Effectiveness and Safety of Vildagliptin Monotherapy or in Combination with Other Antihyperglycemic Agents in Patients with T2DM: A Real-world Observational Study in the Philippines

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Abstract

Introduction: There is an ever-increasing prevalence of type 2 diabetes mellitus (T2DM) in the Philippines. This observational study aimed to evaluate the effectiveness and safety of vildagliptin as monotherapy or combination therapy in patients with T2DM in a real-life setting from the Philippines.

Methods: This 24-week, non-interventional study enrolled adult T2DM patients, receiving vildagliptin either as monotherapy or dual/triple combination therapy. The primary endpoint was change in HbA1c from baseline to week 24. The secondary endpoints included proportion of patients achieving the glycemic goals HbA1c ≤6.5% and ≤7.0%, and safety assessment at week 24.

Results: Of the 385 patients enrolled, 267 (69.35%) completed the study. The mean±standard deviation age was 54.72±11.06 years, HbA1c, body mass index, and diabetes duration were 8.54±1.81%, 27.35±5.58 kg/m^2 and 3.04±4.88 years, respectively. Overall, treatment with vildagliptin resulted in HbA1c reduction of 2.02±1.68 (p<0.0001) from baseline to week 24. At week 24, 60.64% and 74.47% of the patients achieved the glycemic target of HbA1c ≤6.5% and ≤7.0% respectively. Seven serious adverse events (AEs) unrelated to the study drug were reported, most of which (24/28) were mild or moderate in severity; 85.71% of the AEs reported were not drug related. One hypoglycemic event (with vildagliptin/metformin single pill combination (SPC)) and one death (with vildagliptin/metformin free dose and SPC, due to severe pneumonia) were reported at week 12.

Discussion: This observational study showed that treatment with vildagliptin monotherapy or combination therapy for 24 weeks in patients with T2DM in the Philippines provided statistically significant reductions in HbA1c. Overall, vildagliptin (mono or dual/triple therapy) was well-tolerated and demonstrated a favorable safety profile with no new safety signal.

Conclusion: Treatment with vildagliptin as monotherapy or in combination with other antihyperglycemic agents resulted in good glycemic control and was well-tolerated in patients with T2DM in the Philippines, under real-world settings.

Keywords: type 2 diabetes mellitus, observational study, monotherapy, combination therapy

Introduction

Type 2 diabetes mellitus (T2DM), a chronic metabolic disease, is a global epidemic with an estimated prevalence of 425 million people in 2017 worldwide, which is likely to rise to 629 million by 2045.[1]

The increasing prevalence and incidence of T2DM has become an important public health challenge in third-world countries including the Philippines[2] that can be attributed to rapid westernization of diet and lifestyle.[3] T2DM was the sixth leading cause of death in the Philippines in 2014,[4] with an estimated prevalence of 6.9% which accounted for >50,000 deaths in 2015.[5,6] Evidence from the DiabCare 2008 survey of 770 patients with diabetes from the Philippines, reported that only 15% of patients with T2DM achieved the recommended glycemic target of HbA1c <7.0% reflecting poor glycemic control.[7] Inadequate glycemic control and sustained hyperglycemia are associated with an increased risk of developing micro- and macrovascular complications.[8] Metformin is the established first-line oral hypoglycemic agent for T2DM,[9] however, given the progressive nature of T2DM there is a need for additional antidiabetic agents with complementary mechanism of action to achieve glycemic targets.[10] Dipeptidyl peptidase-4 (DPP-4) inhibitors, such as vildagliptin increase the endogenous levels of active incretins, thereby stimulating insulin secretion in a glucose-dependent manner.[11] The glycemic efficacy, reduced risk of hypoglycemia, weight-neutral effect and a favorable benefit-risk profile of vildagliptin has made it an attractive treatment option for the management of patients with T2DM. The efficacy and tolerability of vildagliptin as monotherapy and in combination with other antihyperglycemic agents has been demonstrated in several clinical trials and real-world studies.[12,13]

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Despite evidence suggesting an ever-increasing prevalence of T2DM in the Philippines, there is a limited real-world data available on the effectiveness and tolerability of DPP-4 inhibitors in these patients.[14] The real-world evidence not only complements data generated from randomized clinical trials but also reflects on the day-to-day clinical practices and provides information on the clinical- and cost-effectiveness of a particular treatment in a representative patient population, thereby providing more robust information to healthcare providers and to patients.[15] The aim of this observational study was to assess the effectiveness and safety of vildagliptin as monotherapy or in combination with other antihyperglycemic agents in patients with T2DM from the Philippines under a real-world setting.

Methods

This was a 24-week, non-interventional, prospective, multi-center study in patients with T2DM in the Philippines, conducted between July 2014 and December 2015. Data were collected from at least two study visits: baseline at week 0 (Visit 1), at approximately week 12+4 weeks (optional Visit 2) and at approximately week 24+6 weeks (Visit 3). Men and women aged ≥18 years diagnosed with T2DM who were prescribed with any of the following treatment regimens in accordance with the approved local prescribing information were included in the study:

1. Vildagliptin as monotherapy
2. Vildagliptin in dual combination with metformin, sulfonylurea (SU), or thiazolidinedione (TZD)
3. Vildagliptin in triple combination with SU and metformin
4. Vildagliptin in combination with insulin
5. Vildagliptin plus metformin single pill combination (SPC) as initial therapy
6. Vildagliptin plus metformin SPC as a switch when metformin or vildagliptin alone has not provided adequate glycemic control
7. Vildagliptin plus metformin SPC as a switch for those taking vildagliptin and metformin as separate tablets
8. Vildagliptin plus metformin SPC in combination with SU
9. Vildagliptin plus metformin SPC as an add-on to insulin

Patients contraindicated for the use of vildagliptin, or patients with a history of acute metabolic diabetic complications such as ketoacidosis or hyperosmolar state (coma), or acute or chronic disease such as cardiac or respiratory failure, recent myocardial infarction, shock, or septicemia were excluded. Pregnant or lactating women, patients with alcoholism, diagnosis of type 1 diabetes or secondary diabetes, history of hepatic impairment, including those with pretreatment alanine transaminase or aspartate aminotransferase >2.5 x upper limit of normal, and patients enrolled in the GUARD study were also excluded.

Written informed consent forms were obtained from each patient prior to enrollment. The study design was approved by the local ethics committee and review board and was in accordance with the Declaration of Helsinki.

The primary endpoints were the change in HbA1c from baseline to week 24 following treatment with one of the nine treatment arms mentioned above; and the change in HbA1c from baseline to week 24 in a pooled analysis following treatment with vildagliptin as monotherapy, dual therapy (with metformin (free dose and SPC) or SU/TZD/insulin) or triple therapy (with metformin and SU/insulin). Secondary endpoints included the proportion of patients achieving the glycemic targets of HbA1c ≤6.5% and ≤7.0%, at week 24 in each of the nine treatment arms and in the pooled analysis following treatment with vildagliptin as monotherapy or combination therapy (dual or triple-therapy). Safety assessments included monitoring and recording of adverse events (AEs), serious AEs (SAEs) and hypoglycemic events during the 24-week treatment period.

Assuming a dropout rate of 25%, a sample size of 162 patients in total would provide 80% power to detect a reduction of 1.1% in HbA1c with a standard deviation (SD) of 1.3% and a significance level of 0.05. The full analysis set population (all patients who provided informed consent) was used for the analysis of baseline demographics. The intent-to-treat (ITT) population (patients who had at least one valid post baseline measurement) was used for the analysis of efficacy endpoints and the safety analysis set (patients who received at least one dose of study drug) was used for the safety analysis. The mean change in HbA1c from baseline to final visit was evaluated using a two-sided paired t-test, and chi-square test was used to analyze the proportion of patients achieving glycemic targets. For all the study data, descriptive statistical analysis was performed. The last observation carried forward method was adopted to establish the missing efficacy values and no imputation techniques were applied.

Results

Of the 385 patients enrolled, 267 (69.35%) completed the study. Overall, 118 (30.65%) patients discontinued, primarily due to loss to follow-up (25.45%), followed by administrative problems (3.90%), protocol deviation (0.52%), and death due to pneumonia (0.26%). The mean±SD age of the study population was 54.72±11.06 years, with a majority of patients <60 years of age (64.42%) and women (54.81%). The mean body mass index (BMI) was 27.35±5.58 kg/m^2, duration of T2DM was 3.04±4.88 years, and HbA1c was 8.54±1.81%. The demographic and clinical characteristics of patients at the baseline are presented in Table I.

At week 24, HbA1c decreased significantly from a baseline of 8.54±1.81% with a mean reduction of 2.02±1.68% (p<0.0001) following treatment with vildagliptin monotherapy or combination therapy. The change in HbA1c from baseline

to week 24 for each treatment regimen is presented in Figure 1. For the pooled treatment regimens, the mean HbA1c at baseline was 8.02±1.75% (monotherapy), 8.39±1.66% (dual therapy with metformin (free dose and SPC)), 9.94±3.19% (dual therapy with SU/TZD/insulin), and 9.30±1.79% (triple therapy with metformin and SU/insulin); mean reductions of 1.98±1.43 (p<0.0001), 1.99±1.66 (p<0.0001), 2.21±3.10 (p=0.0648), and 2.11±1.66 (p<0.0001) at week 24 were observed for each respective group (Figure 2).

Approximately 60.64% (171/282) of patients achieved the glycemic target of HbA1c ≤6.5% and 74.47% (210/282) of patients achieved the target of HbA1c ≤7.0% (p<0.0001, for both) following treatment with vildagliptin or vildagliptin combination therapy. The percentage of patients achieving the predefined glycemic targets at week 24 for each treatment regimen is presented in Figure 3. For the pooled treatment regimens, at week 24, 76.60% (n=36) and 78.72% (n=37) of patients achieved the glycemic targets of HbA1c ≤6.5% and ≤7.0% with vildagliptin monotherapy, whereas 66.10% (n=117) and 80.79% (n=143) patients in the dual therapy arm with metformin (free dose and SPC) achieved the predefined glycemic targets, respectively (Figure 4). There was no significant change in weight and waist circumference from baseline to week 12 and week 24. However, there was a significant change in pulse (p=0.0172 and p=0.0283), systolic blood pressure (p<0.0001, for both) and diastolic blood pressure (p=0.0001 and p<0.0001) from baseline to week 12 and week 24, respectively.

Table I. Patient demographics and baseline characteristics (FAS; N=385)

	mean (SD)
Age in years	54.7 (11.1)
<60 years	248 (64.4)
Women	211 (54.8)
Height (cm)	161.3 (10.1)
Weight (kg)	70.2 (16.0)
Waist circumference (cm)	85.1 (22.6)
BMI, (kg/m^2)	27.4 (5.6)
Duration of T2DM in years	3.0 (4.9)
HbA1c*	8.5 (1.8)
Previous medical conditions (≥10%)	
Hypertension	200 (52.0)
Dyslipidemia/hyperlipidemia	193 (50.1)
Family history of diabetes	178 (46.2)
Obesity	56 (14.6)

**ITT population (n=282). Data are expressed as mean (SD) unless indicated otherwise*

BMI, body mass index; FAS, full analysis set; HbA1c, glycated hemoglobin; ITT, intent-to-treat; SD, standard deviation; T2DM, type 2 diabetes mellitus.

A total of 28 AEs were reported in 4.16% patients (16/385). Most of the AEs were either related to metabolism and nutrition disorders or infections and infestations. Of these 14 AEs (50%) were mild, five AEs (17.86%) were moderate, and nine AEs (32.14%) were severe. Most of the AEs (85.71%) were considered to be unrelated to the study treatment (Table II). Seven SAEs were reported in three patients (0.8%) which were not suspected to be drug-related. Of the three patients with SAEs, one patient had cerebrovascular disorder, one patient had leukocytosis and chronic myeloid leukemia and one patient had weight decrease, pneumonia, dyspnea and pallor. Of the 217 patients evaluated for hypoglycemic events at week 12, and 252 patients at week 24, only one hypoglycemic event (0.46%) was reported at week 12 with

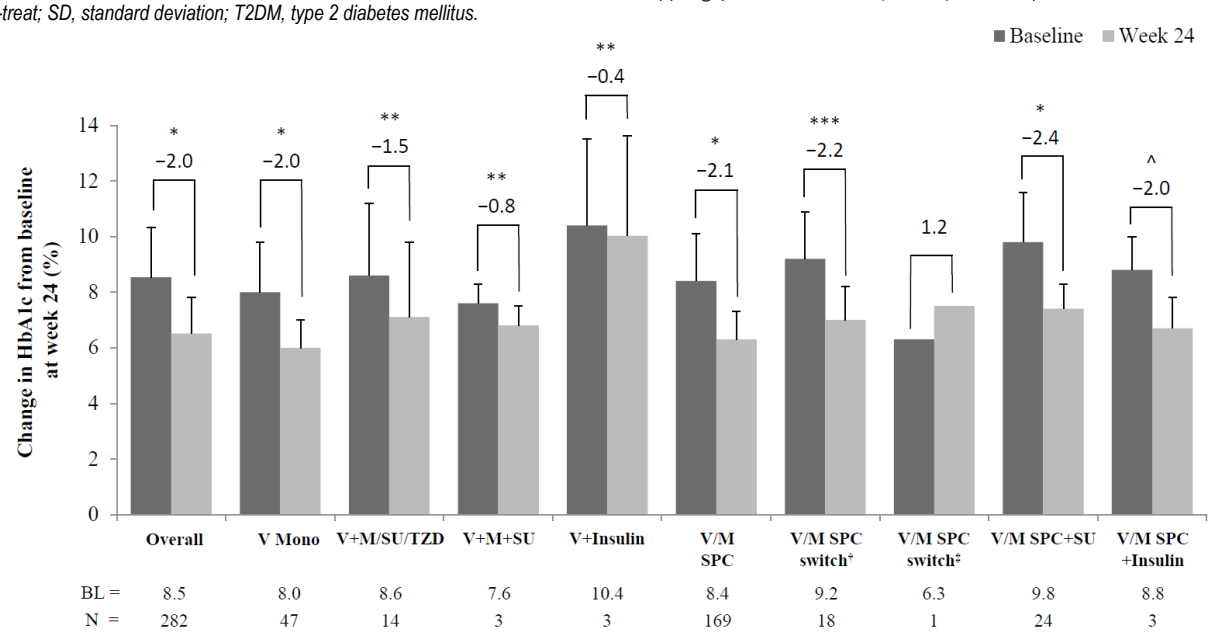

Figure 1. Change in HbA1c from baseline to week 24 for the nine treatment regimens (ITT population)

**p<0.0001; **p=ns; ***p=0.0002; ^p=0.04; †switch when vildagliptin or metformin alone did not provide glycemic control; ‡switch for those taking vildagliptin and metformin as separate tablets. BL, baseline; HbA1c, glycated hemoglobin; ITT, intent-to-treat; M, metformin; ns, not significant; SPC, single pill combination; SU, sulfonylurea; TZD, thiazolidinedione; V, vildagliptin.*

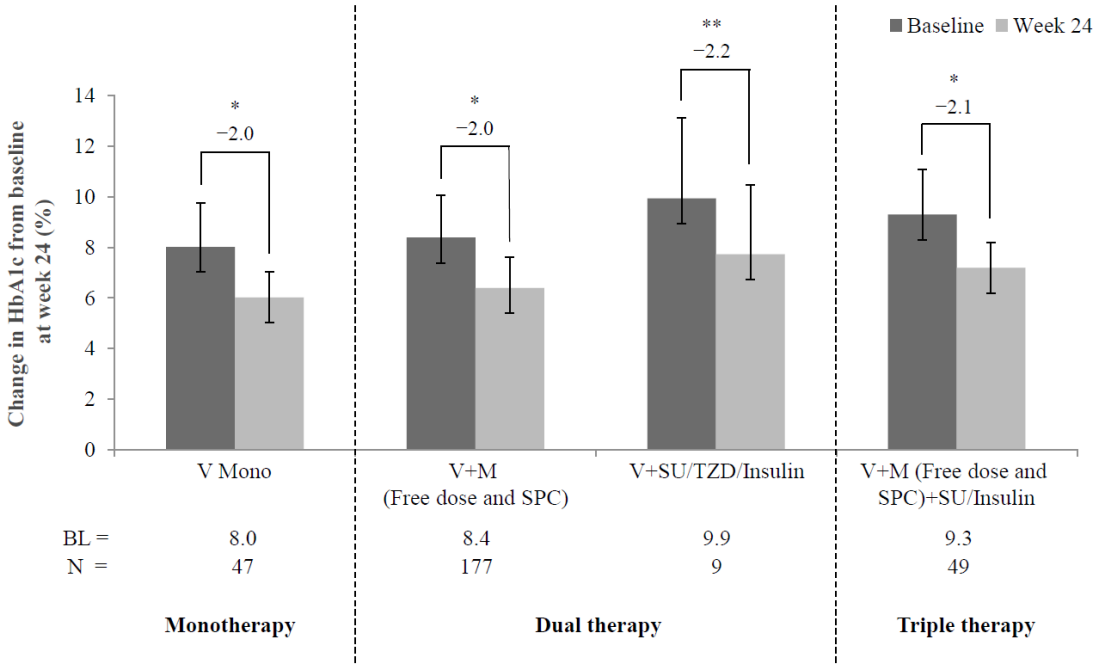

Figure 2. Change in HbA1c from baseline to week 24 for the pooled treatment regimens (ITT population)

**p<0.0001; **p=ns*

BL, baseline; HbA1c, glycated hemoglobin; ITT, intent-to-treat; M, metformin; ns, not significant; SPC, single pill combination; SU, sulfonylurea; TZD, thiazolidinedione; V, vildagliptin.

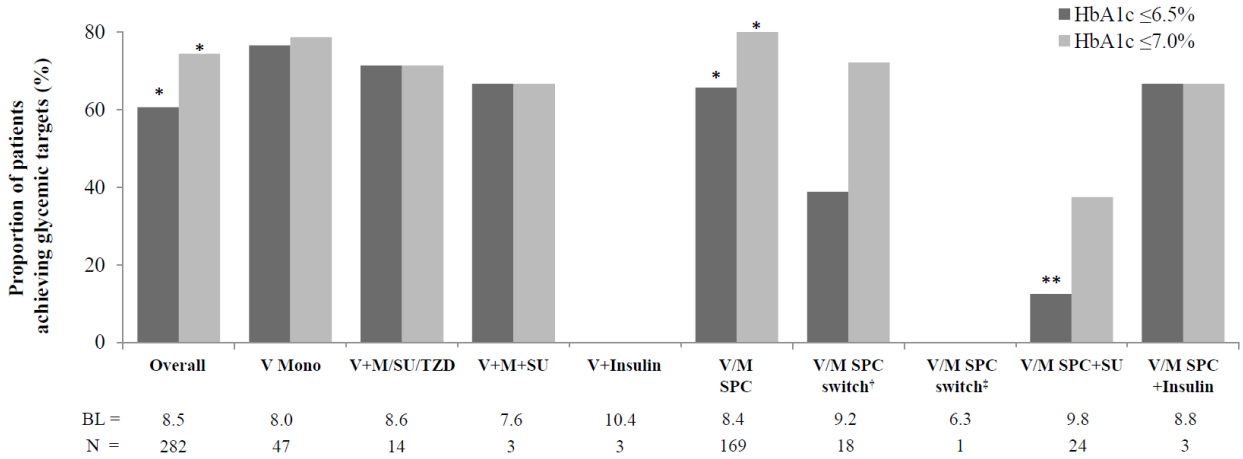

Figure 3. Proportion of patients achieving the HbA1c targets of ≤6.5% and ≤7.0% for the nine treatment regimens (ITT population)

**p<0.0001; **p=0.0006; †switch when vildagliptin or metformin alone did not provide glycemic control; ‡switch for those taking vildagliptin and metformin as separate tablets.*
BL, baseline; HbA1c, glycated hemoglobin; ITT, intent-to-treat; M, metformin; SPC, single pill combination; SU, sulfonylurea; TZD, thiazolidinedione; V, vildagliptin.

vildagliptin plus metformin SPC, which was suspected to be related to the study drug. Of the 254 patients, one death (0.39%) was reported at week 12 which was due to severe pneumonia and not related to the study drug.

Discussion

This observational, multi-center, prospective study showed that treatment with vildagliptin monotherapy or combination therapy for 24 weeks in patients with T2DM in the Philippines provided statistically significant reductions in HbA1c.

The current results are comparable with previously published large real-world multinational studies: the EDGE and GUARD studies (Table III). EDGE, a one-year observational study assessed the effectiveness and tolerability of vildagliptin as add-on to other oral antidiabetes drugs (OADs) versus OAD monotherapy; whereas, GUARD, a 24-week study evaluated the effectiveness, safety and tolerability of vildagliptin with or without metformin in adult patients with T2DM. In the EDGE study (n=45,868), a mean HbA1c reduction of 1.19% (baseline, 8.2±1.3%) with vildagliptin treatment in combination with OADs was reported.[16] Similarly, a sub-analysis of the EDGE study among

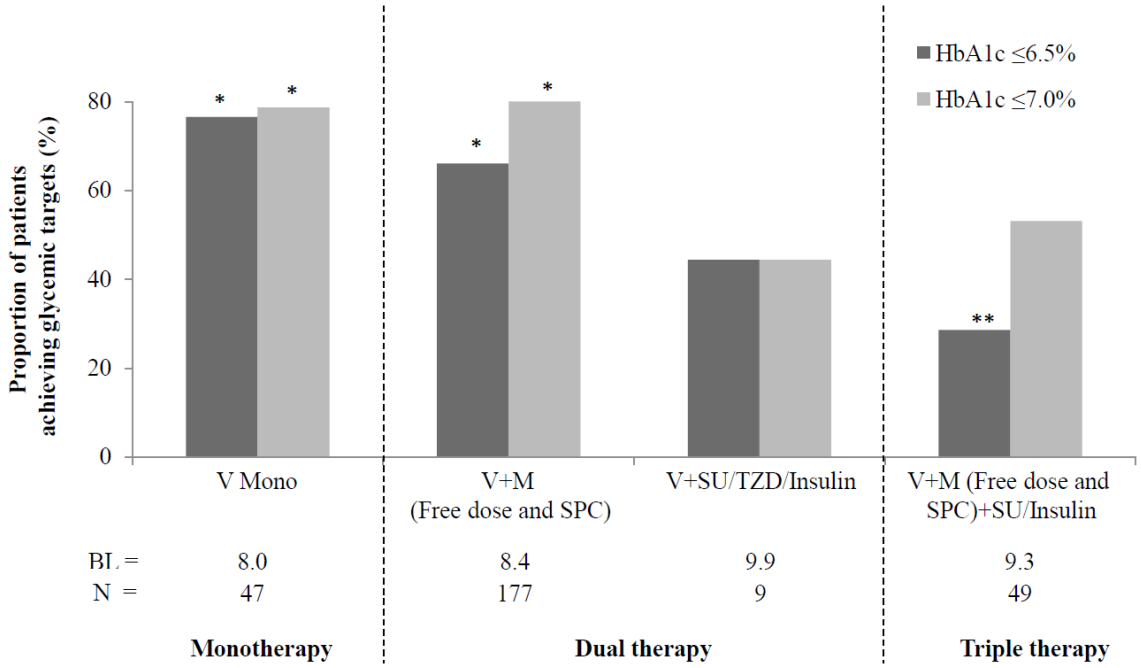

Figure 4. Proportion of patients achieving the HbA1c targets of ≤6.5% and ≤7.0% for the pooled treatment regimens (ITT population)

**p<0.0001; **p=0.0056*

BL, baseline; HbA1c, glycated hemoglobin; ITT, intent-to-treat; M, metformin; Mono, monotherapy; SPC, single pill combination; SU, sulfonylurea; TZD, thiazolidinedione; V, vildagliptin.

Table II. Incidence of adverse events by MedDRA in the safety population (N=385)

Primary system organ class	Safety set n (%)
Diabetes mellitus inadequate control	4 (1.0)
Urinary tract infection	2 (0.5)
Infections and infestations including: osteomyelitis, pneumonia, sepsis, upper respiratory tract infection	1 (0.3)*
Metabolism and nutrition disorders including: dyslipidemia, hyperglycemia, hyperphagia, hypertriglyceridemia, hypoglycemia	1 (0.3)*
Leukocytosis	1 (0.3)
Diarrhea	1 (0.3)
Dyspepsia	1 (0.3)
Asthenia	1 (0.3)
Blood creatinine increase	1 (0.3)
Weight decrease	1 (0.3)
Chronic myeloid leukemia	1 (0.3)
Cerebrovascular disorder	1 (0.3)
Somnolence	1 (0.3)
Stress	1 (0.3)
Cough	1 (0.3)
Dyspnea	1 (0.3)
Pallor	1 (0.3)

** Incidence of each of the events under primary system organ class; N, Total number of subjects in safety population; n, Number of subjects with adverse events. If a subject has multiple occurrence of an adverse event, the subject was presented only once in the respective column of subject count (n) for the corresponding adverse event. Adverse events was coded using MedDRA version 17.*

MedDRA, Medical dictionary for regulatory activities.

patients in the Philippines (n=540) showed a mean reduction of 1.1% from a mean baseline HbA1c of 8.0±1.5% at the study end with vildagliptin.[3] An overall mean reduction in HbA1c of 1.27% (baseline, 8.40±0.86%) in the real-world GUARD study (n=19,331, *p*<0.0001) was observed at week 24 among patients treated with vildagliptin monotherapy or vildagliptin plus metformin combination.[17] In addition, in a sub-analysis among patients from the Philippines, a mean reduction in HbA1c of 1.2% (*p*<0.0001) from a baseline of 7.6±1.1% was observed in the vildagliptin group, and a mean reduction of 1.5±0.1% (*p*<0.0001) from a baseline of 8.1±1.2% was observed for the vildagliptin plus metformin group.[14] Likewise, a 12- and 14-week randomized clinical trial in Japanese patients also showed a reduction of 1.1% and 1.2% in HbA1c (baseline ~8.0%) with vildagliptin plus metformin SPC.[18,19]

Interestingly, the overall mean HbA1c reduction (2.02±1.68%, *p*<0.0001) seen in the present study with vildagliptin monotherapy or combination therapy is comparatively higher than previously published real-world studies in the Philippines (EDGE (1.1%) and GUARD (1.2%)). This may be due to the higher baseline HbA1c (8.54±1.81%) seen in the present study in comparison to the other studies in the Philippines (EDGE (8.0±1.5%) and GUARD (8.0±1.2%)).[3,14] Nevertheless, before considering the influence of other baseline characteristics such as mean age (54.7 years), BMI (27.4 kg/m^2), or diabetes disease duration (3.0 years) on the mean HbA1c reduction, it is important to note other limiting factors such as limited sample size, unequal distribution of patients in the different treatment arms, and initial treatment bias associated with the study.

Table III. Efficacy of vildagliptin as add-on to OADs in comparison with other real-world studies

	Present study	EDGE[16]	EDGE Philippines[3]	GUARD[17]	GUARD Philippines[14]
Study duration	24 weeks	12 months	12 months	24 weeks	24 weeks
Baseline HbA1c	8.5±1.8	8.2±1.3	8.0±1.4	8.4± 0.9	8.1±1.2
HbA1c reduction (%)	2.02	1.19	1.1	1.29	1.5
Proportion of patients achieving glycemic targets (%)					
≤6.5%	60.64	-	-	-	43.0
≤7.0%	74.47	35.15	28.7	42.8	62.7

Data is presented as mean or mean±SD.; HbA1c, glycated hemoglobin; OADs, oral antidiabetes drugs; SD, standard deviation.

At week 24, the following treatment regimens showed reductions in HbA1c levels that were consistent with the overall population: vildagliptin monotherapy (1.98±1.43%; $p<0.0001$), vildagliptin plus metformin SPC as initial therapy (2.07±1.54; $p<0.0001$), vildagliptin plus metformin SPC as switch when metformin or vildagliptin alone has not provided adequate glycemic control (2.17±1.90; $p=0.0002$), vildagliptin plus metformin SPC in combination with SU (2.38±1.49; $p<0.0001$), and vildagliptin plus metformin SPC as add-on to insulin (2.04±0.74; $p=0.041$). A significant reduction ($p<0.0001$) in mean HbA1c was also reported in the pooled analysis of different treatment regimens with vildagliptin: monotherapy (1.98±1.43%), dual therapy with metformin (free dose and SPC; 1.99±1.66%) and triple therapy with metformin (free dose and SPC) plus SU or insulin (2.11±1.66%). These results can be compared with a sub-analysis of the GUARD study among patients from the Philippines that demonstrated HbA1c reductions of 1.2±0.1% ($p<0.0001$) in vildagliptin arm and 1.5±0.1% ($p<0.0001$) in the vildagliptin plus metformin arm.[14]

At week 24, more than half of the patients achieved the glycemic target of HbA1c ≤6.5% (60.64%) and ≤7.0% (74.47%), respectively. Similarly, pooled analysis showed that 76.60% and 78.72% patients achieved the glycemic targets of HbA1c ≤6.5% and ≤7.0% with vildagliptin monotherapy, whereas 66.10% and 80.79% patients in the dual therapy arm with metformin achieved the predefined glycemic targets respectively. Likewise, a significant proportion of patients ($p<0.001$) achieved the predefined glycemic target of <7.0% with vildagliptin (35.15%) compared to the comparators (23.2%) in the EDGE study.[16] The GUARD study showed that 47.2% and 42.8% of the patients achieved the HbA1c target of ≤7.0% at week 24 with vildagliptin and vildagliptin plus metformin respectively[17], whereas in a sub-analysis among patients in the Philippines, the proportion of patients achieving HbA1c ≤7.0% was 66.1% and 62.7% in the vildagliptin and vildagliptin plus metformin group, respectively. In addition, in the GUARD study 48.9% of patients on vildagliptin and 43.0% of patients on vildagliptin plus metformin reached the more stringent HbA1c target of ≤6.5%.[14]

During the 24-week treatment period, seven non-drug-related SAEs were reported. The majority of the AEs (24/28) were considered as mild or moderate in severity with 85.71% of the AEs being unrelated to the study drug. Overall, vildagliptin monotherapy or combination therapy demonstrated a favorable safety profile with no new safety signal. These results are in line with the safety and tolerability profile seen in earlier real-world studies in the Philippines[3,14] as well as in randomized clinical trials with Asian populations.[18,20]

However, this study has certain limitations. Being an observational, multi-center, open-label study, hence it carries a risk of bias in patient selection. Approximately 31% of the enrolled patients did not complete the study as they were under a self-pay healthcare setting. Due to the unequal distribution of patients in each treatment regimen, it is not possible to establish statistical significance. There is also a possibility of over- or under-estimation of treatment effects and AEs, as the data collected was a part of routine medical care of the patients and did not involve standardized data collection procedures.

Conclusions

This observational, multi-center, prospective, open-label study showed that treatment with vildagliptin monotherapy or combination therapy provided good glycemic control and was well-tolerated in patients with T2DM from the Philippines under real-world settings.

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Conflict of interest

Reynaldo Rosales is a member of the Diabetes Advisory Board of Novartis. Cyril Joseph Tolosa is an employee of Novartis Healthcare Philippines Inc.

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