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ORIGINAL RESEARCH

Efficacy and Safety of Vildagliptin as an Add-on to Insulin with or without Metformin in Japanese Patients with Type 2 Diabetes Mellitus: A 12-week, Double-Blind, Randomized Study

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ABSTRACT

Introduction: To assess the efficacy and safety of vildagliptin as add-on therapy in Japanese patients with type 2 diabetes mellitus (T2DM), inadequately controlled on stable long-acting, intermediate-acting, or pre-mixed insulin, with or without concomitant metformin.

Methods: In this 12-week placebo-controlled study, patients were randomized to receive either vildagliptin 50 mg twice daily (bid) or placebo treatment in a 1:1 ratio. The primary endpoint was change in glycated hemoglobin A1c (HbA1c) from baseline to 12-week endpoint. Secondary endpoints included proportion of patients achieving pre-defined HbA1c targets of $\leq$6.5%, <7.0%, and HbA1c <7.0% in patients with baseline HbA1c $\leq$8.0% and change in fasting plasma glucose (FPG) after 12 weeks of treatment. Regular monitoring was performed to record any treatment-emergent adverse events (AEs) and serious adverse events or hypoglycemic episodes.

Results: Of the 156 patients randomized, 96.8% completed the study (vildagliptin, $n = 76$; placebo, $n = 75$). Patient demographics and clinical characteristics were comparable between the groups at baseline. Addition of vildagliptin resulted in statistically significant reductions in HbA1c after 12 weeks ($-1.01 \pm 0.06\%$), with a between-treatment difference of $-0.91 \pm 0.09\%$ ($p < 0.001$). FPG levels reduced from baseline to 12 weeks in the vildagliptin group (-1.2 ± 0.2 mmol/L), with a between-treatment difference of -1.2 ± 0.3 mmol/L which was significant ($p < 0.001$). The proportion of patients achieving HbA1c targets was higher with vildagliptin treatment for all pre-defined

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responder rate categories. The overall incidence of AEs was comparable between groups (vildagliptin, 46.2% vs. placebo, 43.6%). The overall incidence of hypoglycemic events was low and all events were self-treatable without using drug therapy. No severe hypoglycemic events were reported.

Conclusion: Treatment with vildagliptin 50 mg bid as add-on to insulin with or without metformin resulted in statistically significant reductions in HbA1c in Japanese patients with T2DM. Overall, vildagliptin was well tolerated with a safety profile similar to that of placebo in this patient population.

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INTRODUCTION

The increasing prevalence of type 2 diabetes mellitus (T2DM) poses a major health crisis globally. According to International Diabetes Federation estimates, 382 million people were affected with T2DM in 2013. This number is projected to increase up to 600 million by 2035, with Asia alone accounting for 60% of this population [1].

In Japan, approximately 7 million people aged 20–79 years are affected with T2DM and the prevalence is dramatically increasing due to lifestyle changes, genetic predisposition, and the aging population [2, 3]. Mortality related to diabetes was 44% in patients aged <60 years in Japan, China, and other parts of the Western Pacific region [1]. The high prevalence of T2DM is associated with significant economic encumbrance, accounting for up to 6% of the total healthcare budget [3].

Due to the progressive nature of T2DM, treatment intensification with oral antidiabetes drugs (OADs) is often required. However, despite the availability of several OADs and advancements in T2DM management, achieving glycated hemoglobin A1c (HbA1c) goal of <7% is still a challenge in most Asian countries including Japan [4]. Impaired insulin secretion and insulin resistance are two major pathophysiological features where insulin secretory response is severely impaired in T2DM patients, especially among Japanese population [5].

In Japan, insulin is now being used more frequently, with ~30% of patients receiving either a monotherapy or in combination with other OADs [6, 7]. Although pre-mixed insulin lowers fasting plasma glucose (FPG) and post-prandial glucose levels to some extent, it eventually fails to demonstrate adequate control over glycemic excursions [7]. Fear of increased risk of hypoglycemia and weight gain associated with insulin often results in delay in treatment initiation and intensification [8, 9]. In addition, patients undergoing insulin treatment gradually develop a syndrome called Impaired Awareness of Hypoglycemia (IAH), in which the ability to identify the onset of hypoglycemia becomes progressively impaired and thus the complications associated with hypoglycemia increase [10, 11].

Hence, there is a need for OADs as an add-on to insulin that can improve glycemic control without increasing the risk of hypoglycemia and weight gain. Dipeptidyl peptidase-4 (DPP-4) inhibitors such as vildagliptin are being increasingly used for the treatment of diabetes in Japanese patients [12]. Further, concomitant use of insulin and a DPP-4 inhibitor has recently been included in the treatment algorithm [6]. The efficacy and tolerability of vildagliptin in combination with insulin, with or without

metformin, has been demonstrated in randomized clinical trials in global populations including Asians [13–15]. However, there is still a dearth of data on the efficacy and safety of vildagliptin as an add-on therapy to insulin in Japanese patients with T2DM.

This 12-week, randomized, placebo-controlled study aimed to assess the efficacy and safety of vildagliptin 50 mg twice daily (bid) add-on therapy in Japanese patients with T2DM, inadequately controlled on insulin, with or without concomitant metformin treatment.

METHODS

Study Design and Patient Population

This was a 12-week, randomized, double-blind, placebo-controlled study conducted in Japan. Patients were treated with stable once daily (qd) or bid injectable doses (≤1 unit/kg/day) of long-acting, intermediate-acting, or pre-mixed insulin, with or without metformin, for at least 12 weeks prior to screening. Patient visits were scheduled at week −2 (visit 1), week 0, (baseline), and at weeks 4, 8, and 12 (visits 2, 3, and 4, respectively; Fig. 1).

Following a 2-week screening period, men and women, aged between 20 and 75 years, with baseline HbA1c 7–10%, body mass index (BMI) 20–35 kg/m^2, fasting C-peptide ≥0.6 ng/mL (≥0.20 nmol/L), and inadequately controlled on insulin with or without metformin, were randomized. Patients with a history of type 1 diabetes, FPG levels ≥15.0 mmol/L, acute metabolic complications such as ketoacidosis or lactic acidosis, critical liver conditions such as cirrhosis or hepatitis, impaired renal function, congestive heart failure (New York Heart Association Class III or IV), myocardial infarction, stroke or ischemic attacks in past 6 months were excluded from the study. Patients who received rapid- or short-acting insulin except in pre-mixed formulations with either intermediate- or long-acting insulin, or even those on insulin doses taken more frequently than bid, or a total insulin dose exceeding 1 unit/kg/day for the past 12 weeks were also excluded. The dose of insulin was to be maintained within 10% variation from baseline throughout the study unless dose adjustments were required for safety reasons. Patients were stratified based on the use of metformin and type of insulin.

Efficacy and Safety Assessments

The primary endpoint was the change in HbA1c from baseline to 12 weeks. Secondary efficacy endpoints included responder rates based on

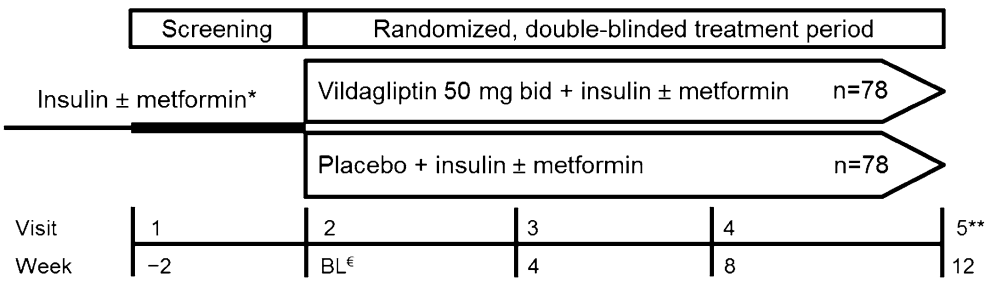

Fig. 1 Study design. *Patients continued on a stable dose of long-acting or intermediate-acting or pre-mixed insulin, and metformin if applicable, throughout the study. *BL*€ Baseline, the first day of blinded study medication. **Each patient was instructed to visit the study site within 13 weeks from baseline. *bid* twice daily

the proportion of patients achieving the pre-defined glycemic targets of HbA1c ≤6.5%, <7.0%, and HbA1c <7.0% in patients with baseline HbA1c ≤8.0%, HbA1c reduction from baseline to endpoint of ≥1% and ≥0.5%, and change in FPG from baseline to study endpoint. Subgroup analysis based on concomitant use of metformin and insulin types were also performed. Safety assessments included vital signs, body weight, standard hematology, urinalysis and biochemistry test results, as well as recording and regular monitoring of treatment-emergent adverse events (AEs) and serious adverse events (SAEs). Patients were educated on hypoglycemic symptoms in the beginning of the screening period where general reviews on possible triggers and identification of symptoms were shared. At baseline visit, patients were provided with a personal calibrated home glucose monitor and were asked to record the hypoglycemic events in a glycemia 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 (severe hypoglycemia) if the patient required assistance of another person or hospitalization. All laboratory assessments were performed at a central facility (LSI Medience Corporation, Tokyo, Japan).

Statistical Analysis

Assuming a withdrawal rate of 5%, a sample size of 152 patients with T2DM treated with insulin were randomized to provide 90% power to detect a clinically significant difference of 0.6% in HbA1c change from baseline between vildagliptin and placebo at a one-sided significance level of 2.5%. nQuery Advisor 7.0 (Statistical Solutions Ltd., Cork, Ireland) was applied for the calculation of sample size based on primary variables of change from baseline in HbA1c at the week-12 endpoint.

Efficacy analyses were performed on the full analysis set (FAS) population, comprising all randomized patients who received at least one dose of study medication and had one post-randomization efficacy measurement. An analysis of covariance (ANCOVA) model, with treatment, type of insulin (long- or intermediate-acting vs. pre-mixed), and use of metformin as classification variables and baseline HbA1c as a covariate, was used to compare the treatment effect in HbA1c reduction after 12 weeks. Changes in FPG levels from baseline to week 12 were also analyzed using ANCOVA model. The least square mean change and difference from baseline for each treatment group, and the associated one-sided 95% confidence interval (CI) and p value for each difference was obtained from the primary analysis model. The percentage of patients who met each of the pre-defined responder criteria was computed and compared using a Chi-Squared test in the FAS. For subgroup analysis, summary of absolute values and changes in HbA1c from baseline to study endpoint were presented on the last observation carried forward-based data for the FAS. Safety analyses were performed on the safety set which included all the patients who received at least one dose of the study drug and were summarized descriptively. All the data analysis for this study was performed using SAS® statistical software (version 9.3, SAS Institute Inc., Cary, NC, USA).

Ethics and Good Clinical Practice

The study protocol was reviewed and approved by the Independent Ethics Committee/

Institutional Review Board at each participating center. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national), the Declaration of Helsinki of 1964, as revised in 2013 and Good Clinical Practice guidelines. Written informed consent was obtained from all patients prior to inclusion in the study. The study is registered with ClinicalTrials.gov, identifier: NCT02002221.

RESULTS

Patient Disposition and Baseline Characteristics

A total of 275 patients were screened based on inclusion/exclusion criteria. Unacceptable laboratory values accounted for 68.9% ($n = 119$) of screening failures. Out of 156 patients randomized, 96.8% (vildagliptin, $n = 76$ and placebo, $n = 75$) completed the study (Fig. 2). The most common reason behind discontinuation was AEs: 2.6% in the vildagliptin and 1.3% in the placebo group. Demographics and baseline characteristics of the patients are presented in Table 1. Both treatment groups were well balanced for baseline characteristics. Men predominated over women (71.2% vs. 28.8%, respectively). The overall mean age ± SD was 59.3 ± 9.3 years, mean BMI was 25.7 ± 3.3 kg/m^2, mean baseline HbA1c was 8.1 ± 0.8%, and mean FPG was 8.9 ± 2.6 mmol/L. The mean duration of T2DM was ~13 years. More patients were on intermediate-acting insulin ($n = 91$) compared to pre-mixed insulin ($n = 65$). The mean daily doses of insulin and metformin were 0.3 ± 0.18 unit/kg/day, and 1047.8 mg/day, respectively.

Efficacy

The mean change in HbA1c over 12 weeks of treatment is represented in Fig. 3a. Vildagliptin demonstrated consistent reductions in mean HbA1c compared to placebo throughout the study. The adjusted mean change in HbA1c from baseline to study endpoint was −1.01 ± 0.06 and −0.11 ± 0.06% in the vildagliptin and placebo groups, respectively, with a between-treatment difference of −0.91 ± 0.09% ($p < 0.001$) (Fig. 3b). The proportion of patients achieving target HbA1c <7% were distinctly higher in the vildagliptin group compared to placebo for all pre-defined responder categories (Table 2). Half the patients (38 out of 76) in the vildagliptin group achieved HbA1c target <7%, compared with 3.9% in the placebo group. In all the subgroups by concomitant metformin use or insulin type, vildagliptin resulted in higher HbA1c reductions than placebo (Table 3). Reductions in FPG were also consistent throughout the study (Fig. 4a). The adjusted mean change in FPG from baseline to endpoint was −1.2 ± 0.2 vs. −0.02 ± 0.2 mmol/L in the vildagliptin and placebo groups, respectively, with a between-treatment difference of −1.2 ± 0.3 mmol/L ($p < 0.001$; Fig. 4b).

Safety

Vildagliptin 50 mg bid added to long-acting, intermediate-acting or pre-mixed insulin, with or without metformin was generally safe and well tolerated. The overall incidence of AEs was similar and comparable between the vildagliptin (46.2%) and placebo (43.6%) groups (Table 4). The most frequent AEs were of the primary system organ class, "infections and infestations" with a slightly lower incidence

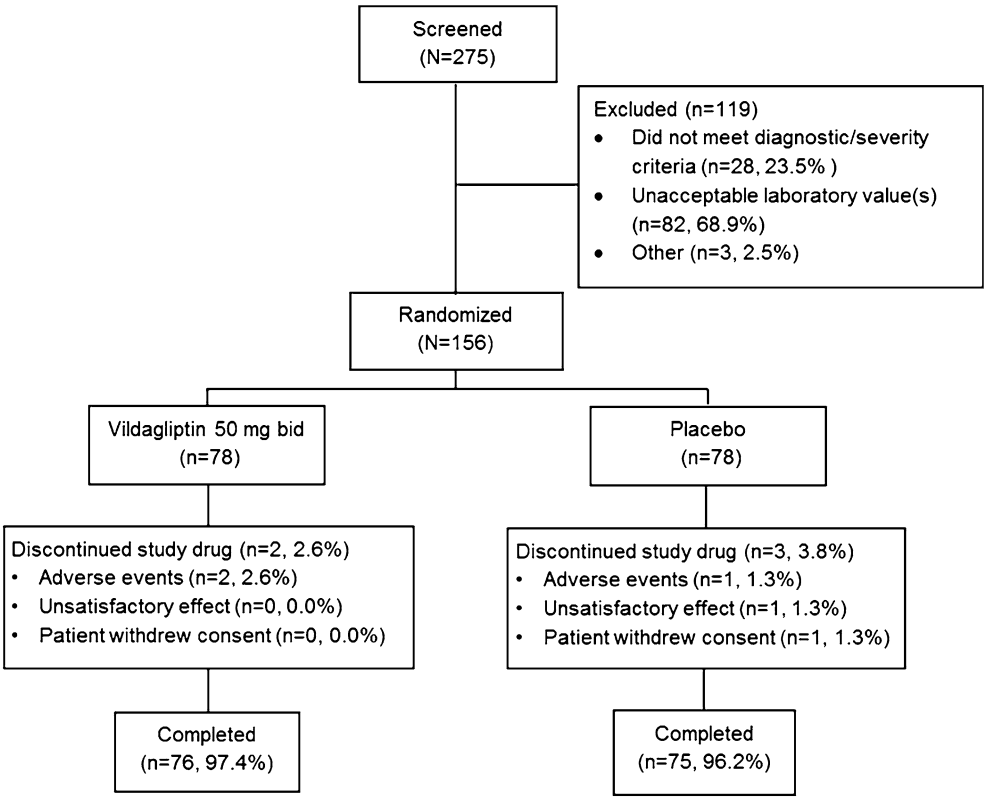

Fig. 2 Patient disposition

in the vildagliptin group compared with placebo group (15.4% vs. 19.2%, respectively). The incidence of AEs was higher in the vildagliptin group for metabolism and nutrition disorders (6.4% vs. 1.3%) compared with placebo. The overall incidence of AEs suspected to be drug related was higher with vildagliptin (23.1%) compared with placebo (12.8%), and this difference was mainly due to events of hunger and hyperhidrosis. No deaths were reported during the study. The incidence of SAEs was infrequent in either of the treatment groups (2.6% in vildagliptin vs. 1.3% in placebo). Body weight remained almost unaltered throughout the study in the vildagliptin group (1.09 kg). The proportion of patients experiencing hypoglycemic events was higher in the vildagliptin group (6.4%, 5 patients) than placebo (1.3%, 1 patient). Nine hypoglycemic events were reported in the vildagliptin group as opposed to 1 event in the placebo group (Table 5). Of the 9 events, 3 were triggered by strenuous exercise, 3 events by missed/delayed meals, and the remaining 3 events had no precipitating events specified. However, there was no severe hypoglycemia or any event reported, leading to study drug discontinuation. The overall incidence of hypoglycemic events was low and all hypoglycemic events were self-treatable using non-drug therapy.

DISCUSSION

This randomized, placebo-controlled, parallel-group study is the first report to demonstrate the efficacy and safety of vildagliptin 50 mg bid as add-on therapy in

Table 1 Patient demographics and baseline characteristics (randomized set)

Parameters	Vildagliptin 50 mg bid (*n* = 78)	Placebo (*n* = 78)	Total (*n* = 156)
Age (years)	58.5 ± 9.6	60.1 ± 9.1	59.3 ± 9.3
≥65 years, *n* (%)	27 (34.6)	28 (35.9)	55 (35.3)
Men, *n* (%)	55 (70.5)	56 (71.8)	111 (71.2)
Body weight (kg)	68.9 ± 11.6	70.4 ± 12.3	69.7 ± 11.9
BMI (kg/m^2)	25.3 ± 3.4	26.0 ± 3.1	25.7 ± 3.3
HbA1c (%)	8.1 ± 0.8	8.1 ± 0.9	8.1 ± 0.8
FPG (mmol/L)	9.0 ± 3.0	8.7 ± 2.0	8.9 ± 2.6
≥8.9 mmol/L, *n* (%)	32 (41.0)	32 (41.0)	64 (41.0)
Duration of T2DM (years)	12.8 ± 9.0	12.9 ± 8.1	12.9 ± 8.6
eGFR (MDRD), mL/min/1.73 m^2, *n* (%)			
Normal, >80	65 (83.3)	59 (75.6)	124 (79.5)
Mild, ≥50 to ≤80	12 (15.4)	18 (23.1)	30 (19.2)
Moderate, ≥30 to <50	1 (1.3)	1 (1.3)	2 (1.3)
Background therapy			
Insulin dose (unit/kg/day)	0.3 ± 0.17	0.3 ± 0.20	0.3 ± 0.18
Insulin with concomitant metformin, *n* (%)	34 (43.6)	34 (43.6)	68 (43.6)
Long- or Intermediate-acting, *n* (%)	21 (26.9)	20 (25.6)	41 (26.3)
Pre-mixed, *n* (%)	13 (16.7)	14 (17.9)	27 (17.3)
Insulin without concomitant metformin, *n* (%)	44 (56.4)	44 (56.4)	88 (56.4)
Long- or Intermediate-acting, *n* (%)	25 (32.1)	25 (32.1)	50 (32.1)
Pre-mixed, *n* (%)	19 (24.4)	19 (24.4)	38 (24.4)
Metformin (*n*)	34	34	68
Metformin total daily dose (mg/day)	1022.1 ± 497.6	1073.5 ± 446.1	1047.8 ± 469.7
≤750 mg, *n* (%)	17 (21.8)	11 (14.1)	28 (17.9)
>750 mg, *n* (%)	17 (21.8)	23 (29.5)	40 (25.6)

Data are expressed as mean ± SD, unless specified otherwise

bid twice daily, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *MDRD* modification of diet in renal disease, *SD* standard deviation, *T2DM* type 2 diabetes mellitus

Japanese patients inadequately controlled on insulin, with or without concomitant metformin. In this study, vildagliptin treatment was well tolerated with a safety profile similar to placebo group and the results were consistent with earlier studies [13–15]. Vildagliptin 50 mg bid treatment demonstrated a clinically and statistically

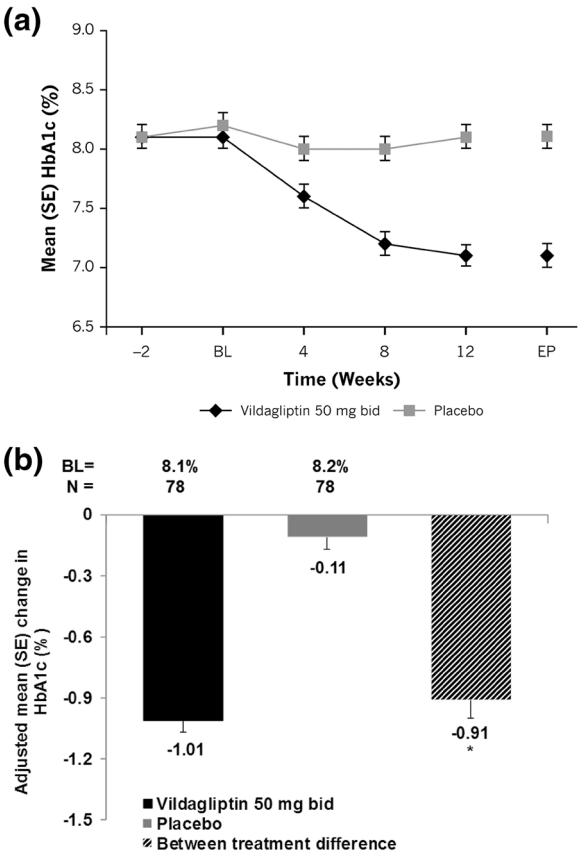

Fig. 3 **a** Mean HbA1c (%) by treatment and visit. Unadjusted means and standard errors (*vertical bars*) are presented. Study endpoint is defined as the final available post-randomization assessment obtained at any visit (scheduled or unscheduled), prior to the start of major changes in insulin background therapy, up to the final scheduled visit including week 12. *bid* twice daily, *BL* baseline, *EP* endpoint, *HbA1c* glycated hemoglobin. **b** Change in HbA1c (%) from baseline to study endpoint. $^{*}p < 0.001$. Study endpoint is defined as the final available post-randomization assessment obtained at any visit (scheduled or unscheduled), prior to the start of major changes in insulin background therapy, up to the final scheduled visit including week 12. *bid* twice daily, *BL* baseline, *HbA1c* glycated hemoglobin, *SE* standard error

significant ($p < 0.001$) reduction in HbA1c, with a between-treatment difference of −0.91% after 12 weeks. Vildagliptin-mediated change in HbA1c was similar in patient subgroups treated with or without concomitant metformin. The efficacy results from this study are consistent with findings from previous trials conducted in Caucasian and Asian populations [13–15]. Vildagliptin treatment also resulted in significant reductions in FPG levels when compared with placebo, with a between-treatment difference of −1.2 mmol/L ($p < 0.001$) which is comparable with previous findings from a 24-week clinical trial (a reduction of −0.8 mmol/L in mean FPG from a baseline of 9.3 mmol/L) [13]. Within subgroups based on insulin type as well as metformin use, vildagliptin demonstrated significantly marked reductions in HbA1c from baseline to endpoint, compared with placebo.

Similar and consistent differences in HbA1c values were observed in all responder rate categories. Half the patients in vildagliptin group achieved an HbA1c target <7%. Differences between treatment with vildagliptin and placebo were statistically significant for all responder rate categories.

Vildagliptin was well tolerated with overall incidence rate of AEs similar to that of placebo (46.2%, vildagliptin vs. 43.6%, placebo). The incidence of hyperhidrosis, hunger, tremor, and hypoglycemia was more common in the vildagliptin group than in the placebo group. The percentage of patients discontinued due to AEs was low and comparable between treatment groups. There were no patients with treatment-emergent hepatic enzyme elevation or deaths reported in the study. The overall incidence of hypoglycemic events was low in both the groups, but was higher in the vildagliptin-treated patients (6.4%, HbA1c ~7%) compared with placebo-treated patients (1.3%, HbA1c ~8%). None of the patients reported any severe hypoglycemia that required assistance of another person. Similar findings about a very low proportion of patients experiencing hypoglycemic events with vildagliptin treatment were reported in previous studies [13–15]. Efficacy and safety

Table 2 HbA1c (%) responder rates (FAS)

Responder criteria	Vildagliptin 50 mg bid (n = 78)	Placebo (n = 78)
N′[a]	78 (100)	78 (100)
Responder criterion		
At least one criterion met	67 (85.9)*	21 (26.9)*
HbA1c ≤6.5%[b]	23/77 (29.9)*	2/78 (2.6)*
HbA1c <7.0%[b]	38/76 (50.0)*	3/77 (3.9)*
HbA1c <7.0% in patients with baseline HbA1c ≤8.0%[c]	33/42 (78.6)*	3/37 (8.1)*
HbA1c reduction ≥1.0%[a]	38 (48.7)*	5 (6.4)*
HbA1c reduction ≥0.5%[a]	62 (79.5)*	20 (25.6)*

Chi-square test for vildagliptin 50 mg bid vs. placebo
bid twice daily, *HbA1c* glycated hemoglobin, *FAS* full analysis set
* $p < 0.001$
[a] Number (percentage) of patients with both baseline and endpoint HbA1c measurements, which were used as the denominator unless, specified otherwise
[b] Denominator includes only patients with baseline HbA1c ≥7% (>6.5%) and endpoint HbA1c measurement
[c] Denominator includes only patients with 7% ≤baseline HbA1c ≤8% and endpoint HbA1c measurement

Table 3 Mean changes in HbA1c (%) from baseline to endpoint by subgroups

Treatment	*n*	Baseline mean (SE)	Mean change (SE)	Range
With metformin				
Vildagliptin 50 mg bid	34	8.2 (0.2)	−1.1 (0.1)	(−2.2 to −0.1)
Placebo	34	8.3 (0.2)	−0.1 (0.1)	(−1.1 to 1.2)
Without metformin				
Vildagliptin 50 mg bid	44	8.0 (0.1)	−0.9 (0.1)	(−2.4 to 0.7)
Placebo	44	8.0 (0.1)	−0.1 (0.1)	(−1.2 to 2.0)
Insulin type: long-acting or intermediate-acting				
Vildagliptin 50 mg bid	46	8.0 (0.1)	−0.9 (0.1)	(−2.2 to 0.7)
Placebo	45	8.3 (0.1)	−0.0 (0.1)	(−1.2 to 2.0)
Insulin type: pre-mixed				
Vildagliptin 50 mg bid	32	8.2 (0.2)	−1.2 (0.1)	(−2.4 to −0.3)
Placebo	33	8.0 (0.2)	−0.2 (0.1)	(−1.1 to 1.0)

Baseline is the measurement obtained on day 1 or the sample obtained on an earlier visit (scheduled or unscheduled) which was closest to day 1, if day 1 measurement is missing. Study endpoint is defined as the final available post-randomization assessment obtained at any visit (scheduled or unscheduled), prior to the start of major changes in insulin background therapy, up to the final scheduled visit including week 12
bid twice daily, *HbA1c* glycated hemoglobin, *SE* standard error

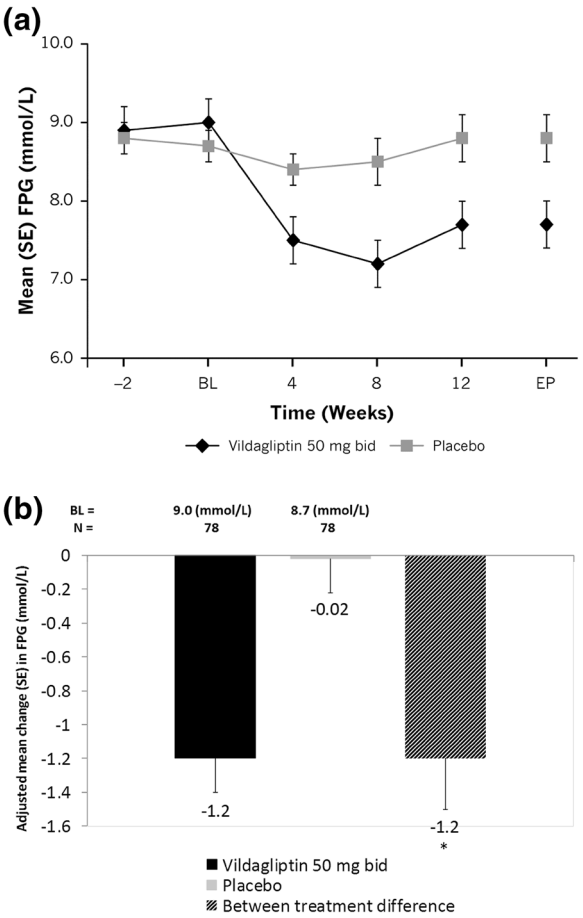

Fig. 4 **a** Mean FPG (mmol/L) by treatment and visit. Unadjusted means and standard errors (*vertical bars*) are presented. *bid* twice daily, *BL* baseline, *EP* endpoint, *FPG* fasting plasma glucose. **b** Change in FPG (mmol/L) from baseline to endpoint by treatment. $^{*}p < 0.001$. Baseline is measurement obtained on day 1, or the sample obtained on an earlier visit (scheduled or unscheduled) which was closest to day 1, if day 1 measurement is missing. Study endpoint is defined as the final available post-randomization assessment obtained at any visit (scheduled or unscheduled), prior to the start of major changes in insulin background therapy, up to the final scheduled visit including week 12. *bid* twice daily, *BL* baseline, *FPG* fasting plasma glucose, *SE* standard error

findings observed from this study are in line with data obtained from other gliptins including alogliptin, saxagliptin, and linagliptin as add-on to insulin in terms of effective HbA1c reduction and similar incidence rates of AEs [16–18].

Table 4 Number (%) of patients who reported common AEs by preferred term (safety set)

Preferred term, n (%)	Vildagliptin 50 mg bid ($n = 78$)	Placebo ($n = 78$)
Any preferred term	36 (46.2)	34 (43.6)
Nasopharyngitis	10 (12.8)	11 (14.1)
Hyperhidrosis	8 (10.3)	2 (2.6)
Hunger	7 (9.0)	3 (3.8)
Tremor	7 (9.0)	4 (5.1)
Asthenia	6 (7.7)	6 (7.7)
Hypoglycemia	5 (6.4)	1 (1.3)
Blood glucose decreased	2 (2.6)	2 (2.6)
Constipation	2 (2.6)	1 (1.3)
Dizziness	2 (2.6)	3 (3.8)
Gastroenteritis	2 (2.6)	0
Palpitations	2 (2.6)	1 (1.3)
Vision blurred	2 (2.6)	2 (2.6)
Abdominal distension	1 (1.3)	2 (2.6)
Cold sweat	0	2 (2.6)
Miliaria	0	2 (2.6)
Non-cardiac chest pain	0	2 (2.6)
Pharyngitis	0	2 (2.6)

A patient with multiple occurrences of an AE under one treatment was counted only once in the AE category
AE adverse event, *bid* twice daily

Insulin therapy is generally associated with increased risk of hypoglycemia, which often is a barrier in achieving good glycemic control. Prolonged use of insulin is associated with IAH, which could also increase the risk of hypoglycemia and complications associated with it [10, 11]. Furthermore, intensive glucose control resulted in severe hypoglycemia requiring assistance in 0.4–1.5% as reported in ADVANCE (ClinicalTrials.gov Identifier, NCT00145925) and ACCORD trials (ClinicalTrials.gov Identifier, NCT00000620) [19, 20].

Table 5 Number of patients who experienced hypoglycemic events by event profile and treatment (safety set)

	Vildagliptin 50 mg bid ($n = 78$)	Placebo ($n = 78$)
Number (%) of patients with at least one hypoglycemic event	5 (6.4)	1 (1.3)
Number of patients with		
One hypoglycemic event	3 (3.8)	1 (1.3)
Two hypoglycemic events	1 (1.3)	0
>2 hypoglycemic events	1 (1.3)	0
Total number of hypoglycemic events	9	1
Severity grade		
Grade 1[a]	9 (100)	1 (100)
Grade 2[b]	0	0
Suspected grade 2[c]	0	0

Data are expressed as *n* (%), unless specified otherwise
bid twice daily
Hypoglycemic events were defined as: [a] Grade 1: symptoms suggestive of hypoglycemia, where the patient was able to initiate self-treatment and plasma glucose measurement was <56 mg/dL
[b] Grade 2: symptoms suggestive of hypoglycemia, where the patient was unable to initiate self-treatment and plasma glucose measurement was <56 mg/dL
[c] Suspected grade 2: symptoms suggestive of hypoglycemia, where the patient was unable to initiate self-treatment and no plasma glucose measurement was available

In the present study, addition of vildagliptin significantly reduced HbA1c by 1.0% in patients treated with a stable dose of insulin. In addition, there were no occurrences of any severe hypoglycemic events, suggesting that a combination therapy of insulin and vildagliptin might be effective in achieving glycemic control without additional risk of hypoglycemia.

The use of combination therapy with insulin and incretins, including DPP-4 inhibitors such as vildagliptin could be beneficial in patients with T2DM inadequately controlled on insulin due to their complementary mechanisms of action [21].

CONCLUSIONS

Treatment with vildagliptin 50 mg bid as add-on to insulin, with or without metformin therapy resulted in a statistically significant reduction in HbA1c in Japanese patients with T2DM. Despite significant improvement in glycemic control, few patients experienced hypoglycemic events with vildagliptin. Importantly, no patient experienced severe hypoglycemia requiring assistance of another person. The addition of vildagliptin could be an effective treatment option in Japanese patients inadequately controlled on insulin regardless of concomitant metformin therapy.

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