Safety and Efficacy of Omarigliptin (MK-3102), a Novel Once-Weekly DPP-4 Inhibitor for the Treatment of Patients With Type 2 Diabetes

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OBJECTIVE

This study was conducted to determine the optimal dose of omarigliptin, a once-weekly (q.w.) dipeptidyl peptidase IV (DPP-4) inhibitor, for the treatment of patients with type 2 diabetes and evaluate the long-term safety of that dose.

RESEARCH DESIGN AND METHODS

In a multicenter, double-blind, 12-week, dose-range finding study, 685 oral antihyperglycemic agent-naïve or washed-out subjects with type 2 diabetes were randomized to one of five once-weekly doses of omarigliptin (0.25 mg, 1 mg, 3 mg, 10 mg, or 25 mg) or placebo. The primary efficacy end point was change from baseline in HbA_{1c}, and secondary end points were 2-h postmeal glucose (PMG) and fasting plasma glucose (FPG). Analysis included all patients who received at least one dose of the study medication. Subjects who completed the base study were eligible to enter a 66-week extension study.

RESULTS

Once-weekly treatment for 12 weeks with omarigliptin provided dose-related reductions in HbA_{1c}, 2-h PMG, and FPG. At week 12, the omarigliptin 25-mg dose provided the greatest glycemic efficacy. The placebo-adjusted least-squares mean reductions from baseline in HbA_{1c}, 2-h PMG, and FPG were −0.72% (−7.8 mmol/mol), −2.5, and −1.3 mmol/L, respectively (all $P < 0.001$). The incidence of adverse events was similar across dose groups, with a low incidence of symptomatic hypoglycemia and no effect on body weight. Omarigliptin was generally well-tolerated throughout the base and extension studies.

CONCLUSIONS

Omarigliptin 25 mg q.w., compared with placebo, provided significant glucose lowering and was generally well tolerated for up to 78 weeks in patients with type 2 diabetes.

Dipeptidyl peptidase IV (DPP-4) inhibitors improve glycemic control in patients with type 2 diabetes by prolonging the half-life of incretin peptides, which stimulate insulin secretion and decrease glucagon release in a glucose-dependent manner (1). Studies with daily DPP-4 inhibitors have demonstrated a good efficacy, safety, and tolerability profile as monotherapy and as an add-on to other antihyperglycemic agents (AHAs) (2–6). Omarigliptin (MK-3102) is a potent, selective, oral DPP-4 inhibitor with a half-life that supports once-weekly dosing (7). Availability of a once-weekly administered oral

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A slide set summarizing this article is available online.

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AHA could represent a paradigm shift in the treatment of type 2 diabetes. Database analyses of prescription records and patient preference surveys suggest that the availability of an efficacious, safe, and well-tolerated weekly oral AHA may offer the potential to improve medication adherence for some patients with type 2 diabetes (8–10). Herein are reported the results of a 12-week dose-range finding study (base study), which was conducted to determine the optimal clinical dose of omarigliptin, and a 66-week extension study that evaluated the long-term safety and tolerability of omarigliptin 25 mg, administered once weekly.

RESEARCH DESIGN AND METHODS

Subjects

Eligible trial participants were male or female patients with type 2 diabetes, 18 to 70 years of age (20 to 70 years of age for Japanese patients), with a BMI >20 kg/m^2 and <43 kg/m^2 (BMI >18 kg/m^2 and <43 kg/m^2 for Japanese patients) who were not on an oral AHA (off AHA medication for $\geq$14 weeks) and had an HbA_{1c} $\geq$7.0% (53 mmol/mol) and $\leq$10.0% (86 mmol/mol). Patients on oral AHA medication monotherapy or low-dose (i.e., $\leq$50% maximum labeled dose of each agent) dual oral combination therapy (except thiazolidinediones) who met the HbA_{1c} inclusion criteria described above after an 8-week washout period were also eligible to participate in the study.

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, hematological disorders, hyperthyroidism, had been previously treated with a DPP-4 inhibitor or a glucagon-like peptide 1 receptor agonist, or required insulin therapy within 14 weeks before signing informed consent.

Laboratory exclusion criteria included a serum creatinine $\geq$1.4 mg/dL (males) or $\geq$1.3 mg/dL (females), estimated glomerular filtration rate <60 mL/min/1.73 m^2 (calculated by the MDRD formula [11]), alanine aminotransferase or aspartate aminotransferase more than two times the upper limit of normal (ULN), creatinine phosphokinase more than two times ULN, hemoglobin $<$11 g/dL (male) or $<$10 g/dL (female), triglycerides >600 mg/dL, or thyroid-stimulating hormone outside the central laboratory normal range.

Study Design

The base study was a multicenter, double-blind, randomized, placebo-controlled, dose-range finding study, followed by an extension study to evaluate longer-term safety and tolerability. The base study included a 1-week screening period, an 8-week washout period for subjects on oral AHAs, a 2-week single-blind placebo run-in period, and a 12-week double-blind treatment period. The extension study lasted 66 weeks. Subjects were randomized to one of five doses of omarigliptin (0.25 mg, 1 mg, 3 mg, 10 mg, or 25 mg once weekly [q.w.]) or placebo in equal ratio. During the base study, omarigliptin and matching placebo were administered in a blinded manner as two capsules once weekly to result in omarigliptin doses ranging from 0 to 25 mg as specified by treatment group assignment. At randomization, subjects were stratified according to their use of oral AHAs at screening and region location (Japan or not Japan). During the base study, subjects who did not meet prespecified glycemic control criteria after randomization were to be rescued with open-label metformin (for details see Supplementary Table 1).

Subjects who completed the base study (with or without initiation of glycemic rescue medication) and who provided written informed consent were eligible to participate in the extension study. A double-blind design was maintained in the extension study. On the basis of unpublished phase I study data, the 25-mg dose of omarigliptin used in the base study was predicted to yield maximum glycemic efficacy. Therefore, in the extension study, subjects randomized to doses of omarigliptin other than 25 mg q.w. were switched to omarigliptin 25 mg q.w. at entry into the extension study, and subjects randomized to omarigliptin 25 mg q.w. continued on 25 mg q.w. Omarigliptin 25 mg or matching placebo was administered to each study subject in a blinded manner once weekly. Down-dosing of omarigliptin was planned in the event that evaluation of the base study data indicated a lower dose achieved maximum efficacy.

Subjects randomized to placebo in the base study were switched to blinded pioglitazone during the extension study to avoid prolonged treatment with placebo; pioglitazone 30 mg or matching placebo was administered to each study subject in a blinded manner once daily. However, because of concerns raised by various health agencies about the long-term use of pioglitazone, a protocol amendment substituted blinded metformin for blinded pioglitazone. Blinded metformin was started at 500 mg q.d. and up-titrated to 1,000 mg b.i.d. At each study site, as subjects were switched from pioglitazone to metformin, subjects on omarigliptin were switched to placebo matching metformin, initially once and then twice daily. Those who were rescued with open-label metformin in the base study did not receive blinded metformin. The placebo/pioglitazone/metformin subjects are henceforth referred to as the placebo/metformin group. No comparison of omarigliptin with metformin was intended in the extension study because treatments were not concurrently initiated and the placebo group switched to metformin at extension entry was no longer the intact group randomized at the beginning of the base period. Rescue therapy during the extension study was open-label glimepiride; if additional rescue was required, subjects were discontinued from the study.

A meal tolerance test (MTT) was conducted at randomization (day 1), at week 12, and at weeks 46 and 78 for those subjects who participated in the extension study. MTTs were performed at trough, 7 days after the last dose of omarigliptin. The standard meal for the MTT consisted of ~460 kcal, with 75 g carbohydrate, 9 g fat, and 18 g protein. The patient was expected to finish the meal within 15 min of beginning to eat. A blood sample for glucose was collected just before ingestion of the meal and at 60 and 120 min from the start of the meal.

The study (Omarigliptin Protocol 006) was conducted in accordance with the principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies.

Study Evaluations

The primary objective of this study was assessment of the safety, tolerability, and efficacy of omarigliptin. The primary hypothesis in the base study was that, compared with placebo, treatment with omarigliptin for 12 weeks would provide greater reduction in HbA_{1c} in a dose-related manner. Secondary hypotheses were that, compared with placebo, 12

weeks of treatment with omarigliptin would provide greater reduction in 2-h postmeal glucose (PMG) and fasting plasma glucose (FPG) in a dose-related manner. An exploratory objective was the assessment of the effect of 12 weeks of treatment with omarigliptin, compared with placebo, on body weight.

The primary objective of the extension study was to assess the safety and tolerability of omarigliptin 25 mg after 78 weeks of treatment. Secondary objectives were to assess the changes from baseline in HbA_{1c}, 2-h PMG, and FPG after 78 weeks of treatment with omarigliptin 25 mg. Change from baseline in body weight after 78 weeks was an exploratory objective.

Efficacy Measurements

Changes from baseline in HbA_{1c}, 2-h PMG, and FPG after 12 and 78 weeks of treatment were evaluated. In addition, the percentages of subjects at HbA_{1c} goals of $<$7.0% (53 mmol/mol) and $<$6.5% (48 mmol/mol) were evaluated at weeks 12 and 78. Plasma DPP-4 activity was measured before dosing omarigliptin on day 1 and at trough at week 12 (7 days after the last dose of omarigliptin) to assess the pharmacokinetic/pharmacodynamic relationship of the drug, using methods previously described (10).

Safety Measurements

Safety assessments included collection of adverse events (AEs), physical examination, vital signs, serum chemistry, hematology, and electrocardiograms.

Statistical Analyses

All statistical tests were conducted at the α = 0.05 (two-sided) level. The primary population for the efficacy analyses consisted of all randomized subjects who received at least one dose of study treatment and had a measurement at baseline or after randomization. Data acquired after the initiation of rescue therapy were treated as missing to avoid the confounding influence of rescue therapy on glycemic parameters. The population for the extension study included subjects who received at least one dose of study treatment during the extension.

For the primary efficacy analyses in the base study, a constrained longitudinal data analysis (cLDA) method of Liang and Zeger (12) was used. The analysis model included treatment, prior oral AHA therapy status (yes/no), geographic region (Japan/not Japan), time, the interaction of time by prior AHA therapy status, and the interaction of time by treatment, with the restriction of a common baseline mean across treatment groups (Supplementary Fig. 3). An unstructured covariance matrix was used to model the correlation among repeated measurements. The primary hypothesis was evaluated by a step-down trend test (13) using linear contrasts from the cLDA model, comparing doses of omarigliptin to placebo at week 12. This procedure first included all doses of omarigliptin and placebo for the test of trend. If a statistically significant result was observed, the highest-dose group was deemed significantly different from placebo. Then, the highest dose was removed from the linear contrast, and the trend test was repeated among the remaining doses. This statistical process proceeded in a stepwise fashion until lack of significance was observed to determine the minimal effective dose. This step-down trend test is a closed testing procedure and preserves the overall type I error rate for testing the primary hypothesis.

Continuous efficacy end points were analyzed using the cLDA model. Analyses of the percentages of individuals at the HbA_{1c} goals of $<$7.0% (53 mmol/mol) and $<$6.5% (48 mmol/mol) at week 12 were conducted using the Miettinen and Nurminen method stratified by prior AHA therapy status (12). The last observation carried forward method was used to determine whether a value met the goal when the HbA_{1c} result at week 12 was not available.

For the extension study, efficacy was evaluated by the estimation of change from baseline in efficacy parameters at week 78 using the LDA model. No hypothesis testing was performed.

The population used for the analysis of safety data consisted of all randomized subjects who received at least one dose of study treatment. The safety population for the extension study included subjects who received at least one dose of the study treatment during the extension. The primary safety analysis excluded data after rescue to avoid the confounding effect of rescue medication. AEs of symptomatic hypoglycemia were prespecified as events of interest and *P* values (for the base study) and 95% CIs for between-treatment differences in the percentage of subjects with events were calculated using the method of Miettinen and Nurminen (14). In the base and the extension studies, for AEs and predefined limits of change with incidence four or more subjects in one or more groups, 95% CIs were calculated for between-group differences using the method of Miettinen and Nurminen (14). Summary statistics were generated for all other end points. A sensitivity analysis of all safety-related data from the base and the extension studies (except for hypoglycemia occurring after the initiation of glimepiride rescue therapy), regardless of presence or absence of rescue therapy, was prespecified in the protocol.

Assuming a conditional SD of 1.0% from an analysis model with baseline as a covariate, a minimum of 95 subjects per group available for the analysis for the primary hypothesis test at week 12 would provide 90% power to detect a true difference of 0.47% in the mean change from baseline in HbA_{1c} at week 12 between two treatment groups (two-sided test, α = 0.05).

RESULTS

Patient Disposition and Characteristics

A total of 1,565 subjects were screened, and 685 subjects were randomized at 126 sites in 21 countries worldwide (Supplementary Fig. 1). The most common reason for screen failure was exclusionary laboratory values, the most common being related to renal function requirements, which were based on the label for the rescue medication metformin.

Of the 685 randomized subjects, 93.4% completed the base study. Rescue therapy was required for ~8% of subjects in the placebo group, 4% of subjects in the 0.25- and 3-mg groups, 3% in the 1- and 10-mg groups, and 1% in the 25-mg group. Of the 640 subjects who completed the base study, 485 (76%) entered the extension study and 374 (77%) completed it. Baseline demographics and efficacy parameters were generally balanced between groups in the base study (Table 1) and the extension study (data not shown).

Efficacy in the Base Study

Results summarized in Table 2 and graphically depicted over time in Fig. 1*A* confirmed the primary study hypothesis that

Table 1—Baseline demographic and anthropomorphic characteristics of base study treatment groups

Parameter	Placebo (*n* = 114)	Omarigliptin once weekly 0.25 mg (*n* = 113)	1 mg (*n* = 115)	3 mg (*n* = 114)	10 mg (*n* = 115)	25 mg (*n* = 114)
Age, years	55.9 ± 8.4	54.3 ± 8.9	55.7 ± 8.5	55.3 ± 8.5	54.4 ± 10.0	55.1 ± 8.8
Male, %	65 (57.0)	65 (57.5)	67 (58.3)	65 (57.0)	56 (48.7)	69 (60.5)
Race						
White	64 (56.1)	60 (53.1)	70 (60.9)	70 (61.4)	64 (55.7)	62 (54.4)
Asian	32 (28.1)	33 (29.2)	33 (28.7)	27 (23.7)	30 (26.1)	30 (26.3)
Multiracial	10 (8.8)	6 (5.3)	4 (3.5)	5 (4.4)	8 (7.0)	12 (10.5)
American Indian or Alaska Native	4 (3.5)	8 (7.1)	6 (5.2)	2 (1.8)	9 (7.8)	3 (2.6)
Black or African American	3 (2.6)	5 (4.4)	2 (1.7)	8 (7.0)	3 (2.6)	7 (6.1)
Native Hawaiian or other Pacific Islander	1 (0.9)	1 (0.9)	0 (0.0)	2 (1.8)	1 (0.9)	0 (0.0)
Ethnicity						
Hispanic or Latino	34 (29.8)	30 (26.5)	35 (30.4)	24 (21.1)	31 (27.0)	37 (32.5)
Not Hispanic or Latino	80 (70.2)	83 (73.5)	80 (69.6)	90 (78.9)	84 (73.0)	77 (67.5)
Body weight, kg	82.1 ± 20.4	82.0 ± 18.8	82.5 ± 17.7	84.1 ± 17.2	82.3 ± 16.5	80.5 ± 17.5
BMI, kg/m^2	29.6 ± 5.3	29.7 ± 5.5	29.9 ± 5.3	30 ± 5.1	30.4 ± 5.2	29.2 ± 5.2
Type 2 diabetes duration, years	5.8 ± 4.6	4.8 ± 4.2	5.3 ± 4.3	5.4 ± 3.9	5.1 ± 4.6	5.9 ± 5.2
Prior AHA use	58 (50.9)	59 (52.2)	59 (51.3)	59 (51.8)	59 (51.3)	59 (51.8)
HbA_{1c}, %	8.1 ± 0.9	8.1 ± 0.9	8.0 ± 0.9	7.9 ± 0.9	8.0 ± 0.9	8.1 ± 1.0
Range	6.6–10.4	6.0–11.3	6.0–10.4	6.7–11.7	6.4–10.7	6.4–11.0
HbA_{1c}, mmol/mol	65.0 ± 9.8	65.2 ± 10.1	63.8 ± 9.4	63.2 ± 9.5	64.4 ± 9.4	65.5 ± 11.1
Range	48.6–90.2	42.1–100.0	42.1–90.2	49.7–104.4	46.4–93.4	46.4–96.7
2-h PMG, mmol/L	13.4 ± 4.0	12.7 ± 3.5	12.7 ± 3.6	13.0 ± 4.5	12.9 ± 4.0	13.6 ± 4.6
FPG, mmol/L	9.6 ± 2.4	9.5 ± 2.5	9.4 ± 2.4	9.4 ± 2.4	9.3 ± 2.1	9.7 ± 2.6

Data are expressed as mean ± SD or as *n* (%), unless otherwise indicated. To convert PMG or FPG in mmol/L to mg/dL, multiply by 18.

after 12 weeks of treatment, omarigliptin compared with placebo provides a greater reduction in HbA_{1c} in a dose-related manner. The greatest HbA_{1c} reduction for omarigliptin was achieved with the 25-mg dose (least squares [LS] mean change from baseline [95% CI] vs. placebo was −0.72% [−0.93, −0.50], −7.8 mmol/mol [−10.2, −5.4], $P <$ 0.001), the top dose studied. A significant trend over the entire range of study doses was observed. The step-down trend test showed a significant trend in HbA_{1c} reduction from placebo through 25 mg, and this significant treatment effect was maintained through the lowest dose of omarigliptin tested (i.e., all doses showing statistical superiority to placebo). The profiles over time for the LS mean change from baseline in HbA_{1c} showed progressive HbA_{1c} reductions throughout the 12-week treatment period for all doses above 0.25 mg, without a clear plateau observed.

Analysis of PMG showed a significant dose-related trend in the reduction from baseline of 2-h PMG at week 12 across all doses of omarigliptin compared with placebo (Table 2 and Fig. 1*B*).

A significant dose-related trend in reduction of FPG from baseline at week 12 was also observed for doses of omarigliptin above 1 mg ($P < 0.001$) compared with placebo (Table 2 and Fig. 1*C*). Near-maximal reduction from baseline in FPG was observed at 4 weeks of treatment with omarigliptin 25 mg q.w.

In the base study, the percentage of subjects reaching HbA_{1c} goals of <7.0% (53 mmol/mol) and <6.5% (48 mmol/mol) generally increased with increasing dose of omarigliptin. At week 12, 33.6% and 13.6% of subjects in the omarigliptin 25-mg group had HbA_{1c} <7.0% and <6.5%, respectively, and 21.8% and 4.5% of subjects in the placebo group reached these goals. The 95% CIs for the risk differences between the omarigliptin 25-mg group and the placebo group, for both goals, excluded 0 (12.4% [0.9, 23.9] for HbA_{1c} <7.0% and 9.5% [2.3, 18.1] for <6.5%).

Omarigliptin demonstrated a dose-dependent inhibition of plasma DPP-4 activity (Supplementary Table 4). Compared with baseline, the omarigliptin 25-mg q.w. dose reduced trough plasma DPP-4 activity at week 12 by 80.7%.

No dose-related changes from baseline in body weight were observed in the omarigliptin groups over time in the base study. The change from baseline (95% CI) in kilograms for the placebo, 0.25-mg 1-mg, 3-mg, 10-mg, and 25-mg groups were −0.6 (−1.0, −0.2), −0.2 (−0.6, 0.1), −0.4 (−0.8, −0.0), 0.2 (−0.2, 0.5), −0.1 (−0.5, 0.2), and −0.0 (−0.4, 0.3), respectively.

Efficacy in the Extension Study

Table 3 summarizes the changes from baseline (week 0) in HbA_{1c} at week 78 for subjects who participated in the extension. The various omarigliptin groups, all of which received 25 mg q.w. during the extension, had reductions in HbA_{1c} at week 78, as generally reflected by the point estimates and 95% CIs. The profiles of change from baseline (week 0) in HbA_{1c} over time for subjects entering the extension study are shown in Fig. 1*D*. Note that the results shown in Fig. 1*D* for the placebo-controlled base study period (weeks 0–12) are derived only from subjects who entered the extension study, not from the entire randomized population. Among the subset of subjects in the omarigliptin 25-mg group in the base study who entered the extension (omarigliptin 25/25-mg group), maximal reduction in HbA_{1c} was observed between week 18 and week 46, with some deterioration thereafter.

Table 2—Efficacy end points at week 12

		Omarigliptin once weekly				
Parameter	Placebo	0.25 mg	1 mg	3 mg	10 mg	25 mg
HbA_{1c}	*n* = 113	*n* = 113	*n* = 115	*n* = 114	*n* = 115	*n* = 114
Change from baseline						
HbA_{1c}, %	0.14 (−0.01, 0.30)	−0.14 (−0.30, 0.01)	−0.36 (−0.51, −0.20)	−0.35 (−0.50, −0.19)	−0.53 (−0.68, −0.37)	−0.57 (−0.73, −0.42)
HbA_{1c}, mmol/mol	1.5 (−0.1, 3.2)	−1.5 (−3.2, 0.2)	−3.9 (−5.6, −2.2)	−3.8 (−5.5, −2.1)	−5.8 (−7.4, −4.1)	−6.3 (−8.0, −4.6)
Change vs. placebo						
HbA_{1c}, %	—	−0.28 (−0.50, −0.06)§	−0.50 (−0.71, −0.28)*	−0.49 (−0.70, −0.27)*	−0.67 (−0.88, −0.45)*	−0.72 (−0.93, −0.50)*
HbA_{1c}, mmol/mol	—	−3.1 (−5.5, −0.7)	−5.4 (−7.8, −3.1)	−5.3 (−7.7, 2.9)	−7.3 (−9.7, −4.9)	−7.8 (−10.2, −5.4)
2-h PMG, mmol/L	*n* = 111	*n* = 112	*n* = 113	*n* = 114	*n* = 114	*n* = 112
Change from baseline	0.4 (−0.1, 1.0)	−0.6 (−1.2, −0.1)	−1.4 (−2.0, −0.9)	−1.5 (−2.1, −1.0)	−1.9 (−2.4, −1.4)	−2.1 (−2.6, −1.5)
Change vs. placebo	—	−1.0 (−1.8, −0.3)‡	−1.8 (−2.6, −1.1)*	−1.9 (−2.7, −1.2)*	−2.3 (−3.1, −1.5)*	−2.5 (−3.3, −1.7)*
FPG, mmol/L	*n* = 113	*n* = 113	*n* = 115	*n* = 114	*n* = 115	*n* = 114
Change from baseline	0.3 (−0.0, 0.6)	0.1 (−0.2, 0.4)	−0.8 (−1.1, −0.5)	−0.6 (−0.9, −0.3)	−0.5 (−0.9, −0.2)	−1.0 (−1.3, −0.7)
Change vs. placebo	—	−0.2 (−0.7, 0.2)†	−1.1 (−1.6, −0.7)*	−0.9 (−1.3, −0.5)*	−0.9 (−1.3, −0.4)*	−1.3 (−1.8, −0.9)*

Change from baseline is the LS mean change from baseline at week 12 (95% CI). Change vs. placebo is the between-treatment difference in the LS mean change from baseline at week 12 (95% CI). To convert PMG or FPG in mmol/L to mg/dL, multiply by 18. §P = 0.012 from trend test for omarigliptin vs. placebo. *$P < 0.001$ from trend test for omarigliptin vs. placebo. ‡P = 0.009 from trend test for omarigliptin vs. placebo. †P = 0.276 from trend test for omarigliptin vs. placebo.

Results reported in Table 3 show that all omarigliptin groups had reductions in 2-h PMG at week 78 compared with baseline, as reflected by the point estimates and 95% CIs. The profiles of change from baseline in 2-h PMG shown in Supplementary Fig. 3*A* demonstrate sustained reductions over time. Results in Table 3 show wide between-group variability in FPG at week 78 compared with baseline. The profiles of change from baseline in FPG over time are shown in Supplementary Fig. 3*B*.

In the extension study, the percentage of subjects reaching HbA_{1c} goals of <7.0% or <6.5% generally increased with increasing dose of omarigliptin. At week 78, 43.5% and 21.7% of subjects in the omarigliptin 25/25-mg group had HbA_{1c} <7.0% and <6.5%, respectively, while 45.8% and 29.2% of subjects in the placebo/metformin group reached these goals.

No notable changes from baseline in body weight were observed in any of the omarigliptin treatment groups (0.25/25 mg, 1/25 mg, 3/25 mg, 10/25 mg, and 25/25 mg) in the extension study.

After completion of the base and extension studies, 4 subjects in the base study (3 subjects in the placebo group and 1 subject in the 1-mg group) and 30 subjects in the extension study (4 subjects in the placebo/metformin and 1, 11, 7, 3, and 4 subjects in the 0.25/25-mg, 1/25-mg, 3/25-mg, 10/25-mg, and 25/25-mg groups, respectively) may have been rescued (i.e., the name of the rescue medication was in the subject's data but the dose of rescue medication was missing). Because these subjects may have been rescued, the data from these subjects after the time point of potential rescue were not included in the primary analysis (which excluded data after rescue) presented in this report. An analysis of the base study that included all data from these subjects (i.e., including data beyond the time point of potential rescue) resulted in negligible or no changes to glycemic parameters compared with the data presented here. A similar analysis of the extension study resulted in a larger change from baseline in HbA_{1c} and FPG and no change in 2-h PMG in the omarigliptin groups.

Safety and Tolerability

In the base study, the incidences of AEs and serious AEs (SAEs), including those that were assessed by the investigator

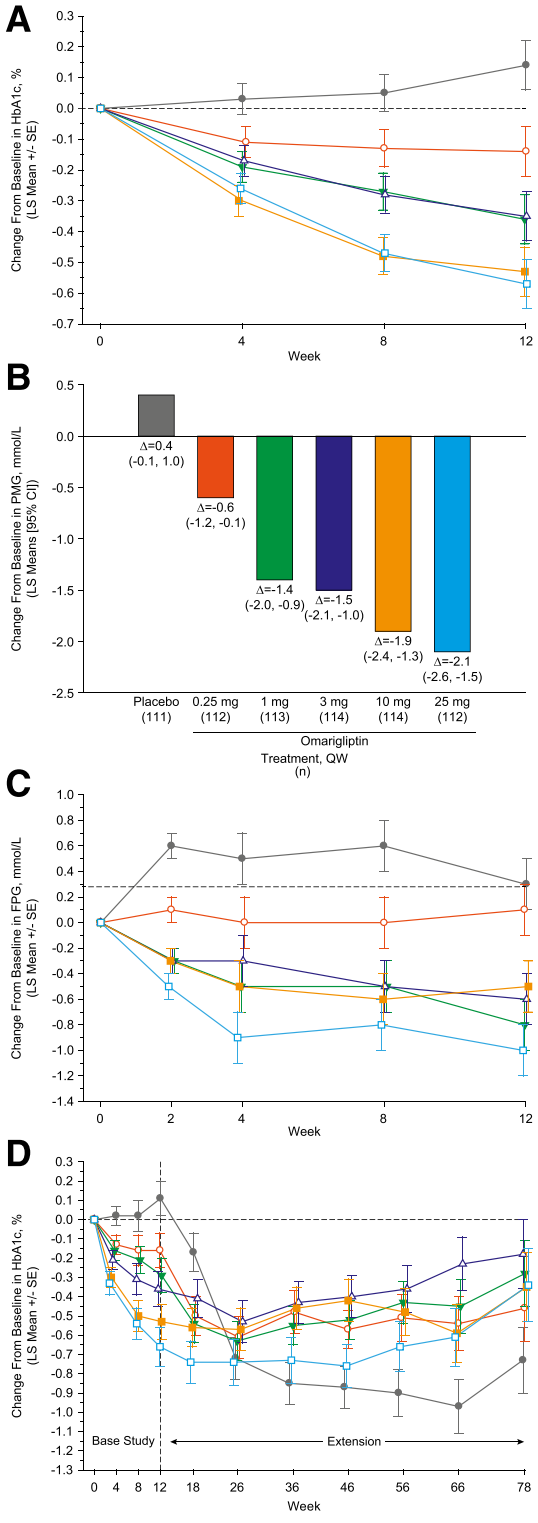

Figure 1—Efficacy measures: HbA_{1c} through week 12 (*A*); PMG change from baseline at week 12 (*B*); FPG through week 12 (*C*); HbA_{1c} through week 78 (*D*). *A* and *C*: Gray circle, placebo; orange circle, omarigliptin 0.25 mg; green triangle, omarigliptin 1 mg; open triangle, omarigliptin 3 mg; orange square, omarigliptin 10 mg; blue square, omarigliptin 25 mg. *D*: Gray circle, placebo/metformin; orange circle, omarigliptin 0.25/25 mg; green triangle, omarigliptin 1/25 mg; open triangle, omarigliptin 3/25 mg; orange square, omarigliptin 10/25 mg; blue square, omarigliptin 25/25 mg. The LS estimates in *A*, *B*, and *C* are based on a model with terms for treatment, prior AHA therapy status (yes/no), geographic region (Japan/not Japan), and the interaction of time by treatment and time by prior AHA therapy status, with a constraint that the mean baseline is the same for all treatment groups. Note that the LS estimates in *D* are obtained from a model with the same terms without the constraint on the mean baseline because this analysis is based on a self-selected subset of randomized patients who entered the extension study.

to be drug-related and those that led to discontinuation, were generally similar between the omarigliptin groups and the placebo group (the 95% CIs for the between-treatment group differences for the omarigliptin groups compared with the placebo group included zero) (Supplementary Table 2). There were no deaths in the base study. The incidences of AEs grouped by Medical Dictionary for Regulatory Activities system organ classes (SOC) and the incidences of specific AEs within individual SOCs were also generally similar between the omarigliptin groups and the placebo group in the base study, and no dose-dependent increases in the incidences of AEs were observed. The incidences of symptomatic hypoglycemia were low in all treatment groups, and no severe hypoglycemia episodes were reported in the base study. There were no reports of acute or chronic pancreatitis in the base study.

In the extension study, the incidences of AEs and SAEs, including those that were assessed by the investigator to be drug-related and those that led to discontinuation, were generally similar between the pooled omarigliptin group and placebo/metformin group (the 95% CIs for the between-treatment group differences for all SOCs included zero) (Supplementary Table 3). During the extension study, 4 of 405 subjects (1.0%) in the pooled omarigliptin group and 1 of 80 subjects (1.3%) in the placebo/metformin group died; all of the fatal AEs were assessed by the investigator to be not related to study drug. The incidences of overall AEs grouped by SOC were generally comparable between the pooled omarigliptin group and the placebo/metformin group (the 95% CIs for the between-treatment group differences for all SOCs included zero). However, numerically higher incidences of overall AEs were observed in the pooled omarigliptin group compared with the placebo/metformin group during the extension study in the Infections and Infestations SOC (primarily due to the increased incidence of the AE of nasopharyngitis), Metabolism and Nutrition Disorders SOC (primarily due to the increased incidence of the AEs of hyperglycemia and hypoglycemia), and the Respiratory, Thoracic, and Mediastinal Disorders SOC (due to a variety of disparate AEs). In the Gastrointestinal Disorders SOC, there was one AE of

Table 3—Efficacy end points at week 78

Parameter	Placebo/metformin	Omarigliptin once weekly				
		0.25/25 mg	1/25 mg	3/25 mg	10/25 mg	25 mg
HbA_{1c}	*n* = 80	*n* = 83	*n* = 91	*n* = 79	*n* = 82	*n* = 70
Baseline						
HbA_{1c}, %	8.2 ± 0.9	8.1 ± 0.9	8.0 ± 0.9	7.9 ± 0.8	8.0 ± 0.9	8.0 ± 0.8
HbA_{1c}, mmol/mol	65.7 ± 9.9	65.4 ± 9.9	64.1 ± 9.8	62.4 ± 8.8	64.4 ± 9.4	64.2 ± 9.3
Change from baseline						
HbA_{1c}, %	−0.73 (−1.07, −0.40)	−0.46 (−0.80, −0.13)	−0.28 (−0.61, 0.06)	−0.18 (−0.52, 0.17)	−0.35 (−0.71, 0.01)	−0.34 (−0.70, 0.03)
HbA_{1c}, mmol/mol	−8.0 (−11.7, −4.3)	−5.1 (−8.8, −1.4)	−3.0 (−6.7, 0.7)	−1.9 (−5.7, 1.9)	−3.9 (−7.8, 0.1)	−3.7 (−7.7, 0.3)
2-h PMG, mmol/L	*n* = 79	*n* = 83	*n* = 91	*n* = 79	*n* = 82	*n* = 70
Baseline	13.6 ± 3.9	13.0 ± 3.6	12.9 ± 3.6	12.6 ± 3.6	13.0 ± 4.3	13.3 ± 4.4
Change from baseline	−2.2 (−3.2, −1.3)	−2.1 (−3.0, −1.1)	−1.2 (−2.1, −0.2)	−1.0 (−2.0, −0.0)	−1.5 (−2.6, −0.5)	−2.4 (−3.4, −1.4)
FPG, mmol/L	*n* = 80	*n* = 83	*n* = 91	*n* = 79	*n* = 82	*n* = 70
Baseline	9.6 ± 2.4	9.5 ± 2.3	9.5 ± 2.5	9.2 ± 1.9	9.2 ± 2.3	9.6 ± 2.6
Change from baseline	−0.6 (−1.5, 0.2)	−0.2 (−1.1, 0.6)	−0.2 (−1.0, 0.6)	−0.0 (−0.9, 0.9)	−0.2 (−1.1, 0.7)	0.2 (−0.7, 1.1)

Baseline and week 78 data are presented as mean ± SD. Change from baseline is the LS mean change from baseline at week 78 (95% CI). To convert PMG or FPG in mmol/L to mg/dL, multiply by 18.

acute pancreatitis attributed to gallstones and one AE of worsening of chronic pancreatitis in the pooled omarigliptin group; both AEs resolved and were assessed by the investigator to be not related to study drug, and both subjects completed the study on the study drug.

There were no reports of pancreatic cancer and no reports of serious hypersensitivity reactions in the base study or the extension study.

In the base study and extension study, there were no notable changes from baseline (week 0) in laboratory safety measures, including liver function, creatinine/estimated glomerular filtration rate, or creatine phosphokinase, in the omarigliptin groups. Serum lipids, including total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides, were generally unchanged. No notable changes from baseline (week 0) at week 12 or week 78 were observed in heart rate or blood pressure (systolic or diastolic) or ECG intervals, including QTc interval.

There were no significant differences in the base and extension studies between the summary AE measures, including and excluding data after glycemic rescue.

CONCLUSIONS

The results of the base study indicated that once-weekly treatment for 12 weeks with omarigliptin provided dose-related reductions in HbA_{1c}, 2-h PMG, and FPG. At 12 weeks, the omarigliptin 25-mg dose was observed to provide the greatest reductions in all three glycemic parameters. The 0.25-mg dose was observed to be the minimal effective dose in lowering HbA_{1c}. The results of the base study also indicated that all doses of omarigliptin were generally well tolerated, with no dose-dependent increase in the incidences of AEs across the doses tested (0.25 mg through 25 mg). Thus, the efficacy and safety results of the base study indicated that omarigliptin at the 25-mg q.w. dose was an appropriate dose to select for longer-term evaluation of omarigliptin in the extension study. The choice of the omarigliptin 25-mg dose was further supported by measurement of trough plasma DPP-4 inhibition, which, in conjunction with exposure-response modeling, indicated that little additional glycemic efficacy would be achieved with doses of omarigliptin greater than 25 mg q.w. (unpublished data).

The reductions in HbA_{1c}, 2-h PMG, and FPG observed with omarigliptin 25 mg in

the base study appear to be generally comparable to those reported in studies of the presently marketed daily DPP-4 inhibitors (2–6). In the case of 2-h PMG, the incorporation of a study design in which the MTT was always performed at trough (day 7) supports the concept that the degree of DPP-4 inhibition observed at trough with the 25-mg dose is sufficient for maximal clinical efficacy. The time courses associated with the reductions from baseline in FPG (near-maximum observed by week 4) and HbA_{1c} are typical of a DPP-4 inhibitor (15,16). The 80.7% DPP-4 inhibition at trough with omarigliptin 25 mg dosed once weekly was determined in an assay that requires 2.5-fold dilution of plasma (10). Of note, the magnitude of trough DPP-4 inhibition observed with omarigliptin 25 mg in this study is similar to the trough inhibition (at 24 h) observed with once-daily dosed sitagliptin 100 mg (Januvia, Merck Sharp & Dohme) using the same assay (17). Using an assay that requires minimal dilution, the observed trough inhibition (168 h postdose and 24 h postdose, respectively) of omarigliptin and sitagliptin are greater than 90% inhibition (18, and data on file).

In the extension study, a reduction in HbA_{1c} and 2-h PMG from baseline (week 0) was observed throughout the 78-week treatment period for all omarigliptin groups. However, variability in these measures and in FPG was observed among the doses, which may reflect the limited subject number in each group. In general, those subjects who were on doses of omarigliptin lower than 25 mg in the base study demonstrated additional efficacy when switched to the (higher) 25-mg dose in the extension study. The plot of HbA_{1c} reduction from baseline at week 78 for the 25-mg dose demonstrates a plateau between week 18 and week 46, with some deterioration thereafter; however, the results across the base and extension studies do not provide a precise assessment of maximal HbA_{1c} efficacy because the measurement at week 18 in this analysis reflects only those subjects randomized to omarigliptin 25 mg in the base study who entered the extension study (25/25-mg group). Some deterioration of glycemic control for all treatment groups occurred late in the extension study (Fig. 1*D* and Supplementary Fig. 2). This may reflect the natural progression of the disease, diminished compliance with diet and exercise, or reduction of treatment efficacy. Although this study was not designed to distinguish among these possibilities, the observation was noted in all treatment groups and was not limited to omarigliptin. In the current study, the placebo/metformin group appears to be experiencing a deterioration of glycemic control by the final evaluation, and a tendency to deterioration of glycemic control over time has previously been observed in studies with daily DPP-4 inhibitors and other classes of AHA, including metformin, with longer-term therapy (19–22).

The incidence of symptomatic hypoglycemia was low in all treatment groups in the base and extension studies, which is consistent with the glucose-dependent mechanism of action of DPP-4 inhibitors. No notable effect on body weight was observed in any of the omarigliptin groups, which is consistent with the generally weight-neutral effect of DPP-4 inhibitors (23). The analysis of AEs and laboratory parameters in the base and extension studies showed that omarigliptin was generally well tolerated, and no safety signals emerged that would indicate that omarigliptin has a safety profile different from that of presently marketed daily-dosed DPP-4 inhibitors.

This phase II dose-ranging study with MK-3102 was designed to provide preliminary efficacy and safety data with the compound compared with a placebo and to identify a clinical dose that could be taken forward to phase III clinical development. The inclusion of an extension study provided a preliminary assessment of longer-term safety, which contributed to accumulating data supporting the compound's continued clinical development.

Because the study was part of an early phase of drug development (phase II), it had the typical limitations consistent with studies conducted during this phase. Owing to the modest sample size, and attendant modest statistical power, inherent to phase II studies, one limitation is the inability to compare the efficacy and safety across different subpopulations of patients randomized into the study or to draw conclusions based on data compared with an active comparator with precision that allows one to draw robust conclusions. This study did recruit a heterogeneous population (i.e., patients either not on or washed out of antihyperglycemic medication), which was appropriate and did not limit achieving the study's primary objective of selecting a dose for further clinical development, partly because the protocol's statistical analysis plan adjusted for prior antihyperglycemic medication in the efficacy analysis.

The absence of an active comparator group is not a limitation of the study because the assessment of efficacy and safety compared with a placebo was appropriate and inclusion of a modestly-sized active-comparator arm would not provide precise assessment of differences between active treatments. Instead, assessment of the DPP-4 inhibition biomarker allowed for limited, indirect comparison with daily DPP-4 inhibitors. More definitive comparisons across a variety of subpopulations and to relevant active comparators will be obtained during the next phase (phase III) of clinical development (MK-3102 studies posted on ClinicalTrials.gov), where the studies conducted are appropriately sized to yield precise comparative estimates to form robust conclusions.

One limitation of the extension study was the inability to enroll all subjects into the extension. This was due to a number of factors, including an unexpected set of events (the issues that arose with the continued use of pioglitazone) that led to a delay in obtaining timely approval of an amendment in some countries. Thus, the subjects who entered the extension do not constitute a fully randomized cohort and may not necessarily reflect the group randomized in the base study.

In summary, omarigliptin 25 mg q.w., compared with placebo, provided significant glucose-lowering and was generally well tolerated for up to 78 weeks, establishing the 25-mg q.w. dose as appropriate for further development. The effect of a once-weekly dosing regimen on patient medication adherence will require assessment in real-world studies in natural settings.

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