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ORIGINAL RESEARCH

Efficacy and Safety of Vildagliptin as Add-on to Metformin in Japanese Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: The objective of this study was to evaluate the efficacy and safety of vildagliptin, a potent dipeptidyl peptidase-4 inhibitor, as an add-on to metformin in Japanese patients with type 2 diabetes mellitus (T2DM).

Methods: This multicenter, 12-week, randomized, double-blind, placebo-controlled, parallel-arm study compared vildagliptin 50 mg bid with placebo in T2DM patients who were inadequately controlled [glycosylated hemoglobin (HbA_{1c}) 7.0–10.0%] on a stable daily dose of metformin monotherapy (250 mg bid or 500 mg bid).

Results: A total of 139 patients were randomized to receive either vildagliptin ($n = 69$) or placebo ($n = 70$). Patient demographics were comparable between the groups at baseline. After 12 weeks of treatment, adjusted mean change in HbA_{1c} was −1.1% in the vildagliptin group (baseline 8.0%) and −0.1% in the placebo group (baseline 8.0%), with a between-treatment difference of −1.0% ($P < 0.001$). Vildagliptin showed a similar reduction in HbA_{1c} of −1.1% for both the subpopulations of patients receiving metformin 250 mg bid or 500 mg bid ($P < 0.001$ vs. baseline). Significantly more patients in the vildagliptin group achieved an HbA_{1c} target of ≤6.5% (30.9%) and <7.0% (64.1%) compared with the placebo group ($P < 0.001$). The between-treatment difference in adjusted mean change in fasting plasma glucose was −1.6 mmol/L ($P < 0.001$) in favor of vildagliptin. Patients in the vildagliptin and placebo groups reported comparable incidences of adverse events (44.1% vs. 41.4%). No deaths or hypoglycemic events were reported in the study.

Conclusions: Vildagliptin 50 mg bid added to metformin improved glycemic control without

Trial registration: Clinical Trials.gov #NCT01497522.

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any tolerability issues and hypoglycemia in Japanese patients with T2DM inadequately controlled on metformin monotherapy.

Keywords: Antidiabetic drug; Dipeptidyl peptidase-4 inhibitor; Glycemic control; Metformin; Randomized trial; Type 2 diabetes mellitus; Vildagliptin

INTRODUCTION

In Japan, the estimated number of individuals with type 2 diabetes mellitus (T2DM) is approximately 7.1 million, which is the ninth largest prevalence in the world [1]. In recent years, the prevalence of T2DM in Japan has increased due to lifestyle changes, genetic predisposition, and an aging population [2, 3]. Most of the Japanese T2DM patients are non-obese with an average body mass index (BMI) of 23–25 kg/m^2, impaired insulin secretion plays a key role in the development of T2DM in these patients [4].

Despite major advances in the management of T2DM and availability of a range of antidiabetic agents, evidence suggests that up to ~60% of patients in Japan [5] fail to achieve the recommended target of glycosylated hemoglobin (HbA_{1c}) levels <7.0% [6].

Metformin is one of the commonly used oral antidiabetic agents (OADs) in Japan. Metformin improves blood glucose levels primarily by inhibiting hepatic glucose production and also improving insulin sensitivity in the liver and skeletal muscles [7]. However, due to the progressive nature of T2DM, long-term glycemic control is difficult to achieve with a single agent, thus often requiring addition of further agents. Addition of a dipeptidyl peptidase-4 (DPP-4) enzyme inhibitor with metformin is beneficial due to their complementary mechanisms of action [8].

Vildagliptin, a potent and selective DPP-4 inhibitor, increases the active levels of incretin hormones, glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP), thereby improving pancreatic α- and β-cell sensitivity to glucose [9]. In large-scale clinical trials, vildagliptin improved glycemic control when given as monotherapy [10] or in combination with metformin [11], sulfonylurea [12], thiazolidinedione [13] or insulin [14], with low risk of hypoglycemia and weight gain. Vildagliptin 50 mg bid showed notable improvement in blood glucose levels and better tolerability compared with placebo [15] or voglibose [16] in Japanese patients with T2DM inadequately controlled on diet and exercise. Combination therapy of vildagliptin with low-dose (500 mg bid) and high-dose (1,000 mg bid) metformin showed improved glycemic control compared with individual monotherapies in a large global study [17]. The high dose of metformin (>750 mg/day) was approved in Japan in 2010. However, there are limited clinical data on the use of DPP-4 inhibitors in combination with metformin (>750 mg/day) in Japanese patients with T2DM. The aim of the present study was to evaluate the efficacy and safety of vildagliptin as add-on therapy in Japanese patients with T2DM inadequately controlled with metformin 500 or 1,000 mg/day. The study was conducted to support registration of the fixed-dose combination of vildagliptin and metformin for the treatment of T2DM in Japan.

MATERIALS AND METHODS

Study Design

This was a 12-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled

study conducted across 20 centers in Japan in patients with T2DM inadequately controlled on metformin and diet/exercise. Following a screening period (visit 1), eligible patients who were on a stable daily dose of metformin (250 mg bid or 500 mg bid) for at least 10 weeks proceeded directly to randomization (baseline, visit 2) to receive either vildagliptin 50 mg bid or placebo as add-on to metformin in a 1:1 ratio. Patients taking OADs other than metformin were switched to either metformin 250 mg bid or 500 mg bid at the investigator's discretion and were randomized after completing a 12-week run-in period (Fig. 1). This was followed by three scheduled visits from baseline (weeks 4, 8, and 12) during which efficacy and tolerability were assessed. Randomization was stratified to adjust for metformin dose in 1:1 ratio in both the treatment groups. The dose of metformin remained unchanged throughout the study and no rescue medication (additional OADs or insulin) was allowed. Patients with unsatisfactory therapeutic effect [fasting plasma glucose (FPG) $\geq$15.0 mmol/L] were to be discontinued from the study.

Study Population

The study enrolled men and women with T2DM, aged $\geq$20 to <75 years, BMI $\geq$20 to $\leq$35 kg/m^2, baseline HbA_{1c} values $\geq$7.0% to $\leq$10.0%, who were inadequately controlled on diet, exercise and metformin monotherapy. The patients were required to be on a stable daily dose of metformin 250 mg bid or 500 mg bid for at least 10 weeks prior to randomization.

The key exclusion criteria included history of type 1 diabetes, diabetes due to pancreatic injury or secondary forms, acute metabolic complications such as ketoacidosis or lactic acidosis, liver diseases such as cirrhosis or hepatitis, impaired renal function, congestive heart failure (New York Heart Association Class III or IV), myocardial infarction, stroke or transient ischemic attacks in the past 6 months. Patients with any of the following laboratory abnormalities at baseline were excluded: FPG $\geq$15 mmol/L; alanine transaminase, aspartate transaminase, or total bilirubin >2 times the upper limit of normal; and fasting triglycerides >5.7 mmol/L.

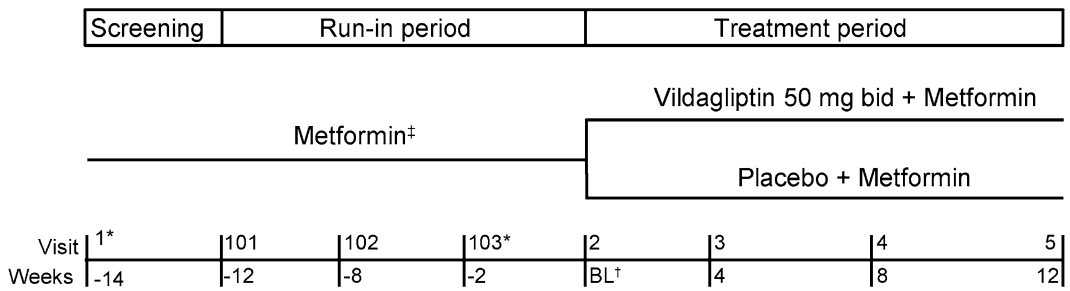

Fig. 1 Study design

Study Endpoints and Assessments

The primary efficacy endpoint was the change in HbA_{1c} from baseline to week 12 or the study endpoint. The key secondary efficacy endpoint was change in HbA_{1c} from baseline to study endpoint within subpopulations of patients treated with vildagliptin and metformin (250 mg bid or 500 mg bid). Other secondary efficacy endpoints included percentage of patients (responder rate) achieving predefined HbA_{1c} targets ($\leq$6.5%, <7.0%, and reductions of $\geq$0.5% and $\geq$1.0%) and change in FPG levels after 12 weeks of treatment. Changes in HbA_{1c} (reported in National Glycohemoglobin Standardization Program units) and FPG were assessed at each scheduled visit (weeks 0, 4, 8, and 12).

Adverse events (AEs) and serious AEs (SAEs) were recorded at each visit, and were assessed for severity, duration, and suspected relationship to the study drug. Standard hematology, biochemistry, liver function tests, urinalysis, vital signs, and body weight were measured at the screening visit and at weeks 0, 4, 8, and 12. Electrocardiograms were recorded at screening and at the last study visit (week 12). Fasting lipid profile was assessed at baseline and at the last study visit. All the patients were provided with a calibrated home glucose monitor and were instructed regarding its use. The patients were educated regarding hypoglycemic symptoms, possible triggers and were asked to record hypoglycemic event in a study diary. Hypoglycemia was defined as symptoms suggestive of hypoglycemia that was further confirmed by a self-monitored blood glucose measurement of <3.1 mmol/L. The event was considered grade 1 if the patient was able to initiate self-treatment, and grade 2 if the patient required assistance of another person or hospitalization. All the laboratory assessments were performed at a central laboratory (Mitsubishi Chemical Medience Corporation, Japan).

Statistical Analysis

A total of 136 patients (68 patients per group) were to be randomized (1:1) to achieve a target sample size of 128 patients (64 per group), assuming a dropout rate of 5%. This sample size would ensure at least 92% power to detect a clinically relevant between-group difference of 0.6% absolute units in HbA_{1c} change from baseline, assuming a one-sided significance level of 0.025, to demonstrate the superiority of vildagliptin 50 mg bid over placebo as add-on to metformin in reducing HbA_{1c} after 12 weeks of treatment. Moreover, randomization was stratified by metformin dose to ensure that patients on metformin 250 mg bid and 500 mg bid each constituted $\sim$50% of the randomized population. The planned sample size of 136 patients (34 patients in each metformin subpopulation in the vildagliptin group) would provide at least 90% power to detect a statistically significant reduction in HbA_{1c} of 0.6% from baseline in each metformin subgroup (250 mg bid or 500 mg bid), assuming a one-sided significance level of 0.025.

The primary and secondary efficacy analyses were based on the full analysis set, which included all randomized patients who received at least one dose of the study drug and had at least one post-randomization efficacy parameter assessment. Changes in HbA_{1c} and FPG from baseline to study endpoint were analyzed using the analysis of covariance model (ANCOVA), with treatment groups and metformin dose as classification variables and baseline HbA_{1c} as covariate. The study endpoint is the final available post-randomization assessment value

at any visit (scheduled or unscheduled) up to final visit (week 12). The between-treatment difference in HbA_{1c} and FPG was also analyzed using ANCOVA. Change in HbA_{1c} from baseline to study endpoint within the metformin subpopulations was analyzed using a paired *t* test. Missing data because of early discontinuation were handled using the last observation carried forward method. The impact of various baseline characteristics (age, gender, BMI, $HbA_{1c,}$ and FPG) on absolute change in HbA_{1c} from baseline to endpoint was analyzed using descriptive statistics. The proportion of responders (HbA_{1c} ≤6.5% at endpoint, HbA_{1c} <7% at endpoint, and reductions in HbA_{1c} ≥0.5% and ≥1%) in each treatment group was computed and compared using the Chi-square test. The data analysis for this study was carried out using SAS software (version 9.2, SAS Institute Inc., Cary, NC, USA). The safety set consisted of all patients who received at least one dose of the study drug. Safety data were summarized descriptively by treatment. The incidences of treatment-emergent AEs were summarized by system organ class (SOC), preferred term (PT), severity, and relationship to the study drug. AEs were coded by primary SOC and PT according to Medical Dictionary for Drug Regulatory Activities (MedDRA version 15.1).

Ethics and Good Clinical Practice

The study protocol was reviewed and approved by the Independent Ethics Committee/ Institutional Review Board at each center. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national), the Helsinki Declaration of 1975, as revised in 2000 and 2008 and Good Clinical Practice guidelines. Informed consent was obtained from all patients for being included in the study. The study is registered with ClinicalTrials.gov, identifier: NCT01497522.

RESULTS

Patient Disposition and Baseline Characteristics

Of the 139 randomized patients (vildagliptin, $n = 69$; placebo, $n = 70$), 133 patients (95.7%) completed the study (Fig. 2). The primary reasons for discontinuation in the study were AEs (3 patients) and protocol deviations (2 patients) (Fig. 2). Patient demographics and baseline characteristics were comparable between the treatment groups (Table 1). Overall mean age, BMI, baseline HbA_{1c}, baseline FPG, and duration of T2DM were 58.1 years, 25.6 kg/m^2, 8.0%, 9.2 mmol/L, and 7.1 years, respectively. The patients were predominantly men (66.2%), and more patients were aged ≥65 years in the

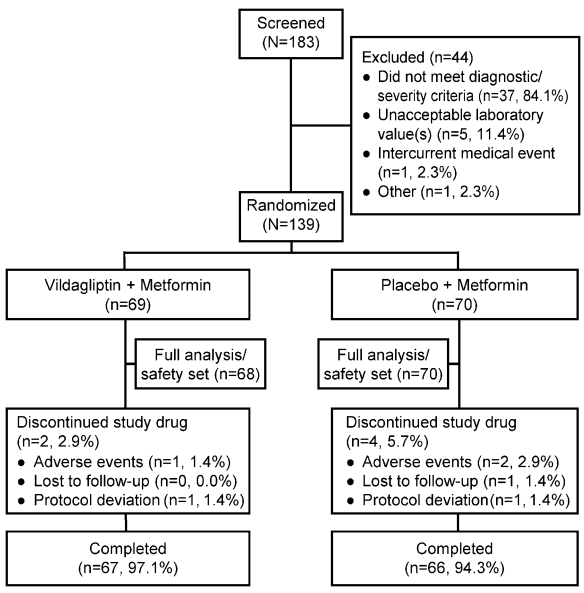

Fig. 2 Patient disposition

Table 1 Patient demographics and baseline characteristics (randomized set)

Parameter	Vildagliptin + metformin $n = 69$	Placebo + metformin $n = 70$	Total $N = 139$
Age, years	58.7 (9.81)	57.5 (9.15)	58.1 (9.47)
≥65 years, *n* (%)	22 (31.9)	16 (22.9)	38 (27.3)
Men, *n* (%)	44 (63.8)	48 (68.6)	92 (66.2)
Body weight, kg	67.9 (12.70)	70.0 (13.02)	68.9 (12.85)
BMI, kg/m^2	25.3 (3.56)	25.9 (4.01)	25.6 (3.79)
HbA_{1c}, %	8.0 (0.83)	8.0 (0.96)	8.0 (0.90)
≤8%, *n* (%)	40 (58.0)	40 (57.1)	80 (57.6)
>8 to ≤9%, *n* (%)	17 (24.6)	14 (20.0)	31 (22.3)
>9%, *n* (%)	12 (17.4)	16 (22.9)	28 (20.1)
FPG, mmol/L	9.1 (1.80)	9.3 (2.40)	9.2 (2.12)
≥8.9 mmol/L, *n* (%)	28 (40.6)	36 (51.4)	64 (46.0)
Duration of T2DM, years	7.2 (6.18)	7.0 (5.92)	7.1 (6.03)
Metformin total daily dose, mg	753.6 (251.81)	750.0 (251.81)	751.8 (250.90)
Metformin ≤500 mg/day, *n* (%)	34 (49.3)	35 (50.0)	69 (49.6)
Metformin >500 mg/day, *n* (%)	35 (50.7)	35 (50.0)	70 (50.4)
eGFR (MDRD), mL/min/1.73 m^2, *n* (%)			
Normal, >80	66 (95.7)	64 (91.4)	130 (93.5)
Mild, ≥50 to ≤80	3 (4.3)	6 (8.6)	9 (6.5)
Moderate, ≥30 to <50	0 (0.0)	0 (0.0)	0 (0.0)

Values are expressed as mean (standard deviation) unless specified otherwise
BMI body mass index, *eGFR* estimated glomerular filtration rate, *FPG* fasting plasma glucose, *HbA_{1c}* glycosylated hemoglobin, *MDRD* modification of diet in renal disease, *OADs* oral antidiabetic drugs, *T2DM* type 2 diabetes mellitus

vildagliptin group (31.9%) than in the placebo group (22.9%).

Efficacy

The mean change in HbA_{1c} during the 12 weeks of treatment was consistently lower with vildagliptin than with placebo (Fig. 3a). The overall adjusted mean change (AMΔ) ± SE in HbA_{1c} was −1.1 ± 0.06% in the vildagliptin group (baseline 8.0%) and −0.1 ± 0.06% in the placebo group (baseline 8.0%), with a statistically significant between-treatment difference of −1.0 ± 0.09% ($P < 0.001$) in favor of vildagliptin (Fig. 3b). Vildagliptin also showed statistically significant reductions from baseline in HbA_{1c} for subpopulations of patients receiving metformin 250 mg bid and 500 mg bid (Table 2). Significantly more patients with vildagliptin achieved HbA_{1c} targets of ≤6.5% (30.9%) and <7.0% (64.1%) compared with placebo ($P < 0.001$). A higher

proportion of patients in the vildagliptin group achieved HbA_{1c} reductions of ≥1% and ≥0.5% than in the placebo group ($P < 0.001$) (Table 3).

The mean changes in HbA_{1c} from baseline to endpoint in the subgroups of patients by age, gender, baseline BMI, baseline HbA_{1c} and baseline FPG are presented in Table 4. The mean changes in HbA_{1c} were greater for vildagliptin compared with placebo across all the subgroups. Mean reductions in HbA_{1c} in the vildagliptin group were higher in the subgroups of patients with higher baseline HbA_{1c} (HbA_{1c} >8% to ≤9% or >9%) or FPG (≥8.9 mmol/L) and in those with lower baseline BMI (<25 kg/m^2).

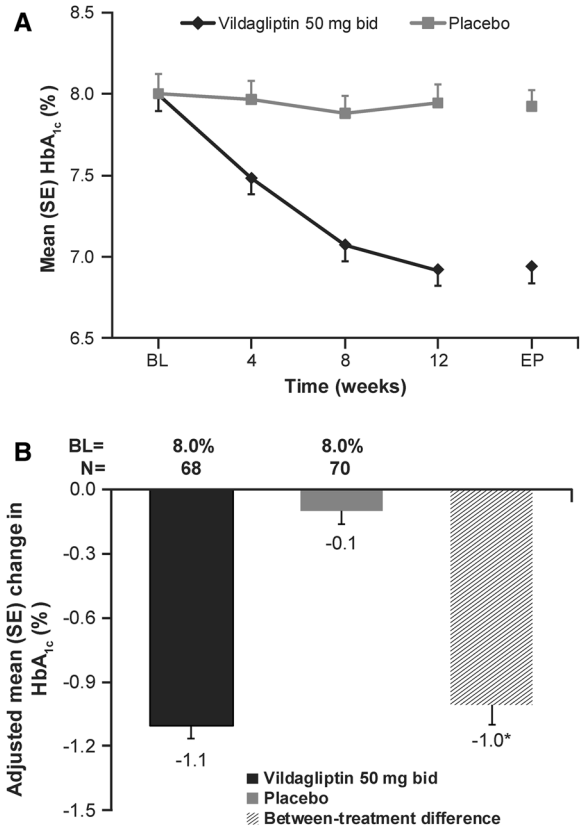

Fig. 3 **a** Mean glycosylated hemoglobin (HbA_{1c}) by treatment and visit (full analysis set). **b** Adjusted mean change in HbA_{1c} from baseline to endpoint (full analysis set). *BL* baseline, *EP* endpoint, *SE* standard error. *$P < 0.001$

Vildagliptin showed sustained reduction in FPG over placebo during the 12 weeks of treatment (Fig. 4a). The AMΔ ± SE in FPG from baseline to endpoint was greater in patients receiving vildagliptin (−1.7 ± 0.16 mmol/L) compared with those receiving placebo (−0.1 ± 0.16 mmol/L), with a between-treatment difference of −1.6 ± 0.22 mmol/L ($P < 0.001$) (Fig. 4b).

Safety

The overall proportion of patients experiencing AEs was comparable between the vildagliptin (44.1%) and placebo (41.4%) groups. The most commonly reported AE by primary SOC was "infections and infestations" (13.2% for vildagliptin and 14.3% for placebo). The most frequently reported AE (≥2% in any group) by PT was "nasopharyngitis" (7.4% for vildagliptin and 5.7% for placebo) (Table 5). While incidence of AEs was low across PTs in both the treatment groups, "amylase increased" was reported in more patients with vildagliptin (4 patients; 5.9%) than with placebo (1 patient; 1.4%) and anemia was more frequent with placebo (3 patients; 4.3%) than with vildagliptin (0 patient). All the events of increased amylase levels were classified as mild and clinically asymptomatic. All the reported AEs were mild or moderate in severity. The incidence of AEs suspected to be related to the study drug was slightly higher in the vildagliptin group than in the placebo group (16.2% vs. 10.0%). One patient in the vildagliptin group and two patients in the placebo group discontinued the study. No SAEs were reported in the vildagliptin group, whereas one SAE of myocardial infarction was reported in the placebo group. There were no deaths during the study. No hypoglycemic events were reported in the study. There was

Table 2 Change in HbA_{1c} (%) in subpopulations of patients taking metformin 250 mg bid or 500 mg bid (full analysis set)

Treatment	*n*	Baseline mean (SE)	Mean change (SE)	95% CI (*P* value)
Vildagliptin + metformin 250 mg bid	34	7.9 (0.13)	−1.1 (0.09)	−1.24, −0.88 ($P < 0.001$)
Vildagliptin + metformin 500 mg bid	34	8.1 (0.15)	−1.1 (0.09)	−1.24, −0.88 ($P < 0.001$)

CI confidence interval, *HbA_{1c}* glycosylated hemoglobin, *SE* standard error

Table 3 HbA_{1c} responder rates (full analysis set)

Responder criteria	Vildagliptin + metformin *n* = 68	Placebo + metformin *n* = 70
HbA_{1c} ≤6.5%, n/N^a (%)	21/68 (30.9)*	2/70 (2.9)
HbA_{1c} <7.0%, n/N^b (%)	41/64 (64.1)*	9/59 (15.3)
Reduction of HbA_{1c} ≥1%, n/N^c (%)	39/68 (57.4)*	3/70 (4.3)
Reduction of HbA_{1c} ≥0.5%, n/N^c (%)	59/68 (86.8)*	13/70 (18.6)

HbA_{1c} glycosylated hemoglobin

* $P < 0.001$

[a] Denominator includes patients with a baseline of HbA_{1c} >6.5% and endpoint HbA_{1c} measurement

[b] Denominator includes patients with a baseline of HbA_{1c} ≥7% and endpoint HbA_{1c} measurement

[c] Denominator includes patients with both baseline and endpoint HbA_{1c} measurements

no change in body weight from baseline to endpoint for both treatment groups (+0.3 kg for vildagliptin and −0.2 kg for placebo). There were no clinically relevant changes or trends in the hematological, biochemical (including lipid parameters), hepatic enzyme, urinalysis parameters, and vital signs in either treatment group.

DISCUSSION

This 12-week, randomized, double-blind study evaluated the efficacy and safety of vildagliptin 50 mg bid in Japanese patients with T2DM inadequately controlled on metformin monotherapy. Vildagliptin produced a statistically significant and clinically meaningful change in HbA_{1c} compared with placebo (−1.1% vs. −0.1%; $P < 0.001$) as add-on to metformin (250 mg bid or 500 mg bid) after 12 weeks of treatment in Japanese patients with T2DM. Despite the lower baseline mean HbA_{1c} and daily dose of metformin in this study, the between-treatment difference (−1.0%) seen was consistent with the findings previously reported in a predominantly Caucasian population, where vildagliptin-treated patients showed a decrease in HbA_{1c} of 1.1% vs. placebo over 24 weeks of treatment [11]. Moreover, the reduction in HbA_{1c} levels reported with vildagliptin therapy was consistent with other DPP-4 inhibitors with different study designs in Japanese population [18–20]. These findings indicate that vildagliptin is effective in Japanese patients with T2DM when added to metformin monotherapy.

Further, vildagliptin showed statistically significant and clinically meaningful reduction

Table 4 Mean changes in HbA_{1c} (%) from baseline to endpoint by subgroups (full analysis set)

Subgroups	Vildagliptin + metformin *n* = 68			Placebo + metformin *n* = 70		
	n	*BL* mean	Change (SE)	*N*	*BL* mean	Change (SE)
Age (years)						
<65	47	7.9	−1.1 (0.08)	54	8.0	−0.1 (0.08)
≥65	21	8.3	−1.1 (0.15)	16	7.9	−0.2 (0.08)
Gender						
Male	44	7.9	−1.0 (0.10)	48	8.1	−0.2 (0.07)
Female	24	8.2	−1.2 (0.09)	22	7.9	−0.1 (0.13)
BMI (kg/m^2)						
<25	32	8.0	−1.2 (0.11)	35	7.8	−0.2 (0.08)
≥25	36	8.0	−0.9 (0.08)	35	8.2	0.0 (0.10)
HbA_{1c} (%)						
≤8	40	7.4	−0.9 (0.07)	40	7.3	0.0 (0.08)
>8 to ≤9	17	8.3	−1.1 (0.14)	14	8.5	0.0 (0.10)
>9	11	9.5	−1.6 (0.26)	16	9.4	−0.3 (0.17)
FPG (mmol/L)						
<8.9	41	7.6	−1.0 (0.08)	34	7.3	−0.1 (0.06)
≥8.9	27	8.6	−1.2 (0.14)	36	8.7	−0.1 (0.11)

BL baseline, *BMI* body mass index, *FPG* fasting plasma glucose, *HbA_{1c}* glycosylated hemoglobin, *SE* standard error

in HbA_{1c} after 12 weeks of treatment in the subpopulation of patients receiving metformin 250 mg bid or 500 mg bid. Treatment with vildagliptin produced greater reduction in HbA_{1c} compared with placebo regardless of age, gender, baseline BMI, HbA_{1c} and FPG. Vildagliptin was efficacious irrespective of the baseline HbA_{1c}. Greater reduction was seen in patients with higher baseline, which is consistent with the results observed in a predominantly Caucasian population [11].

Approximately one-third of patients treated with vildagliptin (30.9%) achieved the predefined HbA_{1c} target of ≤6.5%. Furthermore, almost two-thirds of patients (64.1%) reached the HbA_{1c} target of <7.0%, a goal recommended by the Japanese Diabetes Society [6]. The responder rate (<7.0%) was higher than that reported in a predominantly Caucasian population (55.4%) [11]. Over half of the population (57.4%) achieved an HbA_{1c} reduction of ≥1.0%, and 86.8% of patients reported a reduction of ≥0.5% in the vildagliptin group.

Vildagliptin showed statistically significant reduction in FPG levels vs. placebo ($P < 0.001$) as add-on to metformin monotherapy after 12 weeks of treatment. The decrease in FPG could be attributed to increased active levels of GLP-1 upon twice-daily administration of vildagliptin 50 mg, which enhances insulin secretion and suppresses glucagon levels

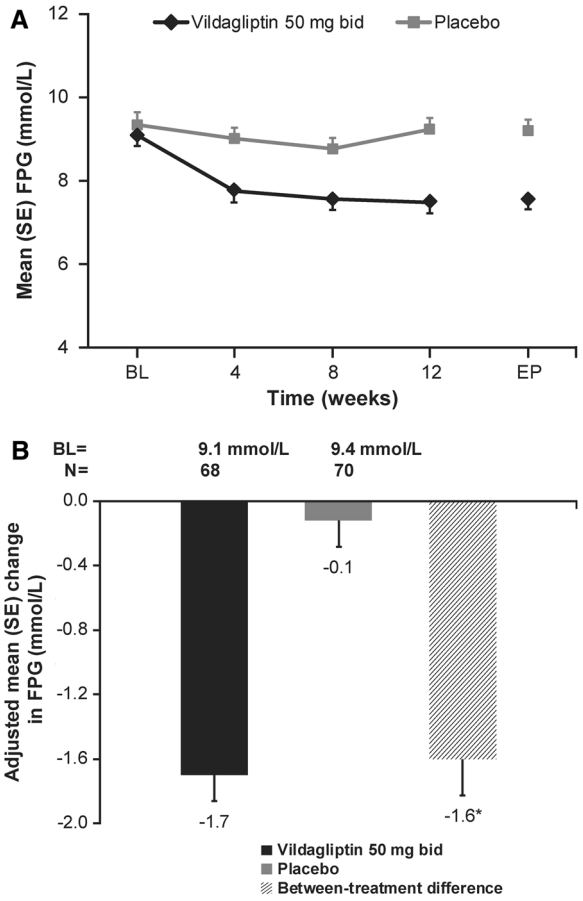

Fig. 4 **a** Fasting plasma glucose (FPG) by treatment and visit (full analysis set). **b** Adjusted mean change in FPG from baseline to endpoint (full analysis set). *BL* baseline, *EP* endpoint, *SE* standard error. $^{*}P < 0.001$

Table 5 Number (%) of patients reporting common adverse events (≥2% in any group) by preferred term (safety set)

Preferred term, *n* (%)	Vildagliptin + metformin *n* = 68	Placebo + metformin *n* = 70
Any preferred term	30 (44.1)	29 (41.4)
Nasopharyngitis	5 (7.4)	4 (5.7)
Amylase increased	4 (5.9)	1 (1.4)
Dental caries	2 (2.9)	0 (0.0)
Gastritis erosive	2 (2.9)	0 (0.0)
Tinea infection	2 (2.9)	0 (0.0)
Lipase increased	2 (2.9)	1 (1.4)
Hypoesthesia	2 (2.9)	0 (0.0)
Anemia	0 (0.0)	3 (4.3)
Diarrhea	0 (0.0)	2 (2.9)
Gastroenteritis	0 (0.0)	2 (2.9)
Alanine aminotransferase increased	0 (0.0)	2 (2.9)
Aspartate aminotransferase increased	0 (0.0)	2 (2.9)
Back pain	0 (0.0)	2 (2.9)
Headache	0 (0.0)	2 (2.9)
Tension headache	0 (0.0)	2 (2.9)

relative to glucose levels, in turn decreasing the endogenous glucose production overnight [21].

Overall, vildagliptin added to metformin was safe with no new safety findings observed in Japanese patients with T2DM. The observed safety profile was similar with previously reported 52-week safety study of vildagliptin add-on to metformin in Japanese patients with T2DM [22], long-term study of vildagliptin add-on to metformin in a predominantly Caucasian population [23], and safety pooled analysis of vildagliptin studies of ≥12 to ≥104 weeks duration [24]. Four patients in the vildagliptin group and one patient in the placebo group reported clinically asymptomatic mild elevations of amylase and/or lipase; however, none of these cases were considered as an AE of acute pancreatitis by the investigators. Similar to the previously reported studies [25], treatment with vildagliptin as add-on to metformin confirmed its weight neutrality in Japanese patients.

There were no incidences of hypoglycemia reported in the study. Absence of hypoglycemic events in the vildagliptin group, in spite of lower mean baseline FPG and HbA_{1c} levels than the

global study [11], confirms the glucose-dependent action of vildagliptin. This is consistent with the results from a previously reported large pooled analysis of global safety data, which showed that vildagliptin, as monotherapy or in combination with metformin, thiazolidinedione, or sulfonylurea, is associated with fewer hypoglycemic events compared with comparators [24].

The notable benefit observed in improving HbA_{1c} levels confirms the complementary mechanism of action of vildagliptin and metformin in Japanese patients with T2DM. Metformin increases the plasma concentration of incretin hormones and enhances the effects of DPP-4 inhibition on the increase of intact GLP-1, which might explain the improved efficacy of vildagliptin in combination with metformin [26].

In conclusion, vildagliptin 50 mg bid as add-on to metformin is effective in reducing HbA_{1c} and FPG levels without any tolerability issues and hypoglycemia in Japanese patients with T2DM inadequately controlled on metformin monotherapy.

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Conflict of interest. Manabu Suzuki is an employee of Novartis Pharma K.K. Izumi Hamada is an employee of Novartis Pharma K.K. Masato Odawara is the independent medical advisor for this study and has received consultancy fees from Novartis Pharma K.K.

Compliance with ethics guidelines. The study protocol was reviewed and approved by the Independent Ethics Committee/Institutional Review Board at each center. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national), the Helsinki Declaration of 1975, as revised in 2000 and 2008 and Good Clinical Practice guidelines. Informed consent was obtained from all patients for being included in the study.

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