


A Randomized, Placebo-Controlled Trial Evaluating the Safety and Efficacy of Adding Omarigliptin to Antihyperglycemic Therapies in Japanese Patients with Type 2 Diabetes and Inadequate Glycemic Control

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ABSTRACT

Introduction: Daily dipeptidyl peptidase-4 (DPP-4) inhibitors are commonly used with other orally administered antihyperglycemic agents (AHA), as combination therapy, to treat Japanese patients with type 2 diabetes. When combination therapy is indicated, use of a once-weekly (q.w.) orally administered DPP-4 inhibitor might be an appropriate therapeutic option for some patients.

Methods: A 52-week trial was conducted to assess the safety and tolerability (primary objectives) and glycemic efficacy (secondary objectives) of the q.w. DPP-4 inhibitor omarigliptin as add-on therapy to five different

classes of orally administered AHA [sulfonylurea (SU), glinide (GL), biguanide (BG), thiazolidinedione (TZD), or α -glucosidase inhibitor (AGI)] commonly used in Japan and having different mechanisms of drug action from DPP-4 inhibitors. The trial consisted of an initial 24-week double-blind, placebo-controlled period during which patients (stratified by background AHA) were randomized to omarigliptin 25 mg q.w. or placebo, followed by a 28-week open-label period during which patients on placebo were switched to omarigliptin.

Results: After 24 weeks, the percentages of patients with adverse events (AEs), serious AEs, drug-related AEs, AEs of symptomatic hypoglycemia, or who discontinued from trial medication because of an AE were generally similar in the omarigliptin and placebo groups, in all background AHA strata and in the overall population. From a mean baseline HbA1c of approximately 8.0%, the placebo-adjusted least-squares mean changes from baseline ranged from -0.80% (AGI stratum) to -1.16% (TZD stratum); $p < 0.001$ for all background AHA strata. During the open-label period, no safety signals emerged with longer-term treatment. At week 52, the change from baseline in HbA1c in the omarigliptin/omariogliptin group was similar to that of the placebo/omariogliptin group.

Conclusions: Addition of once-weekly omarigliptin to AHA therapy with an SU, GL, BG, TZD, or AGI for up to 52 weeks was generally

Omarigliptin Study 015 Group investigators are listed in Electronic Supplementary Material Appendix 1.

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safe and well tolerated, and provided persistent efficacy.

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INTRODUCTION

Type 2 diabetes (T2D) is a progressive disease, and with disease progression patients often require more than one antihyperglycemic agent (AHA) to maintain glycemic control. In this clinical scenario, addition of a second AHA with a complementary mechanism of action is a rational therapeutic approach. In Japan, daily DPP-4 inhibitors are commonly used as first-line therapy and often combined with other classes of orally administered AHA for the treatment of patients with T2D [1]. As a class, DPP-4 inhibitors improve glycemic control in patients with T2D by stabilizing glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide, peptide hormones which enhance insulin secretion and (in the case of GLP-1) suppress glucagon release in a glucose-dependent manner [2].

Omarigliptin (MK-3102) is a highly specific, orally administered DPP-4 inhibitor with pharmacokinetic properties that allow once-weekly (q.w.) dosing [3, 4] that is presently approved in Japan. In clinical trials that compared omarigliptin to both placebo and active comparators, including the daily DPP-4 inhibitor sitagliptin, omarigliptin has been shown to have a safety, tolerability, and efficacy profile similar to that of daily DPP-4 inhibitors [5–10]. One of those trials, which supported approval in Japan, assessed omarigliptin as monotherapy in Japanese patients with T2D [6].

Herein we report the results of a clinical trial that supported approval in Japan that assessed the safety and efficacy of adding omarigliptin to the treatment of Japanese

patients with T2D and inadequate glycemic control while on monotherapy with any of five different classes of orally administered AHA. Each of the five monotherapy background AHAs have a mechanism of action different from that of DPP-4 inhibitors, and all are frequently used in clinical practice in Japan [sulfonylurea (SU), glinide (GL), biguanide (BG), thiazolidinedione (TZD), and α -glucosidase inhibitor (AGI)].

METHODS

Patients

Eligible patients were Japanese, male or female, treated with diet and exercise and a stable dose of an SU, GL, BG, TZD, or AGI (background AHA) as monotherapy and having an HbA1c (NGSP value) of $\geq 7.0\%$ and $\leq 10.0\%$, or treated with dual combination therapy with one of the aforementioned background AHAs and another orally administered AHA and having an HbA1c of $\geq 6.5\%$ and $\leq 9.0\%$. Patients treated with monotherapy were required to be on a stable dose of background AHA for at least 10 weeks if on an SU, GL, BG, or AGI and at least 14 weeks if on a TZD. Patients on dual combination therapy were required to be on a stable dose of background AHA for at least 4 weeks if on an SU, GL, BG, or AGI and at least 8 weeks if on a TZD. Patients were at least 20 years of age if not on a BG and restricted to at least 20 and less than 75 years of age if on a BG. Patients could be on one of the following background AHAs: in the SU stratum, gliclazide, glibenclamide (glyburide), or glimepiride; in the GL stratum, nateglinide, mitiglinide, or repaglinide; and in the AGI stratum, acarbose, voglibose, or miglitol. The BG and TZD strata consisted of patients on metformin and pioglitazone, respectively.

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, or had been previously treated with insulin within 12 weeks prior to screening, or omarigliptin at any time.

Laboratory exclusion criteria included an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² (or <60 mL/min/1.73 m² if on a BG background AHA), alanine aminotransferase or aspartate aminotransferase more than two times the upper limit of normal, thyroid-stimulating hormone outside the central laboratory normal range, hemoglobin <11 g/dL (male) or <10 g/dL (female), triglycerides >600 mg/dL, or C-peptide <0.6 ng/mL.

Study Design

This multicenter trial consisted of two treatment periods. The initial period was a 24-week double-blind, placebo-controlled, parallel-group treatment period in which patients were randomized to omarigliptin 25 mg q.w. or matching placebo. The second period was a 28-week open-label period in which all patients were treated with omarigliptin (patients on placebo in the initial period were switched to omarigliptin). After a screening period of up to 2 weeks, patients on AHA monotherapy entered a 2-week single-blind placebo run-in period; patients on dual AHA therapy entered an 8-week period (which included a 2-week single-blind placebo run-in) during which they were discontinued from the second AHA. During the 2-week single-blind placebo run-in period, all patients took omarigliptin placebo once weekly to ensure proper understanding of the weekly dosing regimen. In addition, 2 weeks prior to randomization (week-2), all patients were required to have an HbA1c (NGSP value) $\geq 7.0\%$ and $\leq 10.0\%$. At week-2, patients in all background AHA strata were required to have a fasting plasma glucose (FPG) ≤ 230 mg/dL and those on an SU were also required to have a FPG ≥ 126 mg/dL.

Patients were stratified according to their background AHA (SU, GL, BG, TZD, or AGI) and randomized in a 2:1 ratio to omarigliptin 25 mg q.w. or matching placebo. Randomization was performed using a sponsor-generated allocation schedule and an interactive voice response or integrated Web response system. Throughout the trial, patients continued on a stable dose of their background AHA, unless glycemic rescue was required or, in the case of the SU stratum,

hypoglycemia occurred. Patients exceeding prespecified glycemic thresholds post-randomization (repeatedly confirmed central laboratory value of FPG >240 mg/dL for week 4–24 and FPG >200 mg/dL for week 24–52) were rescued, first with up-titration of their background AHA, then either with metformin (patients on SU or GL as background AHA) or glimepiride (patients on BG, TZD, or AGI as background AHA). If recurrent hypoglycemia occurred (defined as an FPG or fingerstick glucose ≤ 70 mg/dL with symptoms of hypoglycemia, or FPG or fingerstick glucose <50 mg/dL with or without symptoms of hypoglycemia) without a reasonable explanation (such as increased physical activity or skipped meal), patients whose background AHA was an SU could have the SU down-titrated; patients on other background AHAs were discontinued from trial.

All procedures followed in this trial (Omarigliptin Protocol 015; ClinicalTrials.gov: NCT01697592) were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients in the trial.

Study Evaluations

The primary, secondary, and exploratory objectives of this trial were assessed for each class of background AHA. A pooled analysis of adverse events (AEs) in the overall population (i.e., across background AHA strata) was also performed. The primary objectives were to assess the safety and tolerability of the addition of omarigliptin through 24 weeks and for up to 52 weeks. Secondary objectives were to assess the effect of omarigliptin compared with placebo on change from baseline in HbA1c at week 24 and to assess the change from baseline in HbA1c for up to 52 weeks. The associated HbA1c hypothesis was that after 24 weeks, the addition of omarigliptin, compared with placebo, would provide a greater reduction from baseline in HbA1c. Exploratory objectives were to assess the effect of the addition of omarigliptin on change from baseline in FPG after 24 weeks and for up to 52 weeks.

Safety Endpoints

Safety endpoints included AEs, mean change from baseline at week 24 and week 52 in laboratory parameters, electrocardiogram (ECG), percentages of patients meeting predefined limits of change (PDLC) for laboratory and ECG parameters, vital signs, and body weight. A predefined AE of interest was symptomatic hypoglycemia.

In both periods of this trial, potential cases 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 in a blinded manner by external clinical adjudication committees.

Efficacy Endpoints

Efficacy endpoints were changes from baseline in HbA1c and FPG after 24 and 52 weeks and percentages of patients at HbA1c goal of <7.0% and <6.5% for each background AHA at weeks 24 and 52.

Statistical Analyses

To avoid the confounding influence of rescue therapy, all analyses treated data collected after the initiation of rescue therapy as missing.

The population for analysis of safety data was all randomized patients who received at least one dose of trial treatment. Safety and tolerability were assessed by clinical review of all relevant parameters including AEs, laboratory tests, ECG, PDLCs, vital signs, and body weight. Events of symptomatic hypoglycemia were prespecified as AEs of interest and *p* values and 95% confidence intervals (CIs) for between-treatment group comparisons were calculated. For AEs with incidence of at least four patients in any treatment group, 95% CIs were calculated for between-group comparisons. In both cases the method of Miettinen and Nurminen [11] was used. For other safety endpoints, summary statistics were generated. Change from baseline in body weight at weeks 24 and 52 were analyzed

using the longitudinal data analysis (LDA) method described below for HbA1c, substituting baseline body weight for HbA1c.

The primary population for efficacy analyses included all randomized patients who received at least one dose of study treatment and had a baseline or a post-randomization measurement. For analyses of the change from baseline in HbA1c at week 24, an LDA model [12] was used. The model had terms for treatment, background AHA (SU/GL/BG/TZD/AGI), prior AHA status except background AHA (yes/no), time, and the interaction of time × treatment, time × background AHA, time × prior AHA status except background AHA, background AHA × time × treatment, background AHA × time × prior AHA status except background AHA, background AHA × time × treatment × prior AHA status except background AHA, with a constraint that true mean at baseline is common to all treatment groups (which is valid owing to randomization). An unstructured covariance matrix was used to model the correlation among repeated measurements.

Changes from baseline in FPG were analyzed using the LDA method described for HbA1c, substituting the FPG values for HbA1c.

To determine the change from baseline in HbA1c at week 52, the LDA model was separately applied to each background AHA stratum as a result of non-convergence of the model when all the AHA strata were included simultaneously.

For analysis of percentages of individuals at the HbA1c goals of <7.0% and <6.5% at weeks 24 and 52, the LDA model used for the analysis of HbA1c change from baseline at weeks 24 and 52 was used to impute missing data for weeks 24 and 52 HbA1c. Each patient was categorized as a responder (satisfying the HbA1c (NGSP) specific goal of <7.0% or <6.5%) or non-responder at week 24 or week 52.

To ensure that approximately 100 patients from the SU stratum and approximately 50 patients from other background AHA strata were exposed to omarigliptin for 52 weeks and assuming an approximate 20% discontinuation rate, it was calculated that 568 patients would need to be randomized with a stratification ratio of 2:1:1:1:1 for SU, GL, BG, TZD, and AGI, respectively.

RESULTS

Patient Disposition and Characteristics

Of 772 patients screened, 585 were randomized at 67 sites in Japan (Fig. 1). The most common reasons for patients not being randomized were

meeting laboratory exclusion criteria for parameters including eGFR, AST, ALT, TSH, hemoglobin, TG, or C-peptide (50.6%) and/or not meeting inclusion criteria related to AHA regimen and HbA1c levels. The first patient was screened on October 26, 2012 and the last visit of the last patient was on May 8, 2014. Five hundred and seventy-one (97.6%) of the

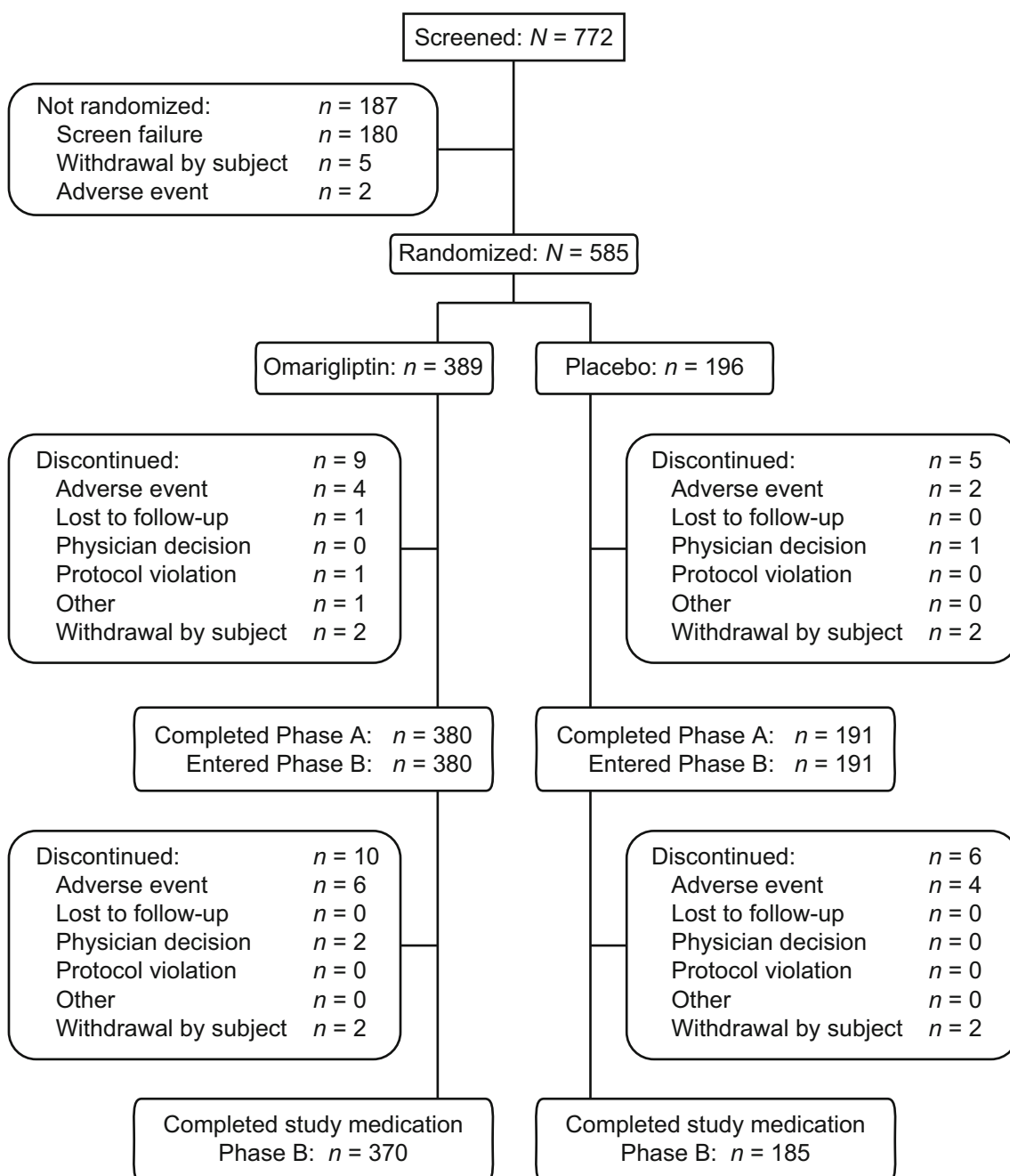


Fig. 1 Patient disposition weeks 0–52

randomized patients completed the placebo-controlled period and 555 (94.9%) completed the open-label period on study medication. At week 24, in the overall population (all strata), 0.5% (2/389 patients) in the omarigliptin group and 2.0% (4/196 patients) in the placebo group required glycemic rescue. Through week 52, 2.8% (11/389 patients) and 2.6% (5/191 patients) required glycemic rescue.

Baseline anthropometric and disease characteristics were generally balanced between omarigliptin and placebo treatment groups for each background AHA (Table 1). The mean age of all study patients was approximately 60 years and approximately 70% of patients were male; the mean body mass index was 25 kg/m², the mean HbA1c level was 8.0%, the mean FPG was approximately 160 mg/dL, and the mean duration of diabetes was approximately 9.5 years. Among patients randomized, 25.6% were discontinued from dual AHA therapy (washed-off of a second AHA). The mean baseline dose and dose range of each background AHA can be found in Supplementary Table S1.

Safety

Double-Blind Placebo-Controlled Period (Day 1–Week 24)

During the double-blind, placebo-controlled period, the percentage of patients with one or more AEs, drug-related AEs, serious AEs, or who were discontinued from trial medication because of an AE was generally similar between the omarigliptin and placebo groups in all of the background AHA strata and in the overall population (Table 2).

The percentage of patients with AEs in any Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) (not shown) or in the percentage of patients with specific AEs with incidence of at least 5% in at least one treatment group in any SOC (Table 2) was also similar between the omarigliptin groups and the placebo groups in all background AHA strata.

When assessed in the overall population, the percentage of patients with AEs in any SOC was generally similar between the omarigliptin group and the placebo group, with the

Table 1 Baseline demographic and anthropometric characteristics of the study population

Characteristic	Sulfonylurea		Glinide		Biguanide		Thiazolidinedione		α-Glucosidase inhibitor	
	Omarigliptin n = 126	Placebo n = 63	Omarigliptin n = 65	Placebo n = 34	Omarigliptin n = 66	Placebo n = 33	Omarigliptin n = 65	Placebo n = 34	Omarigliptin n = 67	Placebo n = 32
Age, years	63 ± 9	63 ± 11	59 ± 11	61 ± 10	59 ± 9	57 ± 9	61 ± 10	61 ± 9	61 ± 11	61 ± 11
Male, n (%)	91 (72.2)	45 (71.4)	46 (70.8)	27 (79.4)	46 (69.7)	23 (69.7)	42 (64.6)	27 (79.4)	46 (68.7)	23 (71.9)
Body weight, kg	65 ± 11	67 ± 14	68 ± 13	69 ± 14	69 ± 14	70 ± 12	72 ± 14	71 ± 13	68 ± 13	65 ± 11
BMI, kg/m ²	24.5 ± 3.4	24.8 ± 3.5	25.1 ± 4.3	25.3 ± 4.1	25.6 ± 4.4	25.9 ± 3.6	27.0 ± 4.2	27.0 ± 4.9	25.3 ± 4.0	24.4 ± 3.7
HbA1c, %	8.1 ± 0.7	8.1 ± 0.6	8.0 ± 0.6	8.0 ± 0.8	7.8 ± 0.6	8.0 ± 0.6	8.2 ± 0.8	7.9 ± 0.8	7.9 ± 0.6	7.9 ± 0.8
Range	6.9–10.0	7.1–9.6	6.9–10.3	6.7–9.8	6.8–9.9	6.9–10.2	7.0–10.0	6.8–10.5	6.9–9.6	7.0–10.1
FPG, mg/dL	165.4 ± 32.0	170.5 ± 34.0	163.5 ± 29.4	164.4 ± 34.7	155.8 ± 26.1	157.6 ± 20.6	163.4 ± 33.6	152.4 ± 24.5	157.7 ± 24.3	159.8 ± 30.7
Duration of type 2 diabetes, years	10.7 ± 5.6	11.5 ± 6.3	8.5 ± 6.2	8.3 ± 5.2	8.4 ± 4.8	6.9 ± 3.5	9.1 ± 6.4	10.3 ± 5.4	8.4 ± 5.5	9.7 ± 5.8
Prior AHA use, yes	43 (34.1)	21 (33.3)	9 (13.8)	4 (11.8)	16 (24.2)	3 (9.1)	19 (29.2)	6 (17.6)	19 (28.4)	10 (31.3)

Data are expressed as mean ± standard deviation or frequency [n (%)]
 BMI body mass index, FPG fasting plasma glucose, AHA antihyperglycemic agent

Table 2 Adverse events summary, specific AEs by system organ class (SOC) with incidence $\geq 5\%$ in ≥ 1 treatment group, and incidences of symptomatic hypoglycemia during the 24-week double-blind period in the overall population and for each background AHA stratum

Patients, n (%)	Sulfonylurea		Glinide		Biguanide		Thiazolidinedione		α -Glucosidase inhibitor		Overall	
	Omarigliptin n = 126	Placebo n = 63	Omarigliptin n = 65	Placebo n = 34	Omarigliptin n = 66	Placebo n = 33	Omarigliptin n = 65	Placebo n = 34	Omarigliptin n = 67	Placebo n = 32	Omarigliptin n = 389	Placebo n = 196
With one or more												
AEs	75 (59.5)	38 (60.3)	35 (53.8)	18 (52.9)	36 (54.5)	21 (63.6)	39 (60.0)	18 (52.9)	34 (50.7)	17 (53.1)	219 (56.3)	112 (57.1)
Drug-related ^a AEs	9 (7.1)	5 (7.9)	5 (7.7)	2 (5.9)	3 (4.5)	0 (0.0)	4 (6.2)	0 (0.0)	0 (0.0)	1 (3.1)	21 (5.4)	8 (4.1)
Serious AEs ^b	2 (1.6)	0 (0.0)	1 (1.5)	1 (2.9)	1 (1.5)	1 (3.0)	4 (6.2)	0 (0.0)	0 (0.0)	2 (6.3)	8 (2.1)	4 (2.0)
Serious drug-related ^a AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Who died	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Who discontinued due to												
An AE	0 (0.0)	0 (0.0)	2 (3.1)	1 (2.9)	0 (0.0)	0 (0.0)	2 (3.1)	0 (0.0)	0 (0.0)	1 (3.1)	4 (1.0)	2 (1.0)
A drug-related ^a AE	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
A serious AE	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (3.1)	2 (0.5)	1 (0.5)
A serious drug-related ^a AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
With specific AEs with incidence $\geq 5\%$ in ≥ 1 treatment group, by SOC ^c												
Gastrointestinal disorders												
Dental caries	4 (3.2)	1 (1.6)	1 (1.5)	0 (0.0)	0 (0.0)	2 (6.1)	2 (3.1)	0 (0.0)	1 (1.5)	0 (0.0)	8 (2.1)	3 (1.5)
Infections and infestations												
Bronchitis	3 (2.4)	1 (1.6)	0 (0.0)	3 (8.8)	0 (0.0)	0 (0.0)	1 (1.5)	2 (5.9)	2 (3.0)	0 (0.0)	6 (1.5)	6 (3.1)
Gastroenteritis	2 (1.6)	0 (0.0)	0 (0.0)	2 (5.9)	4 (6.1)	0 (0.0)	1 (1.5)	1 (2.9)	0 (0.0)	0 (0.0)	7 (1.8)	3 (1.5)
Gingivitis	2 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)	2 (3.0)	0 (0.0)	0 (0.0)	2 (5.9)	0 (0.0)	0 (0.0)	4 (1.0)	3 (1.5)
Influenza	2 (1.6)	1 (1.6)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	3 (4.6)	2 (5.9)	1 (1.5)	0 (0.0)	6 (1.5)	4 (2.0)
Nasopharyngitis	15 (11.9)	15 (23.8)	14 (21.5)	7 (20.6)	11 (16.7)	9 (27.3)	11 (16.9)	5 (14.7)	13 (19.4)	8 (25.0)	64 (16.5)	44 (22.4)
Pharyngitis	2 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)	1 (1.5)	2 (6.1)	0 (0.0)	1 (2.9)	1 (1.5)	0 (0.0)	4 (1.0)	4 (2.0)
Investigations												
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	2 (3.1)	0 (0.0)	2 (3.0)	2 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.0)	2 (1.0)
Metabolism and nutrition disorders												
Hypoglycemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	2 (6.3)	0 (0.0)	3 (1.5)
Hypoglycemia	7 (5.6)	3 (4.8)	1 (1.5)	0 (0.0)	3 (4.5)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	12 (3.1)	3 (1.5)
Musculoskeletal and connective tissue disorders												
Myalgia	0 (0.0)	1 (1.6)	1 (1.5)	1 (2.9)	0 (0.0)	3 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	5 (2.6)

Table 2 continued

Patients, n (%)	Sulfonylurea		Glitide		Biguanide		Thiazolidinedione		α -Glucosidase inhibitor		Overall	
	Omarigliptin n = 126	Placebo n = 63	Omarigliptin n = 65	Placebo n = 34	Omarigliptin n = 66	Placebo n = 34	Omarigliptin n = 65	Placebo n = 34	Omarigliptin n = 67	Placebo n = 32	Omarigliptin n = 389	Placebo n = 196
Respiratory, thoracic, and mediastinal disorders												
Upper respiratory tract inflammation	0 (0.0)	0 (0.0)	1 (1.5)	2 (5.9)	0 (0.0)	1 (3.0)	1 (1.5)	0 (0.0)	1 (1.5)	1 (3.1)	3 (0.8)	4 (2.0)
With one or more AE of symptomatic hypoglycemia ^d	6 (4.8)	2 (3.2)	1 (1.5)	0 (0.0)	2 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (2.3)	2 (1.0)
Between-group difference in percentage (omarigliptin – placebo)	1.6 (–6.5, 7.5)	–	1.5 (–8.8, 8.3)	–	3.0 (–7.6, 10.4)	–	0.0 (–10.2, 5.6)	–	0.0 (–10.8, 5.5)	–	1.3 (–1.5, 3.5)	–

^a Assessed by the investigator to be related to the drug

^b After database lock for the 24-week double-blind period, additional information for the non-serious AE of “cataract” in the omarigliptin group was reported. The new information included that this patient was hospitalized for “cataract” which changed this AE from non-serious to serious. Therefore this patient was not counted as “with serious adverse event” in this table. The change is reflected in the long-term analysis table

^c System organ class defined by the Medical Dictionary for Regulatory Activities (MedDRA) classification system

^d Prespecified AE of interest; symptomatic hypoglycemia: episode with clinical symptoms consistent with hypoglycemia, without regard to glucose level

exception of the eye disorders SOC [3.1% (12/389 patients) versus 0.5% (1/196 patients)] and skin and subcutaneous tissue disorders SOC [5.4% (21/389 patients) versus 1.0% (2/196 patients)] where the percentage of patients with AEs was higher in the omarigliptin group compared with the placebo group (i.e., the lower limit of 95% CIs around the between-group difference versus placebo exceeded 0).

In the eye disorders SOC, the only specific AE that occurred in at least four patients in at least one treatment group was diabetic retinopathy which occurred in 1.5% (6/389) of patients in the omarigliptin group compared with 0.0% (0/196) of patients in the placebo group. The six events of diabetic retinopathy in the omarigliptin group (three patients in SU stratum, one patient in GL stratum, one patient in BG stratum, and one patient in TZD stratum) were all mild in intensity and none were assessed by the investigator to be related to trial medication (omarigliptin) or led to the discontinuation of trial medication. No other AE terms related to diabetic retinopathy (e.g., retinopathy) were reported in either treatment period.

In the skin and subcutaneous tissue disorders SOC, specific AEs that occurred in at least four patients in one or more treatment groups (omarigliptin group versus placebo group) included contact dermatitis [1.0% (4/389 patients) versus 0.5% (1/196 patients)] and eczema [1.3% (5/389 patients) versus 0.5% (1/196 patient)]. All of the AEs of contact dermatitis and eczema were nonserious, mild in intensity, and did not lead to discontinuation from trial medication. All of the AEs of contact dermatitis and three of the five cases of eczema resolved on trial medication (two cases of eczema recovered after the last dose); none of the AEs of contact dermatitis and only one AE of eczema were assessed by the investigator to be related to trial medication. In addition, the incidence of the AE of allergic dermatitis (a term similar to contact dermatitis) was 0.5% (2/389 patients) in the omarigliptin group and 0.0% (0/196 patients) in the placebo group. One of two patients experienced two events of allergic dermatitis; all of the AEs were nonserious, mild in intensity, and did not lead to discontinuation from trial medication (two of the three AEs

resolved on trial medication) and none of the AEs were assessed by the investigator to be related to trial medication.

The percentage of patients with AEs of symptomatic hypoglycemia in the omarigliptin and placebo groups was generally similar in all of the background AHA strata and in the overall population (Table 2). The incidences of hypoglycemia were generally low in all background AHA strata, with the highest incidences being observed in the SU stratum. No severe hypoglycemia was reported in any background AHA stratum in either treatment group.

Open-Label Period (Week 24–Week 52)

Because of the differences in length of exposure to omarigliptin (52 weeks versus 28 weeks), no between-group comparisons can be made between the omarigliptin/omariogliptin groups and the placebo/omariogliptin groups. In the open-label period, AE incidences reported for the placebo/omariogliptin group reflect only those AEs that occurred during the 28 weeks in which patients were exposed to omarigliptin. Of the 196 patients in the placebo group, 191 were switched to omarigliptin at week 24 (see Fig. 1 for reasons for discontinuation of the five subjects).

After 52 weeks, the percentage of patients with AEs in the omarigliptin/omariogliptin groups increased in all background AHA strata compared to 24 weeks, as would be expected from the accumulation of AEs over time (Table 3). No specific AEs emerged in any of the background AHA strata that represented a safety signal associated with longer-term treatment.

In the omarigliptin/omariogliptin group (all strata) the incidences of the AEs of diabetic retinopathy, contact dermatitis, and eczema over the 52-week treatment period (placebo-controlled and open-label periods) were 3.1% (12/389 patients), 1.8% (7/389 patients), and 3.3% (13/389 patients), respectively. In the omarigliptin/omariogliptin group the incidence of allergic dermatitis was 0.8% (3/389 patients) and the incidence of dermatitis was 0.3% (1/389 patients).

During the open-label period (28 weeks), the incidences of the AEs of diabetic retinopathy, contact dermatitis, and eczema in the placebo/omariogliptin group were 0.5% (1/191 patients),

0.5% (1/191 patient), and 2.6% (5/191 patients), respectively. In the placebo/omariogliptin group the incidence of dermatitis was 0.5% (1/191 patients) and there were no AEs of allergic dermatitis.

Over 52 weeks, the incidence of hypoglycemia in the omarigliptin/omariogliptin groups remained generally low, with the highest incidence observed in the SU stratum, compared to other background AHA strata (Table 3). No severe hypoglycemia was reported in any of the background AHA strata.

The types of AEs observed in the placebo/omariogliptin groups in the open-label period (28 weeks) after their switch to omarigliptin 25 mg q.w. were consistent with those observed in the omarigliptin group during the double-blind period (Supplementary Table S2).

Other Safety Evaluations

In both treatment periods, in each background AHA stratum and in the overall population, there were no clinically meaningful changes from baseline in laboratory safety measures, including lipids, liver function, renal function, muscle enzymes, or hematological parameter, and there were no clinically meaningful between-group differences in the percentages of patients meeting the predefined limits of change (PDLC) for safety measures. Omarigliptin had a neutral effect on body weight (Supplementary Table S3). There were no clinically meaningful changes from baseline in heart rate, blood pressure, or ECG intervals (including QTc). There were no adjudication-confirmed cases of pancreatitis or predefined hypersensitivity reaction AEs.

Efficacy

Double-Blind Placebo-Controlled Period (Day 1–Week 24)

Changes from baseline in HbA1c are summarized in Table 4. In all strata, the difference from placebo in change from baseline in HbA1c with omarigliptin treatment was significant ($p < 0.001$). The profile of change from baseline in HbA1c over time showed that in all strata the majority of the treatment effect was observed by

Table 3 Adverse events summary, specific AEs by SOC with incidence $\geq 5\%$ and incidences of symptomatic hypoglycemia in the omarigliptin/omariagliptin treatment group through week 52 in the overall population and for each background AHA stratum

Patients, n (%)	Sulfonylurea + omariagliptin (through week 52) n = 126	Glinide + omariagliptin (through week 52) n = 65	Biguanide + omariagliptin (through week 52) n = 66	Thiazolidinedione + omariagliptin (through week 52) n = 65	α -Glucosidase inhibitor + omarigliptin (through week 52) n = 67	Overall + omariagliptin (through week 52) n = 389
With one or more						
AEs	96 (76.2)	49 (75.4)	53 (80.3)	55 (84.6)	46 (68.7)	299 (76.9)
Drug-related ^a AEs	11 (8.7)	7 (10.8)	2 (3.0)	4 (6.2)	0 (0.0)	24 (6.2)
Serious AEs	6 (4.8)	3 (4.6)	2 (3.0)	4 (6.2)	1 (1.5)	16 (4.1)
Serious drug-related ^a AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Who died	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Who discontinued due to						
An AE	1 (0.8)	3 (4.6)	1 (1.5)	4 (6.2)	0 (0.0)	9 (2.3)
A drug-related ^a AE	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.5)	0 (0.0)	2 (0.5)
A serious AE	1 (0.8)	2 (3.1)	0 (0.0)	1 (1.5)	0 (0.0)	4 (1.0)
A serious drug-related ^a AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
With specific AEs with incidence $\geq 5\%$ in ≥ 1 treatment group, by SOC ^b						
Gastrointestinal disorders						
Constipation	7 (5.6)	5 (7.7)	1 (1.5)	1 (1.5)	2 (3.0)	16 (4.1)
Infections and infestations						
Bronchitis	10 (7.9)	1 (1.5)	0 (0.0)	2 (3.1)	3 (4.5)	16 (4.1)
Gastroenteritis	2 (1.6)	0 (0.0)	4 (6.1)	1 (1.5)	1 (1.5)	8 (2.1)
Influenza	4 (3.2)	0 (0.0)	0 (0.0)	4 (6.2)	1 (1.5)	9 (2.3)
Nasopharyngitis	34 (27.0)	23 (35.4)	24 (36.4)	19 (29.2)	19 (28.4)	119 (30.6)
Metabolism and nutrition disorders						
Hypoglycemia	11 (8.7)	2 (3.1)	3 (4.5)	2 (3.1)	0 (0.0)	18 (4.6)

Table 3 continued

Patients, n (%)	Sulfonylurea + omargliptin (through week 52) <i>n</i> = 126	Glinide + omargliptin (through week 52) <i>n</i> = 65	Biguanide + omargliptin (through week 52) <i>n</i> = 66	Thiazolidinedione + omargliptin (through week 52) <i>n</i> = 65	α-Glucosidase inhibitor + omargliptin (through week 52) <i>n</i> = 67	Overall + omargliptin (through week 52) <i>n</i> = 389
Musculoskeletal and connective tissue disorders						
Arthralgia	1 (0.8)	5 (7.7)	1 (1.5)	3 (4.6)	1 (1.5)	11 (2.8)
Back pain	6 (4.8)	4 (6.2)	4 (6.1)	5 (7.7)	4 (6.0)	23 (5.9)
Nervous system disorders						
Headache	2 (1.6)	0 (0.0)	2 (3.0)	4 (6.2)	3 (4.5)	11 (2.8)
With one or more AE of symptomatic hypoglycemia ^c	10 (7.9)	2 (3.1)	2 (3.0)	1 (1.5)	0 (0.0)	15 (3.9)

^a Assessed by the investigator to be related to the drug

^b System organ class defined by the Medical Dictionary for Regulatory Activities (MedDRA) classification system

^c Prespecified AE of interest; symptomatic hypoglycemia: episode with clinical symptoms consistent with hypoglycemia, without regard to glucose level

Table 4 Efficacy endpoints at weeks 24 and 52

Parameter	SU + omargliptin <i>n</i> = 126	SU + placebo <i>n</i> = 63	GL + omargliptin <i>n</i> = 65	GL + placebo <i>n</i> = 34	BG + omargliptin <i>n</i> = 66	BG + placebo <i>n</i> = 33	TZD + omargliptin <i>n</i> = 65	TZD + placebo <i>n</i> = 34	AGI + omargliptin <i>n</i> = 67	AGI + placebo <i>n</i> = 32
HbA1c, %										
Baseline	8.1 ± 0.7	8.1 ± 0.6	8.0 ± 0.6	8.0 ± 0.8	7.8 ± 0.6	8.0 ± 0.6	8.2 ± 0.8	7.9 ± 0.8	7.9 ± 0.6	7.9 ± 0.8
Change from baseline ^a	-0.84 (-0.94, -0.73)	0.09 (-0.06, 0.24)	-0.68 (-0.89, -0.48)	0.30 (-0.04, 0.64)	-0.94 (-1.10, -0.78)	-0.02 (-0.35, 0.31)	-0.88 (-1.04, -0.73)	0.28 (0.03, 0.53)	-0.74 (-0.89, -0.59)	0.06 (-0.16, 0.28)
Change vs. placebo ^b	-0.93 ^c (-1.10, -0.75)	-	-0.98 ^c (-1.37, -0.60)	-	-0.92 ^c (-1.29, -0.56)	-	-1.16 ^c (-1.45, -0.88)	-	-0.80 ^c (-1.06, -0.54)	-
FPG, mg/dL										
Baseline	165.4 ± 32.0	170.5 ± 34.0	163.5 ± 29.4	164.4 ± 34.7	155.8 ± 26.1	157.6 ± 20.6	163.4 ± 33.6	152.4 ± 24.5	157.7 ± 24.3	159.8 ± 30.7
Change from baseline ^a	-24.4 (-28.9, -19.9)	-6.8 (-12.7, -0.9)	-19.3 (-27.9, -10.7)	2.0 (-11.9, 16.0)	-29.0 (-36.0, -22.0)	-14.4 (-27.4, -1.4)	-28.4 (-35.0, -21.8)	-4.5 (-14.4, 5.3)	-20.4 (-26.8, -14.0)	-8.3 (-17.0, 0.4)
Change vs. placebo ^b	-17.6 ^c (-24.3, -10.8)	-	-21.3 ^d (-36.5, -6.1)	-	-14.6 ^d (-28.4, -0.8)	-	-23.9 ^c (-34.7, -13.0)	-	-12.1 ^d (-21.9, -2.3)	-
Parameter	SU + omargliptin/ omargliptin	SU + placebo/ omargliptin	GL + omargliptin/ omargliptin	GL + placebo/ omargliptin	BG + omargliptin/ omargliptin	BG + placebo/ omargliptin	TZD + omargliptin/ omargliptin	TZD + placebo/ omargliptin	AGI + omargliptin/ omargliptin	AGI + placebo/ omargliptin
week 52										
HbA1c, %										
Change from baseline ^a	-0.45 (-0.58, -0.32)	-0.63 (-0.82, -0.45)	-0.59 (-0.84, -0.34)	-0.43 (-0.88, 0.02)	-0.63 (-0.82, -0.45)	-0.62 (-0.99, -0.24)	-0.63 (-0.82, -0.44)	-0.65 (-0.93, -0.36)	-0.60 (-0.77, -0.43)	-0.79 (-1.03, -0.55)
FPG, mg/dL										
Change from baseline ^a	-8.3 (-14.1, -2.4)	-19.7 (-27.5, -11.9)	-14.7 (-24.1, -5.4)	-4.8 (-21.1, 11.6)	-16.6 (-23.6, -9.7)	-23.4 (-36.7, -10.1)	-17.2 (-23.6, -10.8)	-9.7 (-19.7, 0.4)	-9.3 (-15.1, -3.4)	-22.3 (-30.5, -14.0)

^a Least-squares (LS) mean [95% confidence interval (CI)] based on longitudinal data analysis models described in the "Statistical Analyses" section

^b Difference in LS means (95% CI)

^c $p < 0.001$

^d $p < 0.05$

SU sulfonylurea, GL glimeide, BG biguanide, TZD thiazolidinedione, AGI α -glucosidase inhibitor

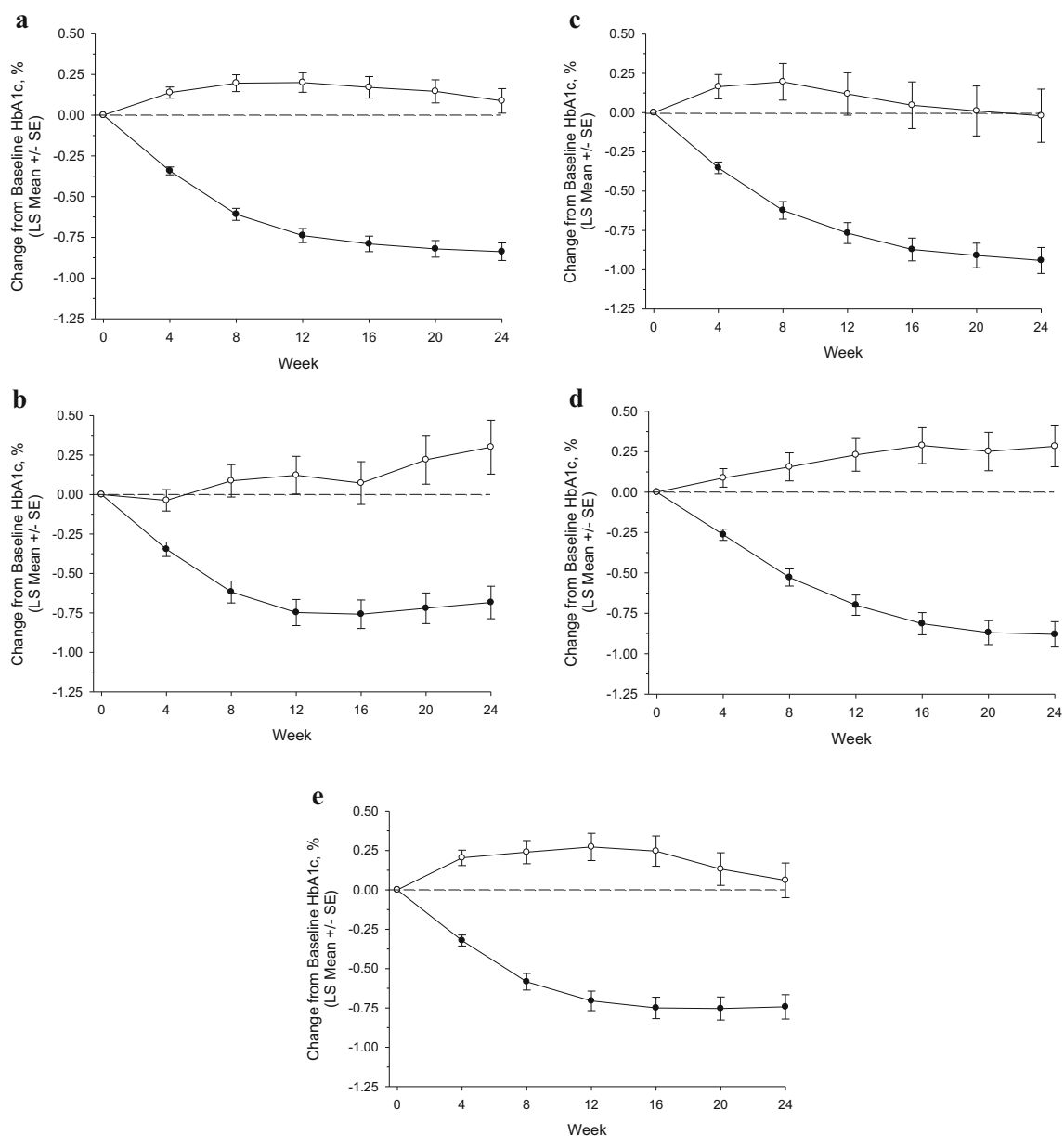


Fig. 2 HbA1c change from baseline (%) through week 24 by background AHA; **a** sulfonylurea; **b** glinide; **c** biguanide; **d** thiazolidinedione; **e** α-glucosidase inhibitor; *filled circle* omarigliptin, *open circle* placebo; based on the longitudinal data analysis model described in the “Statistical Analyses” section

weeks 12–16 (Fig. 2). The percentages of patients achieving an HbA1c of <7.0% and HbA1c of <6.5% at 24 weeks are shown in Supplementary Table S4.

Changes from baseline in FPG are summarized in Table 4. The profile of change from baseline in FPG over time showed that in all strata the majority of the treatment effect was

observed by week 4 and significant reductions were maintained throughout the remainder of the 24-week treatment period (data not shown).

Open-Label Period (Week 24–Week 52)

Changes from baseline in HbA1c in the omarigliptin/omariptin groups are summarized in

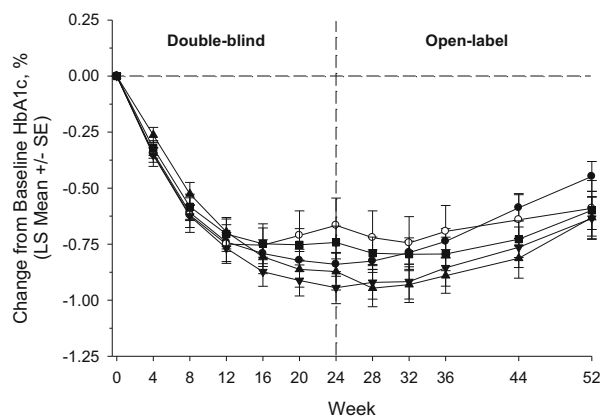


Fig. 3 HbA1c change from baseline (%) through week 52 in the omarigliptin/omariagliptin treatment groups by background AHA; *filled circle* sulfonyleurea; *open circle* glinide; *filled inverted triangle* biguanide; *filled triangle* thiazolidinedione; *filled square* α -glucosidase inhibitor; based on the longitudinal data analysis model described in the “Statistical Analyses” section

Table 4 and shown in Fig. 3. At week 52, persistent reductions in HbA1c levels were observed in the omarigliptin/omariagliptin groups regardless of background AHA. After the switch from placebo to omarigliptin, reductions in HbA1c were observed in all placebo/omariagliptin groups (Table 4, Supplementary Fig. S1). At week 52, reductions in FPG levels were observed in the omarigliptin/omariagliptin groups regardless of background AHA. In the placebo/omariagliptin groups, FPG levels at week 52 were similar to the omarigliptin/omariagliptin groups (Table 4). The percentages of patients achieving an HbA1c of <7.0% and HbA1c of <6.5% at 52 weeks are shown in Supplementary Table S4.

DISCUSSION

In the present trial in Japanese patients with T2D and inadequate glycemic control on monotherapy with one of five orally administered AHA classes (SU, GL, BG, TZD, or AGI), the addition of treatment with once-weekly omarigliptin for up to 52 weeks was generally safe and well tolerated and provided persistent glycemic efficacy. The orally administered background AHAs included in this study were those

commonly used in Japan at the time of the planning and initiation of the trial.

The initial 24-week double-blind period provided an assessment of safety, tolerability, and efficacy compared with placebo, which is a comparator that is considered to provide the most rigorous assessment of the intrinsic safety and efficacy of a test compound. The second period of the trial, a 28-week open-label period, allowed the assessment of safety, tolerability, and efficacy over a longer time period in the omarigliptin/omariagliptin groups.

During the 24-week double-blind period, no notable between-group differences were observed in the percentage of patients with AEs in any background AHA stratum or in the overall population. However, in the overall population, a higher incidence of AEs in the eye disorder SOC and skin and subcutaneous disorder SOC in the omarigliptin group compared with the placebo group led to a review of AEs with the highest incidences in those SOCs (which included diabetic retinopathy, contact dermatitis, and eczema) across the omarigliptin phase 2/3 program.

In a pooled analysis of omarigliptin phase 2/3 trials (conducted both in Japan and outside of Japan) that were placebo- and active-controlled and that included 4467 omarigliptin-exposed patients and 3900 non-exposed, with a median duration of exposure of approximately 398 days, the incidences of AEs of diabetic retinopathy, contact dermatitis, and eczema were reviewed and found to be similar in the omarigliptin-exposed and non-exposed groups (unpublished data; for a description of the trials included in the pooled analysis see Supplemental Appendix).

In that pooled analysis of phase 2/3 omarigliptin trials, there were no notable between-group differences in the incidences of AEs of diabetic retinopathy (0.5% in both treatment groups) or the related AE term retinopathy (0.0% in the omarigliptin-exposed versus 0.2% in the non-exposed group; Supplementary Table S5).

In the pooled analysis there were no imbalances in the incidences of the AE of contact dermatitis or the related AE terms dermatitis, atopic dermatitis, and allergic dermatitis

(Supplementary Table S5). The incidences of the AE of eczema in the omarigliptin-exposed and non-exposed groups in the pooled analysis were 0.6% versus 0.4% (Supplementary Table S5). The pooled analysis suggests that the imbalances in diabetic retinopathy and contact dermatitis observed in this trial are not clinically meaningful. The AE eczema is noted in the labels of one or more of the presently marketed daily DPP-4 inhibitors in Japan.

During the treatment period (24-week placebo-controlled period + 28-week open-label period), no specific AEs emerged that represented a safety signal associated with longer-term drug administration. In the open-label period, the types of AEs observed in the placebo/omarigliptin group were qualitatively similar to those observed in the omarigliptin group during the double-blind period.

A low incidence of hypoglycemia was observed in both treatment periods (double-blind and open-label) across the background AHA strata, with the exception of the SU stratum. This observation is consistent with the glucose-dependent mechanism of action of DPP-4 inhibitors and the observed higher incidence of hypoglycemia when DPP-4 inhibitors are administered with agents that cause hypoglycemia, such as sulfonylureas [13–15].

The magnitude of reductions of HbA1c and FPG were consistent with that observed for daily DPP-4 inhibitors in previous trials in Japanese patients with T2D [16–25]. The reductions from baseline in HbA1c and FPG at week 52 were clinically meaningful, but slightly less than that observed at week 24. However, the reductions at week 52 in the omarigliptin/omarigliptin groups were comparable to those observed in the placebo/omarigliptin groups despite the difference in duration of treatment with omarigliptin (52 weeks versus 28 weeks). This latter fact suggests that the observed increase in HbA1c at week 52 relative to week 24 was possibly due to a loss of trial effect and/or disease progression rather than a loss of omarigliptin efficacy. Similar changes in HbA1c over 52 weeks have been reported in several trials that assessed daily DPP-4 inhibitors as monotherapy and add-on therapy in Japanese patients with T2D [22–25].

The main limitation of this trial is that the conclusions that can be drawn about the safety and tolerability of the addition of omarigliptin to the five classes of AHA in Japanese patients with T2D are based on the relatively limited numbers of randomized patients. In addition, longer-term safety as defined by 52 weeks of exposure was only assessed in the omarigliptin/omarigliptin group. A wider clinical experience with omarigliptin will further define the safety, tolerability, and efficacy of this agent.

CONCLUSIONS

The safety and tolerability profile of once-weekly omarigliptin observed in this trial appears to be consistent with the known safety and tolerability profile of daily DPP-4 inhibitors [26, 27]. The results of this trial suggest that omarigliptin has the potential to be a useful therapeutic option when combination therapy is indicated for the treatment of T2D. In recent years, a patient-centered approach has been recommended for the treatment of T2D [28, 29]. A once-weekly, orally administered AHA has the potential to be a therapeutic option for the individualized care of patients with T2D (e.g., when the patient prefers a weekly regimen; in cases where poor adherence to daily medication has been identified as a barrier to achieving therapeutic goals; or when home healthcare is required and provided only intermittently).

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Disclosures. Ira Gantz is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and own stock and/or hold stock options in the company. Edward A. O'Neill is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and own stock and/or hold stock options in the company. Samuel S. Engel is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and own stock and/or hold stock options in the company. Eseng Lai is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and own stock and/or hold stock options in the company. Taro Okamoto is an employee of MSD K.K., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and own stock and/or hold stock options in the Company. Yuka Ito is an employee of MSD K.K., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and own stock and/or hold stock options in the Company. Asako Sato is an employee of MSD K.K., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and

own stock and/or hold stock options in the Company. Kotoba Okuyama is an employee of MSD K.K., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and own stock and/or hold stock options in the Company. Omarigliptin Study 015 Group investigators are listed in Appendix 1.

Compliance with Ethics Guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients included in the study.

Data Availability. Merck & Co., Inc.'s data sharing policy, including restrictions, is available at http://engagezone.merck.com/ds_documentation.php. Requests for access to the study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

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