

# Effectiveness, Safety and Tolerability of Vildagliptin and Vildagliptin + Metformin in Real-world Setting in the Philippines—Results from the GUARD Study

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## Abstract

**Introduction:** GUARD (vildaGliptin clinical Use in reAl world) was a multinational, prospective, observational study that assessed the effectiveness, safety and tolerability of vildagliptin and vildagliptin+metformin in patients with type 2 diabetes mellitus (T2DM) under real-world conditions across four geographical regions (Asia, the Middle East, Central America and Africa). The current paper discusses the results of patients with T2DM enrolled in the Philippines.

**Methods:** Patients with T2DM who were prescribed vildagliptin or vildagliptin+metformin combination therapy were enrolled and followed as per routine clinical practice for 24 ± six weeks. Primary endpoint was the change in HbA1c from baseline to study end (week 24±6). Key secondary endpoints included proportion of patients reaching target HbA1c ≤7.0%, incidence of hypoglycemic events, adverse events (AEs) and serious AEs (SAEs).

**Results:** A total of 1,117 patients were included in the final analysis, 280 on vildagliptin (of these, eight patients received additional oral antidiabetes medications) and 837 on vildagliptin+metformin. At baseline, the mean (±SD) age of the enrolled population was 54.1±11.5 years, BMI 26.3±4.7 kg/m<sup>2</sup>, HbA1c 8.0±1.2% and T2DM duration 2.3±4.0 years.

At study end, significant mean (±SE) reductions in HbA1c of -1.2±0.1% (p<0.0001) and -1.5±0.1% (p<0.0001) from a baseline of 7.6±1.1% and 8.1±1.2% were observed for the vildagliptin and vildagliptin+metformin group, respectively. A similar proportion of patients achieved HbA1c ≤7.0% in the vildagliptin (66.1%) and vildagliptin+metformin group (62.7%). Changes in body weight and BMI from baseline to week 24±6 were statistically significant (p<0.0001) in both the vildagliptin (-1.5±0.3 kg; -0.6±0.1 kg/m<sup>2</sup>) and the vildagliptin+metformin group (-1.4±0.2 kg; -0.5±0.1 kg/m<sup>2</sup>). The incidence of hypoglycemia was low—six patients reported hypoglycemia in the vildagliptin+metformin group and none in the vildagliptin group. Incidence of adverse events was also low in both the groups (vildagliptin, 8.6% and vildagliptin+metformin, 5.3%).

**Conclusion:** Vildagliptin and vildagliptin+metformin significantly reduced HbA1c with good weight control and low incidence of hypoglycemia in patients with T2DM under real-world conditions in Philippines.

**Key words:** real-world, vildagliptin, type 2 diabetes mellitus, Philippines

## Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is rising alarmingly in the Philippines, with approximately 6.0% of adults aged 20-79 years diagnosed with T2DM.<sup>1</sup> The increase in incidence coupled with emerging healthcare infrastructure poses a significant concern for developing countries like the Philippines. Evidence from the DiabCare 2008 survey in the Philippines reported that only 15% of patients with T2DM achieved the recommended glycemic target of HbA1c ≤7.0%.<sup>2</sup> Inadequate glycemic control increases the risk of various micro and macrovascular complications eventually resulting in morbidity and mortality.<sup>3,4</sup>

Guidelines for management of T2DM recommend metformin as the first-line treatment, unless contraindicated, after diet and lifestyle changes fail to maintain glycemic goal (HbA1c <7.0%).<sup>5-7</sup> However, due to progressive nature of the disease, glycemic control deteriorates over time and most patients require additional therapies to maintain targets.<sup>8,9</sup> Dipeptidyl peptidase-4 (DPP-4) inhibitors such as vildagliptin improve glucose homeostasis by inhibiting the degradation of the incretin hormones thereby enhancing the α- and β-cell response to glucose<sup>10</sup> are being increasingly used as add-on therapy to metformin.<sup>6</sup> The efficacy and safety of vildagliptin as monotherapy and in combination with metformin are well established in various global randomized controlled trials (RCTs)<sup>11-13</sup> and real-world studies.<sup>14,15</sup> However, there is a dearth of data on the effectiveness of DPP-4 inhibitors in patients with T2DM in the Philippines, possibly due to under representation in large RCTs and observational studies. Thus, it is clinically essential to have the evidence from real-world studies in which patients are followed as per usual clinical practice<sup>16</sup> for developing countries like the Philippines.

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Accordingly, a large real-world observational study (vildaGliptin clinical Use in the reAl woRlD (GUARD)) was conducted to evaluate the effectiveness, safety and tolerability of treatment with vildagliptin and vildagliptin+metformin (free or single-pill combination) in a large multi-ethnic population with T2DM. The study recruited 19,331 patients with T2DM from four geographical regions—Asia, the Middle East, Central America and Africa.<sup>17</sup> We present the results from the GUARD study for patients enrolled from the Philippines.

## Methodology

### Study design and patient population

GUARD was a large, open-label, multinational, multicenter, observational study conducted across four geographical regions. In the Philippines, the study was conducted between September 2010 and February 2013 involving private and government, hospitals and clinics. Men and women aged 18 years and above with a confirmed diagnosis of T2DM, who were prescribed treatment with vildagliptin (50 mg bid) or vildagliptin+metformin (free-dose combination or single-pill combination), and who provided consent for data collection were enrolled in the study.

The therapy was prescribed as part of routine clinical practice based on physician's judgment. Key exclusion criteria included contraindications to the medication of interest, requirement for three or more oral antidiabetes drugs (OADs) or insulin at the time of study entry, creatinine clearance <60 mL/min. Despite protocol-specified criteria that excluded patients with a baseline HbA1c >10.0%, a small number of these patients (n=26 (0.02%)) were enrolled and their data were included for analysis. Data from three routine clinic visits were recorded i.e. the baseline visit (Day 1), visit 2 (week 12±4) and a final visit (visit 3) at the end of the study (week 24±6).

The study was designed and conducted in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including Philippine Department of Health Administrative Order no. 47-a series 2001, Philippine FDA Circular no. 2012-007 and Pharmaceutical and Healthcare Association of the Philippines, Code of Practice 2013), Guidelines for Good Pharmacoepidemiology Practices (GPP) and with the ethical principles laid down in the Declaration of Helsinki. The protocol was approved by the respective institutional review board/ independent ethics committee/ research ethics board.

### Study Assessments

The primary effectiveness endpoint was change in HbA1c from baseline after 24±6 weeks of treatment with vildagliptin and vildagliptin+metformin. The key secondary endpoints included proportion of patients reaching target HbA1c of ≤7.0% and ≤6.5% at week 24±6, changes in body weight and body mass index (BMI) from baseline to week 24±6, proportion of patients who discontinued treatment due to unsatisfactory therapeutic effect or the need of an additional OAD or insulin, and the number of patients who had hypoglycemia. HbA1c drops across the various baseline HbA1c categories (≤8.0%, >8.0%–9.0%, >9.0%–10% & >10.0%) were also assessed in both the groups.

Safety and tolerability were assessed by means of adverse event (AE) and serious AE (SAE) reporting. Additionally, treatment effectiveness, tolerability and compliance were assessed at the final visit by the investigator using a subjective evaluation scale of 'below average', 'average', 'good' or 'very good'.

### Statistical analysis

Taking into account a 20% drop-out rate and standard deviation of 1.5%, a sample size of 300 patients would ensure estimation of mean change in HbA1c at a 95% confidence interval width of 0.38%. Patients who received one dose of study drug and with one post-baseline efficacy assessment constituted the full analysis set (FAS). The last available post-baseline value was carried forward to accommodate the missing values due to early discontinuations. All the analyses were performed in the FAS population.

The changes from baseline to week 24±6 in HbA1c, body weight and BMI were assessed using a two-sided t-test with an  $\alpha$ -level of 5%. Proportion of patients reaching HbA1c targets ≤7.0% and ≤6.5%, HbA1c drops across the various baseline HbA1c categories, number of patients who discontinued due to unsatisfactory effectiveness or who needed an additional OAD or insulin and safety results were summarized descriptively. Analysis of data was performed using the SAS® statistical package (SAS Institute Inc, North Carolina, USA) version 9.2.

## Results

### Patient disposition and baseline characteristics

Of the 1,149 patients recruited, 32 patients were excluded from the final analysis as they were receiving three or more OADs or insulin at study entry. Out of 1,117 patients included in the final analysis, 280 patients were on vildagliptin (of these, eight patients received other OADs) and 837 patients were on vildagliptin+metformin. Nine

**Table 1: Patient disposition**

| n (%)                              | Vildagliptin | Vildagliptin+Metformin | Total      |
|------------------------------------|--------------|------------------------|------------|
| <b>Patients</b>                    | 280          | 837                    | 1117       |
| Completed                          | 229 (81.8)   | 720 (86.0)             | 949 (85.0) |
| Discontinued                       | 51 (18.2)    | 117 (14.0)             | 168 (15.0) |
| <b>Reasons for discontinuation</b> | 1 (0.4)      | 3 (0.4)                | 4 (0.4)    |
| Lost to follow-up                  | 43 (15.4)    | 111 (13.3)             | 154 (13.8) |
| Withdrew consent                   | 1 (0.4)      | 3 (0.4)                | 4 (0.4)    |
| Protocol deviation                 | 2 (0.7)      | 1 (0.1)                | 3 (0.3)    |
| Adverse event(s)                   | 2 (0.7)      | 1 (0.1)                | 3 (0.3)    |
| Unsatisfactory therapeutic effect  | 1 (0.4)      | 1 (0.1)                | 2 (0.2)    |
| Death                              | 1 (0.4)      | 0 (0.0)                | 1 (0.1)    |
| Missing information                | 1 (0.4)      | 0 (0.0)                | 1 (0.1)    |

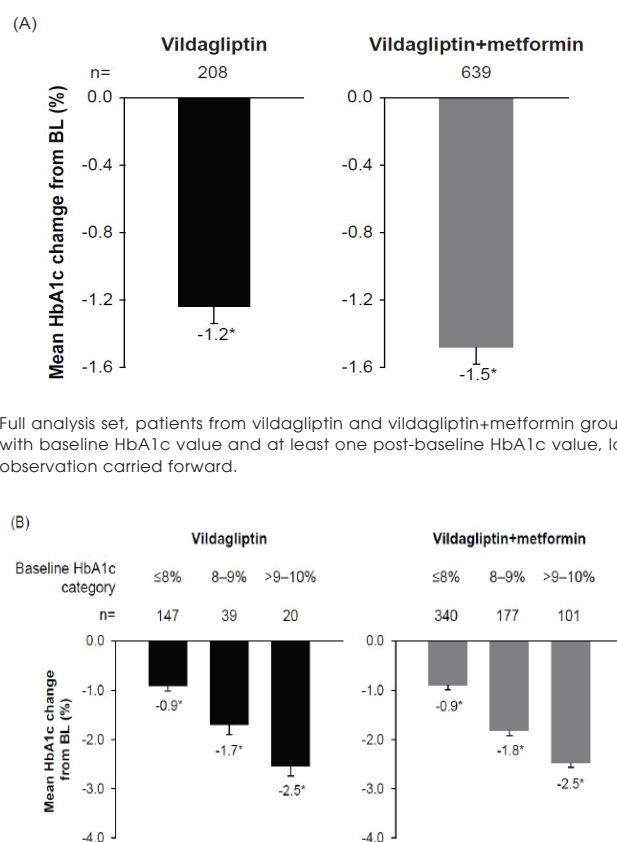
Full Analysis Set

hundred forty nine (85%) patients completed the study. A detailed patient disposition is presented in Table 1. The overall mean ( $\pm$ SD) age of patients was  $54.1 \pm 11.5$  years, with mean diabetes duration  $2.3 \pm 4.0$  years, HbA1c  $8.0 \pm 1.2\%$  and BMI  $26.3 \pm 4.7$  kg/m<sup>2</sup>. Majority of the patients were Asians (98.9%) (Table II).

Treatment with vildagliptin and vildagliptin+metformin significantly reduced HbA1c from baseline to week 24 $\pm$ 6 (Figure 1A). The mean ( $\pm$ SE) change in HbA1c at week 24 $\pm$ 6 was  $-1.2 \pm 0.1\%$  from a baseline of  $7.6 \pm 1.1\%$  ( $p < 0.0001$ ) in the vildagliptin group and  $-1.5 \pm 0.1\%$  from a baseline of  $8.1 \pm 1.2\%$  ( $p < 0.0001$ ) in the vildagliptin+metformin group. Reductions in HbA1c from baseline to week 24 $\pm$ 6 were significant ( $p < 0.0001$ ) across the various baseline HbA1c categories in the vildagliptin (except for the category  $>10.0\%$ , which had only two patients) and vildagliptin+metformin groups (Figure 1B). The proportion of patients achieving HbA1c  $\leq 7.0\%$  was 66.1% and 62.7% (both groups combined, 63.6%) in the vildagliptin and vildagliptin+metformin group, respectively. Further, 48.9% of patients on vildagliptin and 43.0% of patients on vildagliptin+metformin (both groups combined, 44.5%) reached the more stringent HbA1c target of  $\leq 6.5\%$  (Figure 2).

The change in body weight from baseline to week 24 $\pm$ 6 was statistically significant ( $p < 0.0001$ ) in both the vildagliptin ( $-1.5 \pm 0.3$  kg) and the vildagliptin+metformin group ( $-1.4 \pm 0.2$  kg). Similarly, modest but significant reductions ( $p < 0.0001$ ) from baseline to week 24 $\pm$ 6 were also observed for BMI in the vildagliptin ( $-0.6 \pm 0.1$  kg/m<sup>2</sup>) and vildagliptin+metformin group ( $-0.5 \pm 0.1$  kg/m<sup>2</sup>).

**Figure 1:** HbA1c change (mean $\pm$ SE) from baseline to week 24 (A) overall and (B) HbA1c categories (full analysis set). \* $p < 0.0001$  versus BL (two sided t-test). BL, baseline



Full analysis set, patients from vildagliptin and vildagliptin+metformin groups with baseline HbA1c value and at least one post-baseline HbA1c value, last observation carried forward.

HbA1c reductions for the category  $>10\%$  were  $-4.0 \pm 0.1\%$ ,  $p = 0.02$  (vildagliptin group,  $n = 2$ ) and  $-3.4 \pm 1.8\%$ ,  $p < 0.0001$  (vildagliptin+metformin group,  $n = 21$ ). Full analysis set, patients from vildagliptin and vildagliptin+metformin groups with baseline HbA1c value and at least one post-baseline HbA1c value, last observation carried forward.

**Table II: Demographics and baseline characteristics (Full Analysis Set)**

| Parameter                                      | Vildagliptin<br>(n=280) | Vildagliptin+<br>metformin<br>(n=837) | Total<br>(N=1117) |
|------------------------------------------------|-------------------------|---------------------------------------|-------------------|
| Age, years                                     | 55.4±12.5               | 53.7±11.1                             | 54.1±11.5         |
| Age group, n (%)                               |                         |                                       |                   |
| <65 years                                      | 214 (76.4)              | 709 (84.7)                            | 923 (82.6)        |
| ≥65 years                                      | 66 (23.6)               | 128 (15.3)                            | 194 (17.4)        |
| Gender, n (%)                                  |                         |                                       |                   |
| Men                                            | 121 (43.2)              | 344 (41.1)                            | 465 (41.6)        |
| Women                                          | 159 (56.8)              | 493 (58.9)                            | 652 (58.4)        |
| Race, n (%)                                    |                         |                                       |                   |
| Asian                                          | 278 (99.3)              | 827 (98.8)                            | 1105 (98.9)       |
| Caucasian                                      | 0 (0.0)                 | 2 (0.2)                               | 2 (0.2)           |
| Black                                          | 1 (0.4)                 | 1 (0.1)                               | 2 (0.2)           |
| Other                                          | 1 (0.4)                 | 7 (0.8)                               | 8 (0.7)           |
| Weight <sup>a</sup> , kg                       | 66.0±12.4               | 67.5±12.5                             | 67.1±12.5         |
| BMI <sup>b</sup> , kg/m <sup>2</sup>           | 25.7±4.5                | 26.5±4.8                              | 26.3±4.7          |
| <30 kg/m <sup>2</sup> , n (%)                  | 210 (75.0)              | 624 (74.6)                            | 834 (74.7)        |
| ≥30 kg/m <sup>2</sup> , n (%)                  | 30 (10.7)               | 139 (16.6)                            | 169 (15.1)        |
| Duration of T2DM <sup>c</sup> , years          | 1.8±4.2                 | 2.5±3.9                               | 2.3±4.0           |
| HbA1c <sup>d</sup> , %                         | 7.6±1.1                 | 8.1±1.2                               | 8.0±1.2           |
| ≤8%, n (%)                                     | 171 (61.1)              | 389 (46.5)                            | 560 (50.1)        |
| >8–9%, n (%)                                   | 45 (16.1)               | 201 (24.0)                            | 246 (22.0)        |
| >9–10%, n (%)                                  | 20 (7.1)                | 117 (14.0)                            | 137 (12.3)        |
| >10%, n (%)                                    | 2 (0.7)                 | 24 (2.9)                              | 26 (2.3)          |
| Prior metformin treatment <sup>e</sup> , n (%) | 47 (16.8)               | 493 (58.9)                            | 540 (48.3)        |

Data are expressed as mean±SD unless otherwise indicated. bid, twice daily; BMI, body mass index; SD, standard deviation; T2DM, type 2 diabetes mellitus. (a) weight data missing for 47 patients; (b) BMI data missing for 114 patients; (c) duration of diabetes data missing for three patients; (d) HbA1c data missing for 148 patients; (e) prior metformin dose data missing for two patients.

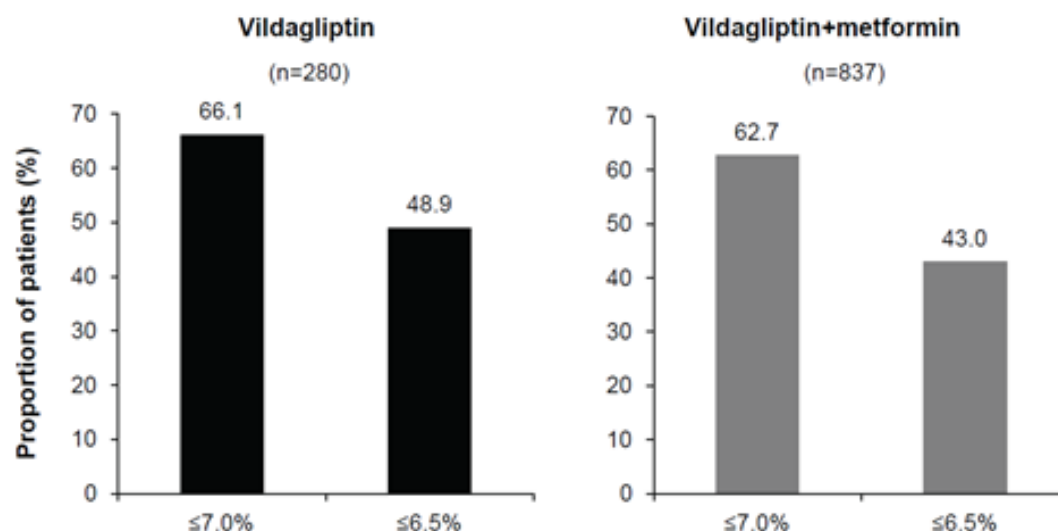
None of the patients reported hypoglycemia in the vildagliptin group, whereas six patients (0.7%) reported hypoglycemia in the vildagliptin+metformin group. One patient in each treatment group discontinued due to unsatisfactory therapeutic effect or needed additional OAD or insulin therapy. AEs were reported by 24 (8.6%) and 44 (5.3%) patients in the vildagliptin and vildagliptin+metformin group, respectively. Most of the AEs were mild or moderate in severity. There was one non drug-related SAE of cardio-pulmonary arrest in the vildagliptin group which resulted in death. The safety data are summarized in Table III. At week 24±6, the investigators rated effectiveness, tolerability and compliance after treatment with vildagliptin

and vildagliptin+metformin as 'very good' or 'good' for majority of the patients. The decision to continue treatment after study end was made for 83.6% and 87.7% of the patients in the vildagliptin and vildagliptin+metformin groups, respectively.

## Discussion

GUARD is one of largest observational studies in the Philippines that assessed the real-world effectiveness of the DPP-4 inhibitor, vildagliptin in patients with T2DM. The results of the current study showed that treatment with vildagliptin and vildagliptin+metformin provided clinically relevant red-

**Figure 2:** Proportion of patients achieving HbA1c target  $\leq 7.0\%$  and  $\leq 6.5\%$  at week 24 (full analysis set)



Full analysis set, patients from vildagliptin and vildagliptin+metformin groups with baseline HbA1c value and at least one post-baseline HbA1c value, last observation carried forward.

**Table III: Overall safety profile (full analysis set)**

| Subjects with events, n (%)                  | Vildagliptin (n=280) | Vildagliptin+metformin (n=837) | Total (N=1117) |
|----------------------------------------------|----------------------|--------------------------------|----------------|
| Adverse event(s) (AEs)                       | 24 (8.6)             | 44 (5.3)                       | 68 (6.1%)      |
| AEs related to study drug*                   | 4** (1.4)            | 16# (1.9)                      | 20 (1.8)       |
| Serious AEs                                  | 1 (0.4)              | 0 (0.0)                        | 1 (0.1)        |
| <b>Discontinuation due to AEs</b>            | 2 (0.7)              | 1 (0.1)                        | 3 (0.3)        |
| Hypoglycemia                                 | 0 (0.0)              | 6 (0.7)                        | 6 (0.5)        |
| Deaths                                       | 1 (0.4)              | 0 (0.0)                        | 1 (0.1)        |
| Most common AEs by preferred term $\geq 1\%$ |                      |                                |                |
| Urinary tract infection                      | 4 (1.4)              | 0 (0.0)                        | 4 (0.4)        |
| Hyperlipidemia                               | 3 (1.1)              | 4 (0.5)                        | 7 (0.6)        |

\*In case an AE had missing relationship to medication of interest then it was assumed to be suspected. \*\*abdominal distention (n=2), blood creatinine increased, dizziness, tremor, cough, rhinitis allergic (all n=1); #hypoglycemia (n=6), dizziness (n=2), palpitations, abdominal distention, hyperglycemia, muscular weakness, neuropathy peripheral, tremor (all n=1)

uctions in HbA1c with low incidence of hypoglycemia and good weight control.

The overall baseline HbA1c of 8.0% in the current study is similar to that observed in the Philippines subanalysis of the Effectiveness of Diabetes control with vildaGliptin and vildagliptin/mEtformin (EDGE) study<sup>18</sup> indicating that in real-world clinical practice in the Philippines treatment intensification is being done at HbA1c  $\sim 8.0\%$ , while the recommendation is  $\sim 7.0\%$ . As this delay in intensification predisposes patients to microvascular complications,<sup>4</sup> it is important to maintain good glycemic control which might be achieved by increased interaction between physicians

and patients regarding disease management, as suggested by a recent global survey.<sup>19</sup>

HbA1c reductions in the current study are in accordance with findings from RCTs and other non-interventional studies of vildagliptin like EDGE.<sup>14,15</sup> Also, the HbA1c drop in the current study is similar to that observed in the GUARD pooled analysis, which suggests that despite known differences in epidemiology, healthcare infrastructure and dietary patterns, the efficacy of vildagliptin is same in Filipino patients with T2DM as observed across the four geographical regions. Higher drops in HbA1c were observed in patients with high baseline HbA1c compared to patients

with low baseline HbA1c, which is in-line with the observations from earlier RCTs.<sup>11</sup> Further, these findings are in accordance with a recent analysis, which concluded that treatment with vildagliptin shows consistency in terms of HbA1c reduction between RCTs and real-world conditions unlike sulfonylureas (SUs).<sup>20</sup>

An important clinical consideration is that in the current GUARD study HbA1c reduction was associated with modest but statistically significant decrease in body weight from baseline and low hypoglycemic event rate similar to the reports from RCTs.<sup>13</sup> The incidences of total AEs and SAEs were low in both the groups and similar to that reported in the Philippine subanalysis of the EDGE study.<sup>18</sup> Overall vildagliptin and vildagliptin+metformin were well tolerated.

However, there are some limitations as observed in the conduct of the study—open-label, observational design carries a risk of bias in patient selection which is not governed by strict exclusion and inclusion criteria, as evidenced by the fact that patients with HbA1c >10.0% were recruited in the study. AEs might have been underreported, as the reporting was on voluntary basis. There were some missing data on baseline parameters like HbA1c, body weight, BMI, possibly due to recruitment from remote individual centers. Despite the limitations, the study has provided valuable real-world data regarding the effectiveness of vildagliptin and vildagliptin+metformin in usual care conditions in the Philippines. Such real-world data is representative of the standard of care provided by the emerging healthcare infrastructure of the Philippines.

## Conclusion

The current study showed that treatment with vildagliptin and vildagliptin+metformin significantly improved glycemic control with low incidence of hypoglycemia and good weight control under real-world conditions in patients with T2DM in the Philippines.

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## Conflict of Interest

Rosales\* is a member of the Diabetes Advisory Board of Novartis. Domingo\* is an employee of Novartis Healthcare Philippines, Inc. and Javier\*\* was an employee of Novartis Healthcare Philippines, Inc when the study was performed, currently he is an employee of GlaxoSmithKline, Philippines.

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