight.

In summary, despite the use of prohibited metformin in this study, which is likely to have biased the study against the omarigliptin group, the HbA1c lowering with omarigliptin at week 24 was clinically meaningful, and was maintained over the remaining 30 weeks of the trial. The finding in this trial of the use of prohibited medication highlights the potential problem of non-adherence to the protocol in clinical research, which may be an underappreciated phenomenon that can undermine the research endeavor. Participants acting on their own, without knowledge of the protocol, and without proper monitoring by investigators and trial staff, have the potential to affect trial results and lead to mischaracterization of a drug. An accurate assessment of the efficacy of omarigliptin is best characterized by the efficacy observed in multiple trials across the development program, including the head-to-head study with the daily DPP-4 inhibitor sitagliptin [4], which suggests that the efficacy of omarigliptin is similar to that of sitagliptin.

Declarations

Conflict of interest

PH reports grants and/or personal fees from Merck, AstraZeneca, Hanmi, GlaxoSmithKline, Novo Nordisk, Sanofi, Biocon, Janssen, National Institute for Care, and MHRA during the conduct of the study. RRS, IG, CI, EAON, LJ, AP, SS, SSE, KDK, and EL are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and may own stock and/or hold stock options in the Company.

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Author contribution

PH, RRS, IG, CI, EAON, LJ, AP, SS, SSE, KDK, and EL 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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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.diabres.2017.10.018.

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