

Efficacy and Safety of a Single-Pill Combination of Vildagliptin and Metformin in Japanese Patients with Type 2 Diabetes Mellitus: A Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

Introduction: The use of dipeptidyl peptidase-4 inhibitors in combination with metformin is increasing in Japanese patients with type 2 diabetes mellitus (T2DM), but no single-pill combination (SPC) is currently available in Japan. The objective of this study was to assess the efficacy and safety of vildagliptin/metformin SPC in Japanese patients with T2DM inadequately controlled with vildagliptin monotherapy.

Trial registration: ClinicalTrials.gov, #NCT01811485.

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Methods: This was a 14-week, randomized, double-blind, parallel-group, placebo-controlled trial. 171 patients with T2DM inadequately controlled [HbA1c (glycosylated hemoglobin) 7.0–10.0%] with vildagliptin 50 mg twice daily (bid) were randomized (2:1) to receive either a vildagliptin/metformin SPC ($n = 115$) or matching vildagliptin/placebo SPC ($n = 56$).

Results: Baseline demographics and background characteristics were generally comparable between the treatment groups. The change in HbA1c [mean \pm standard error (SE)] was $-0.8 \pm 0.1\%$ in the vildagliptin/metformin SPC (baseline HbA1c, $7.9 \pm 0.1\%$) group and $0.1 \pm 0.1\%$ in the vildagliptin/placebo SPC (baseline HbA1c, $8.0 \pm 0.1\%$) group, with a between-treatment difference of $-1.0 \pm 0.1\%$ ($P < 0.001$) in favor of the vildagliptin/metformin SPC group. The proportion of patients achieving target HbA1c $< 7.0\%$ was significantly higher with vildagliptin/metformin SPC compared with vildagliptin/placebo SPC (45.8% vs. 13.5%, $P < 0.001$). The overall incidences of adverse events (AEs) were 43.5% in the vildagliptin/metformin SPC and 67.9% in the

vildagliptin/placebo SPC group. The incidences of serious AEs were low in both the treatment groups (0.9% vs. 3.6%, respectively). Body weight remained constant throughout the study in both the treatment groups. There were no deaths or hypoglycemic events during the study.

Conclusions: Switching Japanese patients with T2DM requiring treatment intensification, from vildagliptin monotherapy to a vildagliptin/metformin SPC (50/250 or 50/500 mg) was efficacious and safe, eliciting significant reduction in HbA1c without increased risk of hypoglycemia and weight gain.

Keywords: Dipeptidyl peptidase-4 inhibitor; Metformin; Single-pill combination; Type 2 diabetes mellitus; Vildagliptin

INTRODUCTION

The worldwide prevalence of type 2 diabetes mellitus (T2DM) continues to rise dramatically, with Asian countries contributing more than half of the world's diabetic population [1, 2]. Currently, 7.2 million individuals aged between 20 and 79 years are affected by T2DM in Japan [1]. T2DM clinical practice guidelines by the American Diabetes Association [3] and International Diabetes Federation [4] suggest starting treatment with metformin unless contraindicated, followed by the addition of other oral antidiabetic drugs (OADs) if patients fail to achieve glycosylated hemoglobin (HbA1c) goal <7.0%. The Japan Diabetes Society (JDS) suggests starting pharmacotherapy with any OAD depending on the physiological status of the patient after diet and exercise failure [5]. Most of the

Japanese patients with T2DM have a tendency to a low body mass index (BMI); and as insulin secretion deficiency plays a predominant role in disease pathology [6], insulin secretagogues are the preferred first-line treatment option in Japan. Recently, Japanese patients with T2DM are being increasingly treated with dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., vildagliptin) [7], which increase insulin secretion from β -cells in a glucose-dependent manner [8]. Moreover, the progressive nature of the disease warrants treatment intensification with other antidiabetic agents having complementary mechanism of action to maintain glycemic control over long term [5].

The mechanistic synergy between vildagliptin and metformin [8, 9], and the efficacy and safety of vildagliptin added to metformin in Japanese patients with T2DM inadequately controlled with metformin monotherapy has already been demonstrated [10]. However, the benefit of switching patients, who are treated with vildagliptin and require additional treatment, to vildagliptin and metformin has not been established. So far, no DPP-4 inhibitor/metformin single-pill combination (SPC) is available in Japan. Such a SPC has the additional benefit of a reduced pill burden, and potentially better compliance [11]. Moreover, the efficacy of low-dose metformin [250 mg twice daily (bid)] has not been studied previously in a randomized trial setting in Japanese patients with T2DM. Accordingly, the current study was aimed to assess the efficacy and safety of vildagliptin/metformin SPC at doses of 50/250 and 50/500 mg in Japanese patients with T2DM inadequately controlled with diet, exercise and vildagliptin monotherapy.

MATERIALS AND METHODS

Study Design

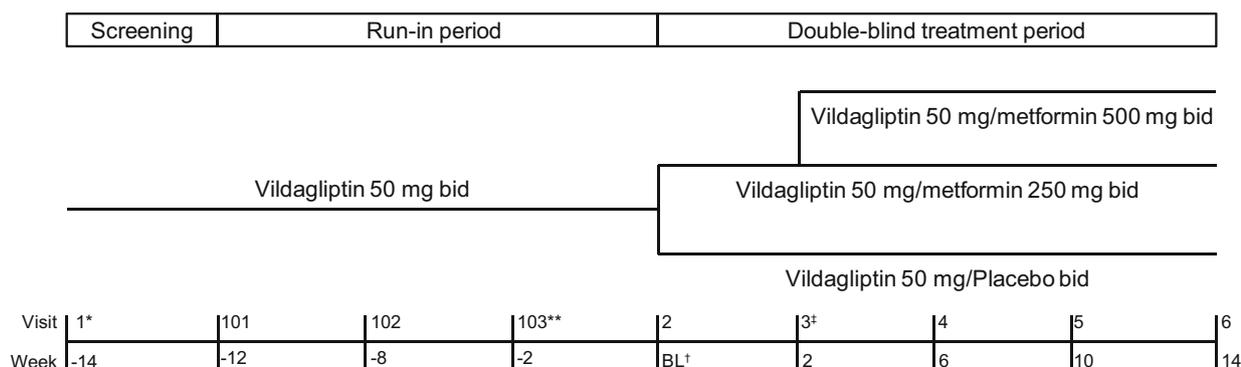
This 14-week, multicenter, double-blind, parallel-group, placebo-controlled, randomized study was conducted across 30 centers in Japan from May 2013 to February 2014. Patients with T2DM inadequately controlled (HbA1c 7.0–10.0%) with diet, exercise and vildagliptin monotherapy were eligible for inclusion. Following the screening visit (visit 1), eligible patients on vildagliptin 50 mg bid monotherapy for at least 10 weeks proceeded directly to randomization (baseline, visit 2). Whereas patients taking other OADs were switched to vildagliptin 50 mg bid and were asked to complete a 12-week run-in period (visit 101) before randomization (Fig. 1).

Eligible patients were randomized (2:1) to receive either vildagliptin/metformin SPC (hereafter called the vilda/met group) or vildagliptin/placebo SPC (hereafter called the vilda/placebo group). In the vilda/met treatment group, patients were randomized (1:1) to receive either vilda/met 50/250 or

50/500 mg bid (Fig. 1). In the vilda/met group, all patients started double-blind treatment with vilda/met 50/250 mg bid, and patients randomized to the subgroup vilda/met 50/500 mg bid were up-titrated after 2 weeks. Efficacy and safety were assessed at baseline and at weeks 2, 6, 10, and 14. No rescue medication was allowed, and patients with unsatisfactory therapeutic effect [fasting plasma glucose (FPG) ≥ 15.0 mmol/L] were discontinued from the study.

Study Population

The study included patients with T2DM aged ≥ 20 to < 75 years, BMI ≥ 20 to ≤ 35 kg/m², and who were inadequately controlled (HbA1c $\geq 7.0\%$ to $\leq 10.0\%$) by diet and vildagliptin 50 mg bid monotherapy. The key exclusion criteria were: FPG ≥ 15.0 mmol/L; history of type 1 diabetes, acute metabolic conditions such as ketoacidosis, lactic acidosis; patients with congestive heart failure (New York Heart Association Class III or IV); myocardial infarction, or coronary artery bypass surgery in the past 6 months, unstable angina in the past



*Patients who met all criteria and on stable dose of vildagliptin 50 mg bid for at least 10 weeks proceeded directly to visit 2 (randomization). Patients at visit 1 who met all the criteria but were taking antidiabetic drugs other than vildagliptin entered the 12-week run-in period and proceeded to visit 101. **Eligibility assessment for patients who entered the run-in period. [†]Baseline, the day of randomization. [‡]Up titration of patients randomized to vildagliptin/metformin 50/500 mg bid from vildagliptin/metformin 50/250 mg bid. Bid, twice daily

Fig. 1 Study design

3 months; acute or chronic liver disease; or impaired renal function.

Study Endpoints and Assessments

Change in HbA1c from baseline to study end in all vilda/met groups was the primary efficacy endpoint. The secondary endpoints included: HbA1c change from baseline to study end in the subgroups of patients by metformin dose, percentage of patients achieving HbA1c target (<7.0%)/reduction of $\geq 0.5\%$ and change in FPG from baseline to study end. HbA1c values are reported in National Glycohemoglobin Standardization Program units (NGSP, %).

Safety assessments included collecting all adverse events (AEs), serious AEs (SAEs) data with their severity and suspected relationship to the study drug, regular assessments of hematology, biochemistry, vital signs and body weight. All the laboratory assessments were performed at a central laboratory (Mitsubishi Chemical Medience Corporation, Tokyo, Japan). Patients were asked to record hypoglycemic events in a study diary. Hypoglycemia was defined as symptoms suggestive of hypoglycemia, further confirmed by self-monitored blood glucose measurement of <3.1 mmol/L. The event was considered severe if the patient required assistance of another person or hospitalization.

Statistical Analysis

Assuming a dropout rate of 5%, 171 patients were to be randomized in a ratio of 2:1 (vilda/met 114; vilda/placebo: 57) to achieve the target sample size of 162. This sample size would ensure 90% power to detect a between-group difference of 0.6 absolute units in HbA1c at a one-sided significance level of 0.025 and a standard deviation of 1.1%. The sample size of

57 patients in each vilda/met subgroup would ensure 90% power with a one-sided significance level of 0.025 to detect a reduction of 0.5 absolute units in HbA1c from baseline at a standard deviation of 1.0%. Statistical analysis was performed using SAS 9.2 (SAS Institute Inc., Cary NC, USA).

All randomized patients who received at least one dose of the study drug and had at least one post-randomization efficacy parameter (HbA1c, FPG) assessment constituted the full analysis set (FAS). The primary and secondary efficacy analyses were based on FAS. The changes in HbA1c and FPG from baseline to study endpoint [final available assessment value at any visit up to the final visit (week 14)] reported as mean \pm SE were analyzed using the analysis of covariance model, with treatment as a classification variable and baseline value as a covariate. The last observation carried forward method was used for imputing missing data.

Chi-squared test was used to assess and compare the proportion of responders in the two groups. Safety data were summarized descriptively by treatment for the safety analysis set which included all the patients who received at least one dose of the study drug.

Ethics and Good Clinical Practice

The independent Ethics Committee/Institutional Review Board at each center reviewed and approved the study protocol. 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 1975, as revised in 2000 and 2008. Informed consent was obtained from all patients for being included in the study. The study is registered with ClinicalTrials.gov, identifier: NCT01811485.

RESULTS

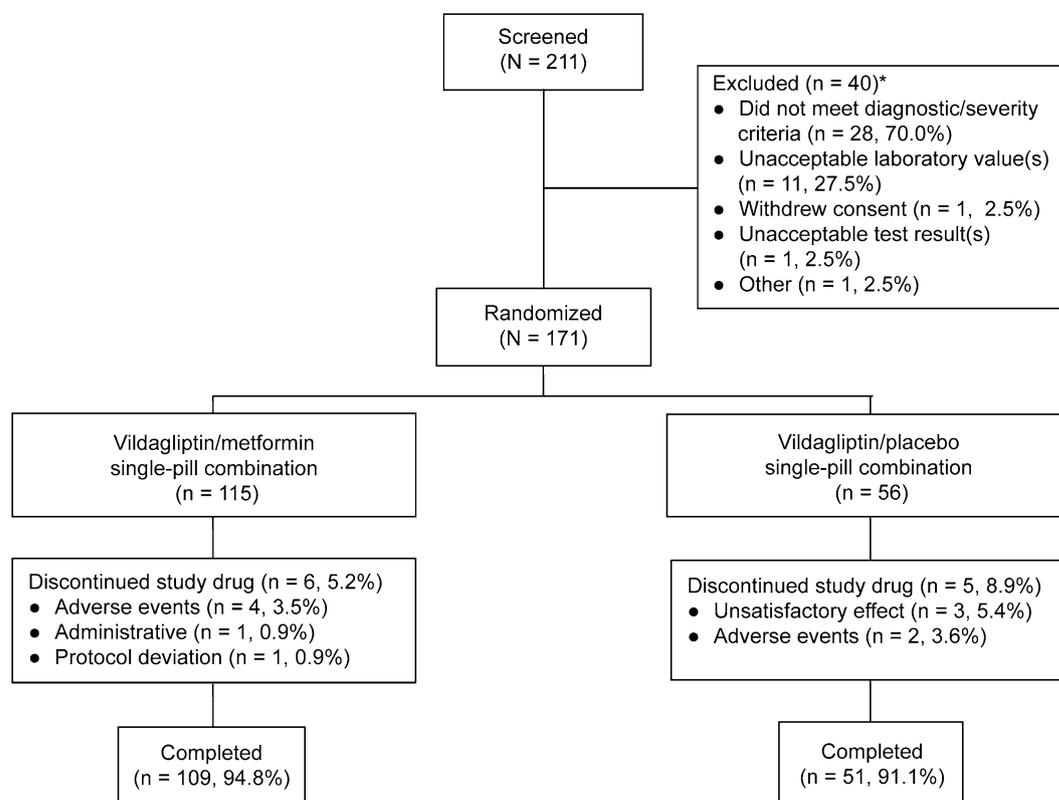
Patient Disposition and Baseline Characteristics

A total of 171 patients were randomized (vilda/met, $n = 115$; vilda/placebo, $n = 56$) of which 160 (93.6%) patients completed the study. The most common reasons for discontinuations were AEs in the vilda/met group (3.5%) and unsatisfactory therapeutic effectiveness in the vilda/placebo group (5.4%) (Fig. 2). Patient demographics and baseline characteristics were comparable between the two treatment groups (Table 1). The patients had an overall age (mean \pm SD) 57.0 ± 10.5 years, BMI 25.8 ± 3.4 kg/m², FPG 8.8 ± 1.8 mmol/L and T2DM duration 7.0 ± 6.6 years. Baseline HbA1c

was similar between the two groups (Table 1). Almost 80% of the patients received concomitant medications at baseline. The most frequently used concomitant medications were lipid-lowering drugs (42.1%) and antihypertensives (39.8%).

Efficacy

The mean HbA1c change over 14 weeks is shown in Fig. 3a. After 2 weeks, the mean HbA1c levels were lower in all vilda/met groups compared with the vilda/placebo group. At week 14, a statistically significant between-treatment difference in (mean \pm SE) HbA1c of $-1.0 \pm 0.1\%$ ($P < 0.001$), in favor of the vilda/met group was observed (both doses combined) (Table 2). Statistically significant



*More than one reason for discontinuation during the screening period

Fig. 2 Flow diagram depicting patient disposition

Table 1 Patient demographics and baseline characteristics (randomized set)

Parameters	Vildagliptin/metformin SPC <i>n</i> = 115	Vildagliptin/placebo SPC <i>n</i> = 56	Total <i>N</i> = 171
Age (years)	57.5 ± 10.9	56.2 ± 9.8	57.0 ± 10.5
≥65 years [<i>n</i> (%)]	35 (30.4)	11 (19.6)	46 (26.9)
Men [<i>n</i> (%)]	82 (71.3)	40 (71.4)	122 (71.3)
Body weight (kg)	69.6 ± 12.5	72.0 ± 11.3	70.4 ± 12.1
BMI (kg/m ²)	25.5 ± 3.4	26.5 ± 3.3	25.8 ± 3.4
HbA1c (%)	7.9 ± 0.8	8.0 ± 0.8	7.9 ± 0.8
≤8% [<i>n</i> (%)]	77 (67.0)	37 (66.1)	114 (66.7)
>8 to ≤9% [<i>n</i> (%)]	23 (20.0)	11 (19.6)	34 (19.9)
>9% [<i>n</i> (%)]	15 (13.0)	8 (14.3)	23 (13.5)
FPG (mmol/L)	8.8 ± 1.7	8.9 ± 2.0	8.8 ± 1.8
≥8.9 mmol/L [<i>n</i> (%)]	49 (42.6)	23 (41.1)	72 (42.1)
Duration of T2DM (years)	7.0 ± 6.5	7.1 ± 6.9	7.0 ± 6.6
eGFR (MDRD) [mL/min/1.73 m ² , <i>n</i> (%)]			
Normal >80	106 (92.2)	53 (94.6)	159 (93.0)
Mild ≥50 to ≤80	9 (7.8)	3 (5.4)	12 (7.0)

Data are expressed as mean ± standard deviation, unless specified otherwise

BMI body mass index, *eGFR* estimated glomerular filtration rate, *FPG* fasting plasma glucose, *HbA1c* glycosylated hemoglobin, *MDRD* modification of diet in renal disease, *SPC* single-pill combination, *T2DM* type 2 diabetes mellitus

reductions ($P < 0.001$) in HbA1c from baseline were also observed for the vilda/met 50/250 mg bid and vilda/met 50/500 mg bid subgroups (Fig. 3b). The placebo-corrected difference for the change in HbA1c was -0.8% [95% confidence interval (CI) -1.0% , -0.6%] and -1.2% (95% CI -1.4% , -1.0%) in the vilda/met 50/250 and 50/500 mg subgroups, respectively.

The proportion of patients who achieved either an HbA1c of $<7.0\%$ or an HbA1c drop of $\geq 0.5\%$ at week 14 was significantly higher ($P < 0.001$) for the vilda/met group compared

with the vilda/placebo group (Table 3). 32.1% and 59.3% of patients in the vilda/met 50/250 mg and vilda/met 50/500 mg subgroups, respectively, achieved HbA1c $<7.0\%$. Absolute mean changes in HbA1c from baseline to endpoint were greater in the vilda/met group for the various subgroups of patients defined by age, gender, baseline BMI, baseline HbA1c and baseline FPG. In the vilda/met group, mean reductions in HbA1c were numerically higher for patients with higher baseline HbA1c values.

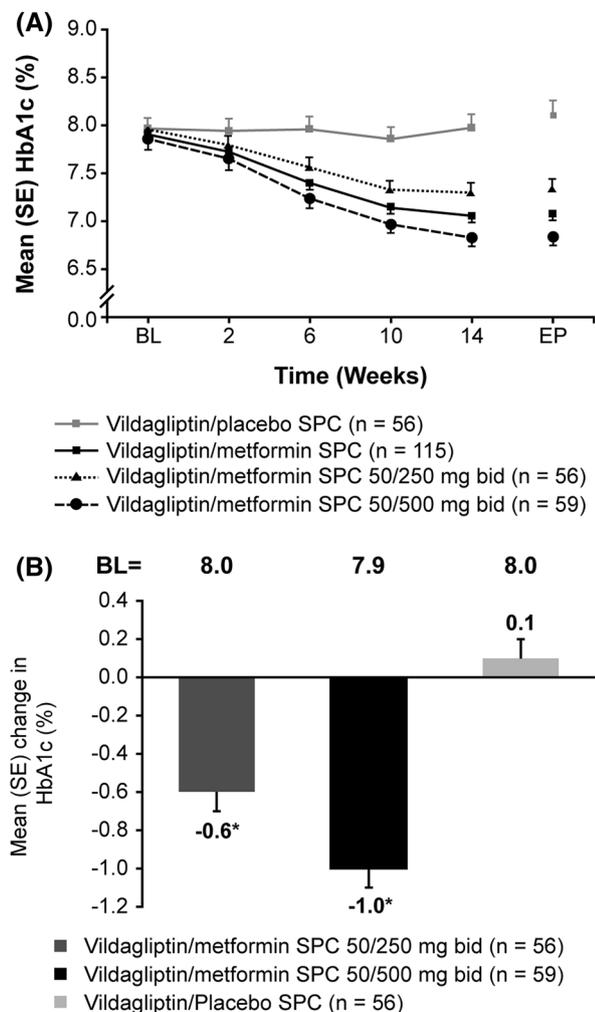


Fig. 3 a Mean glycosylated hemoglobin (HbA1c %) by treatment and visit (full analysis set). b Adjusted mean change in HbA1c from baseline to endpoint (full analysis set). * $P < 0.001$. BL baseline, EP endpoint, SE standard error, SPC single-pill combination

The mean FPG over 14 weeks is shown in Fig. 4. The mean change in FPG from baseline to endpoint was greater for patients receiving vilda/met (-0.7 ± 0.2 mmol/L) compared with those receiving vilda/placebo (0.9 ± 0.2 mmol/L), with a statistically significant between-treatment difference of -1.6 ± 0.3 mmol/L ($P < 0.001$). The placebo-corrected reductions in FPG from baseline to endpoint were -1.5 ± 0.3 (95% CI $-2.1, -0.8$) and -1.8 ± 0.3

(95% CI $-2.4, -1.2$) mmol/L in the vilda/met 50/250 mg and 50/500 mg subgroups, respectively.

Safety

The overall safety profile is summarized in Table 4. The incidence of AEs was lower in the vilda/met group (43.5%) compared with the vilda/placebo group (67.9%). The incidences of AEs were similar between the two vilda/met subgroups (44.6% and 42.4% for vilda/met 50/250 and 50/500, respectively). Most of the AEs were mild or moderate in severity. The most frequently reported AEs by system organ class (SOC) were ‘infections and infestations’ (16.5% vs. 25.0%) and gastrointestinal disorders (16.5% vs. 14.3%) in the vilda/met and vilda/placebo groups, respectively. Nasopharyngitis was the most frequently reported AE in both the groups (9.6% for vilda/met vs. 17.9% for vilda/placebo). Discontinuations due to AEs were low in both the groups (3.5% and 3.6% in the vilda/met and vilda/placebo groups, respectively).

Three patients reported SAEs: syncope and convulsion in one patient in the vilda/met 50/500 mg subgroup; epiglottitis and gastric cancer in one patient each in the vilda/placebo group. There were no deaths in the study. There were no hypoglycemic events reported in either group. Asymptomatic mild elevations in pancreatic enzymes were reported in six patients. However, none of the events were considered as AEs of acute pancreatitis by the investigator and all patients completed the study. Body weight remained constant in both the groups after 14 weeks of treatment: $+0.1 \pm 0.1$ kg (baseline, 69.5 ± 12.6 kg) in the vilda/met group and $+0.2 \pm 0.2$ kg (72.1 ± 11.3 kg) in the vilda/placebo group.

Table 2 ANCOVA results for change in HbA1c (%) from baseline to endpoint (full analysis set)

Treatment	N	Baseline mean (SE)	Adjusted mean change (SE)	Difference in adjusted mean change		
				Mean (SE)	95% CI	P value
Vildagliptin/metformin SPC (both doses combined)	115	7.9 (0.1)	−0.8 (0.1)	−1.0 (0.1)	−1.2, −0.8	<0.001
Vildagliptin/placebo SPC	56	8.0 (0.1)	0.1 (0.1)			

ANCOVA analysis of covariance, CI confidence interval, HbA1c glycosylated hemoglobin, SE standard error, SPC single-pill combination

Table 3 HbA1c (%) responder rates (full analysis set)

Responder criteria	Vildagliptin/metformin SPC n = 115	Vildagliptin/placebo SPC n = 56
HbA1c <7.0% [n/N** (%)]	49/107 (45.8)*	7/52 (13.5)
Reduction of HbA1c ≥0.5% [n/N† (%)]	85/115 (73.9)*	9/56 (16.1)

HbA1c glycosylated hemoglobin, SPC single-pill combination

* P < 0.001

** Denominator includes patients with baseline HbA1c ≥ 7.0% and endpoint HbA1c measurement

† Denominator includes patients with both baseline and endpoint HbA1c measurements

DISCUSSION

This is the first randomized clinical study of an SPC of DPP-4 inhibitor and metformin in Japanese patients with T2DM. The goal of the study was to assess the efficacy and safety of vildagliptin/metformin SPC over 14 weeks in Japanese patients with T2DM inadequately controlled by diet, exercise, and vildagliptin monotherapy.

The present study showed that vildagliptin/metformin SPC is efficacious, safe and well-tolerated in Japanese patients with T2DM. The HbA1c reduction observed with the SPC (−0.8%; baseline: 7.9%) in patients inadequately controlled by vildagliptin monotherapy was similar to the earlier reported drop in HbA1c with free-dose combination of vildagliptin/metformin in

patients inadequately controlled by metformin monotherapy [10]. Almost half of patients treated with vilda/met SPC achieved the JDS recommended glycemic target of HbA1c <7.0% [5] with three-fourths of patients demonstrating a clinically relevant drop in HbA1c (≥0.5%) [12], thus, highlighting the benefit of switching patients who are inadequately controlled with vildagliptin monotherapy to the vildagliptin/metformin SPC. The mean reduction in FPG levels was also significantly higher for the vilda/met group compared with the vilda/placebo group, which is consistent with the mechanism of action of metformin to decrease the overnight hepatic glucose production [13]. The data presented here are the first data to establish the clinical efficacy of metformin 250 mg bid in Japanese patients, as such closing an important gap. Even this low metformin dose resulted in

clinically relevant glycemic benefit with an HbA1c difference of 0.8% vs. vilda/placebo group.

The overall incidence of AEs was lower in the vilda/met group compared with the vilda/placebo group. This can be mostly attributed to a higher incidence of mild events of nasopharyngitis, all of which were considered unrelated to the study drug. This is

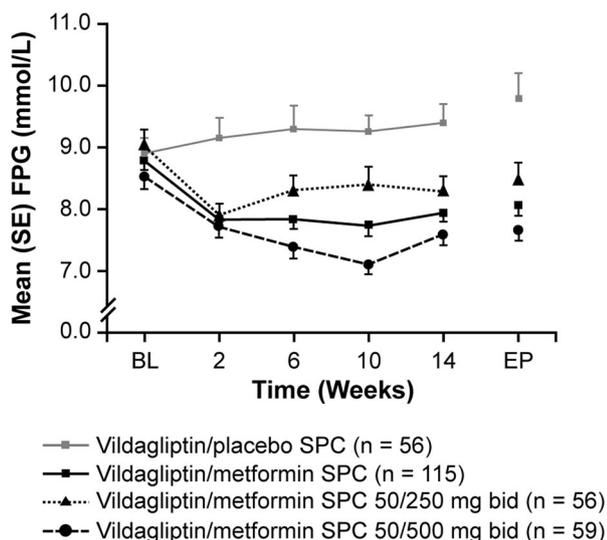


Fig. 4 Mean fasting plasma glucose (mmol/L) by treatment and visit (full analysis set). *BL* baseline, *EP* endpoint, *SPC* single-pill combination

likely a chance finding, given that the only treatment change in this patient was adding placebo treatment to already existing vildagliptin treatment. There were no hypoglycemic events reported in this study, despite the significant improvement in the glycemic control with the SPC, which is consistent with the earlier known safety profile of vildagliptin in Japanese patients with T2DM [14, 15] and a potential vildagliptin mediated protective effect against hypoglycemia through enhanced gastric inhibitory polypeptide [9]. There was no weight gain over 14 weeks of treatment in both the groups reconfirming the previously established weight neutrality effect of metformin [16]. Overall, the safety and tolerability of the vilda/met group were in line with the known safety profile of vildagliptin as a single agent or as a free combination with metformin [10, 14, 15].

Treatment with SPC of vildagliptin/metformin targets the multiple pathophysiological abnormalities of T2DM such as impaired insulin secretion, increased endogenous glucose production, and decreased utilization of glucose, in turn helping patients

Table 4 Overall summary of adverse events (safety set)

<i>n</i> (%)	Vildagliptin/ metformin SPC (<i>n</i> = 115)	Vildagliptin/ metformin SPC 50/250 mg (<i>n</i> = 56)	Vildagliptin/ metformin SPC 50/500 mg (<i>n</i> = 59)	Vildagliptin/ placebo SPC (<i>n</i> = 56)
Adverse events (AEs)	50 (43.5)	25 (44.6)	25 (42.4)	38 (67.9)
AEs related to the study drug	20 (17.4)	10 (17.9)	10 (16.9)	12 (21.4)
Serious AEs	1 (0.9)	0 (0.0)	1 (1.7)	2 (3.6)
Discontinuation due to AEs	4 (3.5)	1 (1.8)	3 (5.1)	2 (3.6)
Hypoglycemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AEs adverse events, *SPC* single-pill combination

to maintain good glycemic control. Metformin complements the mechanism of action of vildagliptin by raising absolute levels of glucagon like peptide-1 (GLP-1) [9]. Furthermore, SPC formulations have advantages such as reduced pill burden, improved convenience and adherence over free-dose combinations [17]. Results from a meta-analysis showed that SPC reduces the risk of non-compliance by 26% compared with the free-dose combination [11].

CONCLUSION

In conclusion, robust glucose-lowering efficacy along with good safety and tolerability makes the vildagliptin/metformin SPC an attractive treatment option for Japanese patients with T2DM who require additional treatment beyond vildagliptin monotherapy.

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Conflict of interest. Masato Odawara is the independent medical advisor for this study and has received consultancy fees from Novartis

Pharma K.K., Tokyo, Japan. Mika Yoshiki is an employee of Novartis Pharma K.K., Tokyo, Japan. Misako Sano is an employee of Novartis Pharma K.K., Tokyo, Japan. Izumi Hamada is an employee of Novartis Pharma K.K., Tokyo, Japan. Valentina Lukashevich is employed by and owns shares in Novartis. Wolfgang Kothny is employed by and owns shares in Novartis.

Compliance with ethics. The independent Ethics Committee/Institutional Review Board at each center reviewed and approved the study protocol. 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 1975, as revised in 2000 and 2008. Informed consent was obtained from all patients for being included in the study. The study is registered with ClinicalTrials.gov, identifier: NCT01811485.

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