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Original article

Real-life safety and efficacy of vildagliptin as add-on to metformin in patients with type 2 diabetes in Turkey – GALATA study

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Abstract

Objective:
To evaluate tolerability/safety and the efficacy of the combination of vildagliptin plus metformin in a real-life population of patients with type 2 diabetes mellitus (T2DM).

Research design and methods:
This multicenter, single-arm, 6 month, observational, prospective cohort study was conducted at 39 centers across Turkey. T2DM patients on vildagliptin and metformin for ≤4 weeks were enrolled regardless of their previous antidiabetic therapy.

Main outcome measures:
Efficacy was evaluated by measuring hemoglobin A1c (HbA1c) levels. Tolerability/safety parameters evaluated included hypoglycemic events, gastrointestinal events, peripheral edema and weight gain.

Results:
This study enrolled 665 patients with a mean ± standard deviation (SD) age of 55.1 ± 10.2 years and female predominance ($n = 394$, 59.2%). Safety was assessed in all enrolled patients. Hypoglycemia was reported in 10 (1.5%) patients (95% confidence interval = 0.8–2.7%). Efficacy was assessed in 289 (43.5%) patients treated for 6 ± 1 months; these patients showed a mean decrease in HbA1c of 0.8% from baseline value of 7.8% ($p < 0.001$). The percentages of patients who achieved HbA1c targets of ≤6.5% and ≤7.0% were significantly increased, from 10.7% to 33.6% and from 22.1% to 52.6%, respectively ($p < 0.001$ each). The decrease in HbA1c was independent of baseline HbA1c (≤8% vs. 8–10% vs. ≥10%), age (≤65 vs. >65 years) and body mass index (<30 vs. ≥30 kg/m^2) ($p < 0.001$ each). In total, 136 adverse events (AEs) were observed in 71 (10.7%) patients; 10 (1.5%) patients experienced hypoglycemia and gastrointestinal AEs were most commonly reported ($n = 29$, 4.4%).

Conclusions:
In a 'real-life' setting, the vildagliptin and metformin combination was associated with significant improvements in reaching target HbA1c levels, even in elderly and obese patients with T2DM. Moreover, vildagliptin and metformin demonstrated a good overall tolerability/safety profile.

Introduction

Type 2 diabetes mellitus (T2DM) is a common chronic and progressive disease that is predicted to affect 592 million adults worldwide by 2035, in accordance with its rapid increase in incidence and prevalence[1,2]. The Turkish diabetes prevalence study (TURDEP-I) conducted in 1997–1998 reported that T2DM prevalence in individuals aged ≥20 years was 7.2%[3], whereas the Turkish

Epidemiology Survey of Diabetes, Hypertension, Obesity and Endocrine Disease (TURDEP-II) performed 12 years later found that the prevalence of T2DM in Turkey had increased to 13.7%[4].

Due to the progressive nature of the disease, guidelines for T2DM management recommend a stepwise multi-medication approach that involves the initiation of lifestyle modification, medical nutritional therapy and exercise, followed by the addition of metformin monotherapy as a first-line treatment, proceed to a two-drug combination if needed to reach individualized hemoglobin A1c (HbA1c) targets after 3 months[5–7]. However, no consensus has been reached on the ideal second-line drug(s), but the general principle is based on combining antidiabetic agents with different mechanisms of action[6,8–12]. The 2012 ADA-EASD guidelines recommend that drug selection be based on specific patient preferences, characteristics, and susceptibilities to side effects, potential for weight gain and hypoglycemia, and overall tolerability[9]. Since even occasional hypoglycemia may be devastating, reducing the likelihood of hypoglycemia is of specific importance in the choice of antihyperglycemic agent(s)[9].

Dipeptidyl peptidase-4 (DPP-4) inhibitors improve α- and β-cell sensitivity to glucose by increasing concentrations of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), stimulating insulin and suppressing glucagon secretion in a glucose dependent manner[13,14]. DPP-4 inhibitors are therefore considered good adjuncts to metformin, enhancing glycemic control without inducing weight gain or causing episodes of hypoglycemia[10,13–17]. Vildagliptin is a DPP-4 inhibitor that has been shown to be effective in improving β-cell function and reducing insulin resistance by increasing the ability of pancreatic α and β cells to sense and respond appropriately to glucose[18,19]. The efficacy, safety and tolerability of the combination of vildagliptin and metformin have been confirmed in several randomized controlled trials (RCTs)[20–24].

Given the primary role of dysfunctional pancreatic β cells rather than impaired insulin sensitivity in development of T2DM[25,26] and the inherently progressive nature of the T2DM disease with typical decline in islet function by already almost 50% at the time of initial diagnosis[25], a need for T2DM treatments that maintain or increase existing pancreatic β cell function or mass has been emphasized in the appropriate management of this highly prevalent disease[8]. Neither sulfonylureas nor metformin were shown to protect β cells from apoptosis and thus attenuate the decline in islet function in pre-clinical studies[27,28]. Drugs modulating the incretin system, on the other hand, i.e. the DPP-4 inhibitors via augmenting endogenous GLP-1 and GIP levels, have been suggested to meet this need[29] in relation to fewer side effects and likelihood of offering protection of β cells from accelerated apoptosis which otherwise leads to reduced pancreatic β cell mass and thus, at least in part, the impaired islet function[8,26–28]. Accordingly, data from clinical studies in T2DM patients have confirmed that DPP-4 inhibitors improve markers of β cell function[30,31].

Given the remarkable increase in the prevalence of the disease in Turkey consistent with the worldwide increasing trends, data from observational studies are needed to complement RCTs by providing data on the efficacy and safety/tolerability of treatment strategies in real-life clinical practice[10,32]. Therefore, the GALATA (GALvus safety and efficacy Assessment in Turkish populAtion) study, a 6 month prospective, single-arm cohort study in patients with T2DM, was the first observational multicenter study in Turkey designed to determine the tolerability/safety and efficacy of vildagliptin add-on to metformin, in routine daily practice.

Patients and methods

Study population

This multicenter, single-arm, 6 ± 1 month observational, prospective cohort study enrolled T2DM ≥18 year old outpatients, receiving vildagliptin and metformin as the only antidiabetic therapy for ≤4 weeks. Patients remained on vildagliptin and metformin regimen per se during the entire study period. This study was performed between February 2011 and May 2013 by endocrinologists and internal medicine specialists from 39 tertiary-care centers including university and research/training hospitals across Turkey.

Exclusion criteria included requirement for ≥3 oral antidiabetics (OADs); insulin treatment; history of acute metabolic diabetic complications, including ketoacidosis or hyperosmolar coma, during the past 6 months; renal impairment (creatinine clearance <60 mL/min); acute events that may affect renal functions (including dehydration, serious infection, shock, iodine-containing contrast compounds); any acute or chronic condition that could lead to tissue hypoxia (such as myocardial infarction, shock, sepsis within the past 6 months, or cardiac or respiratory failure requiring pharmacological treatment); impaired hepatic function (pre-treatment alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels higher than 2.5 times the upper normal limit), cirrhosis or portal hypertension; history of alcohol abuse or acute alcohol intoxication; known sensitivity or allergy to the study drugs or to other drugs of the same class or to the excipients in these drugs; pregnancy or breastfeeding; or type 1 or secondary DM (e.g. from Cushing's disease or acromegaly).

Since the study was designed to investigate real-life clinical practice, the choice of treatment for individual patients was based solely on the investigator's decision

before the study. Patients who decided to receive vildagliptin and metformin per se as antidiabetic treatment were enrolled in the study. The investigator was not requested to perform any additional tests, analyses or follow-up procedures aside from those involved in daily practice. The study did not impose any obligation on the investigator regarding treatment. Therefore, no specific schedule was developed for frequency and time of follow-ups, with the investigator determining the frequency of patient monitoring. To improve data quality, it was recommended that patients be assessed at least once between the baseline and the final visit at 6 ± 1 months, although the decision was at the discretion of the investigator.

Written informed consent was obtained from each subject following a detailed explanation of the objectives and the protocol of the study. The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and was approved by the Ministry of Health in line with the local regulatory requirements.

Study parameters

The primary study endpoint was rate of hypoglycemic events, while efficacy was the secondary end-point. Hypoglycemia decision was mainly based on the clinical judgment of the investigator. To better reflect real-life situations, hypoglycemia was defined as the presence of cholinergic symptoms, including tachycardia, palpitation, and/or shivering; central symptoms, including stupor, hunger, blurred vision, motor dysfunction, confusion and misbehavior; or as self-measured low plasma glucose levels.

The safety population consisted of all enrolled patients. Tolerability related conditions commonly observed during oral antidiabetic treatment (hypoglycemic events, gastrointestinal events, peripheral edema and weight gain) were questioned. All adverse and serious adverse events were documented at each visit and classified according to the Medical Dictionary for Regulatory Activities (MedDRA).

Efficacy was evaluated by assessing changes in glycemic parameters, including fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and hemoglobin A1c (HbA1c) levels.

Demography (age and gender) and medical characteristics (duration of T2DM and drug dosages) were recorded at baseline. Anthropometric measurements (body weight and body mass index [BMI]), vital signs (heart rate and blood pressure), glycemic parameters (FPG, PPG, HbA1c) and the proportion of patients who achieved HbA1c targets of $\leq$7.0% and $\leq$6.5% were evaluated as changes from baseline to the end of the study at 6 ± 1 months (150–210 days). Efficacy was also evaluated in patients sub-grouped by baseline HbA1c levels ($\leq$8% vs. 8–10% vs. $\geq$10%), age ($\leq$65 vs. >65 years) and BMI (<30 vs. $\geq$30 kg/m^2).

Statistical analysis

The study assumed that the documented incidence of symptomatic hypoglycemic events would be 1% with vildagliptin and metformin and 3% with other OADs. Assuming a documented symptomatic hypoglycemic event incidence of 1%, a sample size of 820 patients was required to ensure a power of 99% at a significance level of 0.05. An a priori 35% dropout rate was assumed, resulting in a planned 1125 patients in this study. However, only 665 patients could be recruited during the study period. Nevertheless, the calculated power of the study was above the lower limit deemed acceptable (80%) in applied and clinical medical research, both for 665 patients (97.6%) and for 289 patients followed up for 6 ± 1 months; 83%, based on *post hoc* power analysis.

Due to the 'real life' nature of the trial, the collected data consisted only of the available results; no action was taken regarding any missing data.

All statistical analyses were performed using the Statistical Package for the Social Sciences (version 21.0, SPSS Inc., Chicago, IL, USA). Changes from baseline in numeric variables (HbA1c level, FPG, PPG, body weight and BMI) were analyzed by repeated measures variance, using covariance effects of study center, follow-up duration and follow-up visit number. Data were expressed as mean $\pm$ standard deviation (SD), median (minimum to maximum), and percentage. Where appropriate, 95% confidence intervals (CIs) were determined. A p value <0.05 was considered statistically significant.

Results

Patients' disposition, demographics and clinical characteristics

A total of 665 patients were enrolled in the study. The whole population was used for demographics, baseline characteristics, tolerability, and safety analyses. Patients' mean $\pm$ SD age was 55.1 ± 10.2 years and 59.2% of the patients were female. Mean $\pm$ SD duration of T2DM was 62.3 ± 63.4 months, with 34.1% of these patients having the disease for more than 5 years. Biguanides (metformin, 78.5%), followed by sulfonamides (16.8%), were the most common antidiabetic agents received by patients prior to vildagliptin and metformin initiation (Table 1). Vildagliptin dosage was median 100 mg (range 50–100), and metformin dosage was median 2000 mg (range 500–3000). Of the 665 enrolled patients, 289 (43.5%) were evaluated at 6 ± 1 months (median follow-up 186.0 days); only data from these patients were analyzed for efficacy, in agreement with the study protocol. Of the 178 (26.8%) patients who discontinued the study, most (146, 22.0%) were lost to follow-up (Figure 1).

Anthropometric measurements and vital signs

Mean ± SD body weight changed from 84.1 ± 15.6 kg at baseline to 83.1 ± 16.4 kg at 6 ± 1 months ($p = 0.038$, $n = 245$), as did mean ± SD BMI, from 32.1 ± 6.4 kg/m^2 to 31.7 ± 6.3 kg/m^2 ($p = 0.011$, $n = 244$). There was no change in systolic blood pressure whereas mean ± SD diastolic blood pressure decreased from 79.8 ± 10.4 to 78.2 ± 9.5 mmHg ($p = 0.040$, $n = 242$). In contrast, mean ± SD heart rate increased from 80.4 ± 8.5 to 85.3 ± 20.2 beats per minute (bpm) ($p = 0.001$, $n = 226$).

Table 1. Baseline demographic and clinical characteristics of patients.

Demographics	
Age, years ($n = 657$)	55.1 ± 10.2
≤65 years	538 ± 80.9
>65 years	119 ± 17.9
Gender ($n = 665$)	
Female	394 (59.2)
Diabetes mellitus duration, months ($n = 597$)	62.3 ± 63.4
<60 months	372 ± 55.9
≥60 months	227 ± 34.1
Anthropometrics	
BMI, kg/m^2 ($n = 613$)	31.9 ± 6.0
Body weight, kg ($n = 619$)	84.4 ± 15.4
Laboratory findings	
FPG, mg/dL ($n = 654$)	158.3 ± 49.5
FPG, mmol/l ($n = 654$)	8.79 ± 2.75
PPG, mg/dL ($n = 514$)	227.3 ± 78.6
PPG, mmol/l ($n = 514$)	12.62 ± 4.36
HbA1c, % ($n = 634$)	7.9 ± 1.4
Creatinine, mg/dL	0.8 (0.2; 0.3–1.9)
Previous antidiabetic medications[a]	*n* (%)
Biguanides (metformin)	522 (78.5)
Sulfonamides	112 (16.8)
Thiazolidinediones	35 (5.3)
Dipeptidyl peptidase 4 (DPP-4) inhibitors	34 (5.1)
Glinides	32 (4.8)
Alpha glucosidase inhibitors (acarbose)	27 (4.1)
Insulins	10 (1.5)

[a]Medications used prior to vildagliptin and metformin initiation.
SD: standard deviation; BMI: body mass index; FPG: fasting plasma glucose; PPG: postprandial plasma glucose; HbA1c: hemoglobin A1c.
Values are mean (SD), mean (SD; min–max) or *n* (%).

Hypoglycemia

Sixteen hypoglycemic events were reported in 1.5% ($n = 10$, 95% CI: 0.8–2.7%) of patients. The rate of hypoglycemia adjusted for 1000 patient-treatment years was 10.5% ($n = 70$, 95% CI: 8.4–13.1%). Eleven events were mild in severity. Although 13 events were suspected to be study drug related, treatment discontinuation was made in only one patient who experienced a severe hypoglycemic event. The patient completely recovered following discontinuation. Five patients completed the trial and four patients were lost to follow up. The highest number of hypoglycemic events observed in a single patient was four. The most frequently observed symptoms of hypoglycemia were hunger, sweating, blurred vision, tachycardia, tremor, weakness and dizziness, respectively. Previous episodes of hyper/hypoglycemia and unusual physical activity/exercise just before the event were the other noticeable components of the patient history in patients with hypoglycemic events.

Glycemic parameters

Glycemic parameters significantly improved with 6 months of vildagliptin and metformin treatment. The mean ± SD FPG level decreased from 155.1 ± 43.5

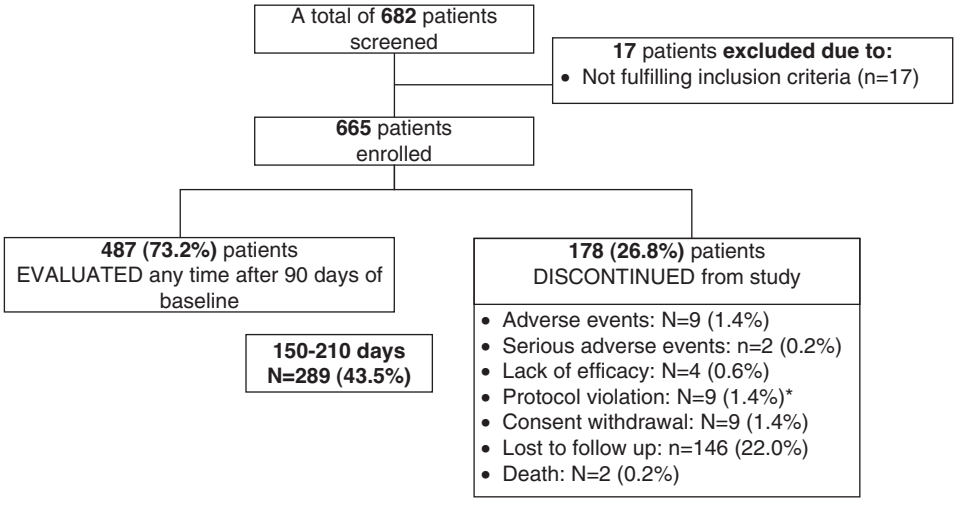

Figure 1. Patients' disposition regarding total enrolled patients ($n = 665$), discontinued patients ($n = 178$) and patients subjected to efficacy analysis ($n = 289$).

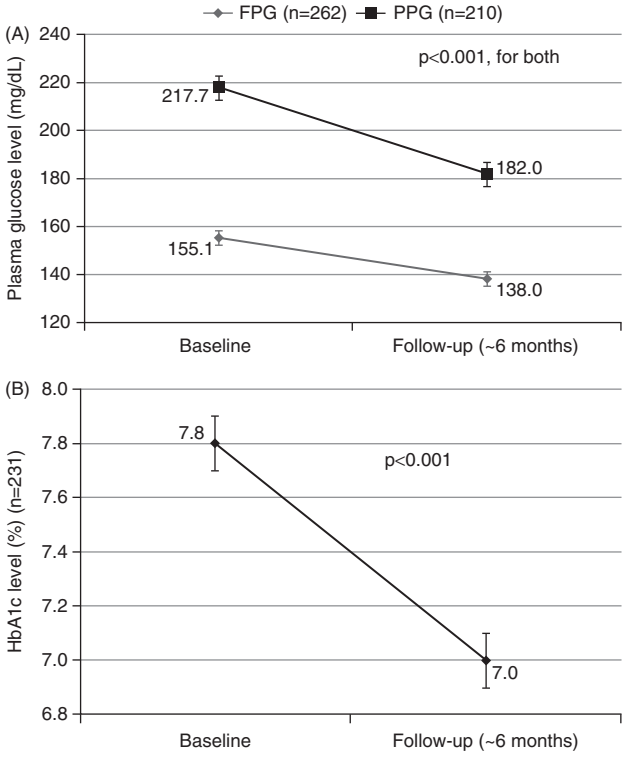

Figure 2. Glycemic parameters in patients treated with vildagliptin and metformin. Mean ± SD changes from baseline. (A) Fasting plasma glucose (FPG; mg/dL) and postprandial plasma glucose (PPG; mg/dL). (B) Hemoglobin (Hb) A1c (%). These results are from patients with both baseline and 6 ± 1 months of follow-up data.

(8.61 ± 2.41 mmol/l) to 138.0 ± 44.9 mg/dL (7.66 ± 2.49 mol/l) (17.1 mg/dL [0.95 mmol/l], $p < 0.001$). The change was 35.7 mg/dL (1.98 mmol/l) for mean ± SD PPG (from 217.7 ± 76.3 to 182.0 ± 69.9 mg/dl [12.08 ± 4.23 to 10.10 ± 3.88 mmol/l]) (Figure 2A and Table 2). Mean ± SD HbA1c improved by 0.8% and decreased from 7.8 ± 1.3 to 7.0 ± 1.4 ($p < 0.001$) (Figure 2B and Table 2). The percentages of patients who achieved HbA1c targets of ≤6.5% and ≤7.0% increased as well ($p < 0.001$ each, Table 2). These changes were independent of baseline HbA1c (≤8% vs. 8–10% vs. ≥10%), age group (>65 vs. ≤65 years) and BMI (<30 vs. ≥30 kg/m^2) (Tables 3–5).

Safety and tolerability

During the course of the study, 71 (10.7%) patients experienced 136 adverse events (AEs), while gastrointestinal disorders (32 events in 29 [4.4%] patients) were the mostly commonly observed category according to system-organ classification. Sixty-nine (50.7%) of these events was suspected to be study drug related and observed in 27 (4.0%) patients. Overall, 4 (2.9%) AEs were reported to be severe: hypoglycemia and fatigue in a single patient;

Table 2. Changes in glycemic parameters from baseline to 6 ± 1 months – efficacy data set ($n = 289$).

	N	Baseline Mean ± SD	6 ± 1 months Mean ± SD	p Value
FPG				
(mg/dL)	262	155.1 ± 43.5	138.0 ± 44.9	<0.001
(mmol/L)		8.61 ± 2.41	7.66 ± 2.49	
PPG				
(mg/dL)	210	217.7 ± 76.3	182.0 ± 69.9	<0.001
(mmol/L)		12.08 ± 4.23	10.10 ± 3.88	
HbA1c (%)	231	7.8 ± 1.3	7.0 ± 1.4	<0.001
Target achievement	289	*n* (%)	*n* (%)	
HbA1c ≤6.5%		31 (10.7)	97 (33.6)	<0.001
HbA1c ≤7.0%		64 (22.1)	152 (52.6)	<0.001

FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; PPG: postprandial plasma glucose; SD: standard deviation.

two patients hospitalized and died in neurology clinics (one due to cerebrovascular trauma as a result of falling and the other one with a history of heart failure, myocardial infarction and coronary by-pass surgery due to a cerebrovascular hemorrhage). Six-week pregnancy was reported in a patient who had been treated with vildagliptin and metformin for 2 months and treatment was discontinued. Spontaneous abortion occurred after 1 month of discontinuation and was suspected to be drug-related (Table 6).

Most commonly observed gastrointestinal adverse events were nausea ($n = 7$, 1.1%), diarrhea ($n = 6$, 0.9%) and constipation ($n = 4$, 0.6%). No severe gastrointestinal adverse events were reported, whereas seven patients experienced moderate and 21 experienced mild gastrointestinal adverse events (severity was not evaluated for one patient). Only six of 29 gastrointestinal events were suspected to be related to the study drug. Gastrointestinal adverse events required no intervention in 21 patients, resulted in treatment withdrawal in two patients, transient withdrawal of the drug or dose adjustment in five patients, initiation of additional treatment in one patient, and hospitalization in none of the patients. Overall, gastrointestinal adverse events were continuing in three patients at the last visit, while resolved in 26 patients. Of the other tolerability related AEs, weight gain and peripheral edema were reported in nine (1.4%) and six (0.9%) patients, respectively.

Blood amylase/lipase levels showed slight to moderate elevation in one (0.2%) patient and study drug was stopped. Pancreatitis was not reported in any case. Hepatic enzymes (AST/ALT) increased in three (0.5%) patients; events were suspected to be treatment related and after discontinuation of the drug complete recovery occurred. Urine creatinine increase and proteinuria were observed in one (0.2%) patient. The case was not suspected to be study drug related, treatment continued and

Table 3. Glycemic parameters at baseline and 6 ± 1 months of follow-up in patients grouped by baseline HbA1c levels – efficacy data set ($n = 289$).

	Patients with baseline HbA1c ≤8%				Patients with baseline HbA1c 8–10%				Patients with baseline HbA1c ≥10%			
	N	Baseline Mean ± SD	6 ± 1 months Mean ± SD	*p* Value	*N*	Baseline Mean ± SD	6 ± 1 months Mean ± SD	*p* Value	*N*	Baseline Mean ± SD	6 ± 1 months Mean ± SD	*p* Value
FPG (mg/dL)	166	139.6 ± 30.2	131.4 ± 37.2	0.006	68	168.3 ± 34.1	142.0 ± 48.1	<0.001	20	228.9 ± 60.3	174.3 ± 67.1	0.006
(mmol/L)		7.75 ± 1.68	7.29 ± 2.06			9.34 ± 1.89	7.88 ± 2.67			12.7 ± 3.35	9.67 ± 3.72	
PPG (mg/dL)	136	195.9 ± 62.4	176.1 ± 69.7	0.047	56	247.3 ± 71.1	185.0 ± 56.8	<0.001	13	308.5 ± 113.8	226.2 ± 104.6	0.007
(mmol/L)		10.87 ± 3.46	9.77 ± 3.87			13.73 ± 3.95	10.27 ± 3.15			17.12 ± 6.32	12.55 ± 5.80	
HbA1c (%)	155	7.1 ± 0.6	6.7 ± 1.0	<0.001	58	8.8 ± 0.6	7.2 ± 1.4	<0.001	18	11.0 ± 0.9	8.6 ± 2.4	<0.001

FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; PPG: postprandial plasma glucose; SD: standard deviation.

complete recovery occurred. The overall change for hepatic enzymes and creatinine levels did not point out an increase in patients having both baseline and a repeat laboratory evaluation at 6 ± 1 months.

Discussion

Real-life studies have gained importance in recent years, as they reflect routine clinical experience and provide an opportunity to observe how drugs work in daily life. The GALATA study was the first observational study to investigate the tolerability/safety and efficacy of a DPP-4 inhibitor, namely vildagliptin, as add-on to metformin in adult T2DM patients in Turkey. Its findings revealed that vildagliptin and metformin therapy was associated with no significant tolerability or safety concerns, while contributed to improved glycemic control, irrespective of baseline HbA1c, age or BMI. These results therefore confirmed the tolerability/safety profile and efficacy of vildagliptin in both RCTs and real-life trials and provided additional information on the use of vildagliptin and metformin combination therapy in patients with T2DM in clinical practice[10,14,20–24,33–36].

Low hypoglycemic potential is important in the management of T2DM[9]. A recent meta-analysis reported that DPP-4 inhibitor monotherapy was associated with lower risks of hypoglycemia and gastrointestinal AEs than metformin monotherapy, with the combination of vildagliptin and metformin reported to have better efficacy than metformin monotherapy without increasing the incidence of any AEs[15]. In the GALATA study, the tolerability and safety of vildagliptin and metformin treatment were evaluated by monitoring AEs, with special focus on hypoglycemia, gastrointestinal events, weight gain and peripheral edema, all of which are well known side effects of OADs. The tolerability/safety profile of vildagliptin and metformin treatment in our study population was consistent with the data from the RCTs, indicating that vildagliptin causes fewer hypoglycemic events than other OADs, is beneficial in controlling weight, does not induce edema, and is responsible for fewer gastrointestinal AEs[20–22]. Our finding, that only 1.5% of patients experienced hypoglycemia during the course of study, suggests that vildagliptin and metformin treatment is associated with a low incidence of hypoglycemia, as well as enabling patients to achieve targeted glycemic control[37].

Weight stability in our patients was in agreement with previously reported favorable effects of vildagliptin and metformin combination treatment[38] and confirmed that DPP-4 inhibitors were weight neutral drugs[5].

Overall, AE rate in this study (10.7%) was comparable to that observed in a previous vildagliptin and metformin observational study (9.5%) with a similar duration[10].

Table 4. Glycemic parameters at baseline and 6 ± 1 months of follow-up in patients grouped by age – efficacy data set ($n = 289$).

	Age ≤65 years				Age >65 years			
	N	Baseline Mean ± SD	6 ± 1 months Mean ± SD	*p* Value	*N*	Baseline Mean ± SD	6 ± 1 months Mean ± SD	*p* Value
FPG								
(mg/dL)	220	153.0 ± 41.0	136.9 ± 44.7	0.002	37	156.8 ± 52.5	143.2 ± 44.5	<0.001
(mmol/L)		8.48 ± 2.28	7.60 ± 2.48			8.70 ± 2.91	7.95 ± 2.47	
PPG								
(mg/dL)	180	214.2 ± 72.8	179.7 ± 68.6	0.002	29	241.2 ± 95.9	195.4 ± 77.9	<0.001
(mmol/L)		11.89 ± 4.04	9.97 ± 3.80			13.39 ± 5.32	10.84 ± 4.32	
HbA1c (%)	193	7.9 ± 1.4	7.0 ± 1.4	<0.001	35	7.6 ± 1.2	7.1 ± 1.2	<0.001
Target achievement	237	*n* (%)	*n* (%)		47	*n* (%)	*n* (%)	
HbA1c ≤6.5%		25 (10.5)	84 (35.4)	<0.001		6 (12.8)	12 (25.5)	<0.001
HbA1c ≤7.0%		55 (23.2)	126 (53.2)	<0.001		9 (19.1)	22 (46.8)	<0.001

FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; PPG: postprandial plasma glucose; SD: standard deviation.

Table 5. Glycemic parameters at baseline and 6 ± 1 months of follow up in patients grouped by body mass index (BMI) – efficacy data set ($n = 289$).

	BMI <30 kg/m^2				BMI ≥30 kg/m^2			
	N	Baseline Mean ± SD	6 ± 1 months Mean ± SD	*p* Value	*N*	Baseline Mean ± SD	6 ± 1 months Mean ± SD	*p* Value
FPG								
(mg/dL)	102	153.4 ± 44.8	136.4 ± 40.6	<0.001	149	153.9 ± 42.4	139.4 ± 48.8	<0.001
(mmol/L)		8.51 ± 2.49	7.57 ± 2.25			8.54 ± 2.35	7.74 ± 2.70	
PPG								
(mg/dL)	82	218.0 ± 74.6	183.2 ± 63.5	<0.001	124	216.1 ± 77.5	182.3 ± 74.0	<0.001
(mmol/L)		12.10 ± 4.14	10.17 ± 3.52			11.99 ± 4.30	10.12 ± 4.11	
HbA1c (%)	92	7.7 ± 1.4	6.9 ± 1.4	<0.001	136	7.9 ± 1.3	7.1 ± 1.4	<0.001
Target achievement	111	*n* (%)	*n* (%)		163	*n* (%)	*n* (%)	
HbA1c ≤6.5%		16 (14.4)	39 (35.1)	<0.001		15 (9.2)	53 (32.5)	<0.001
HbA1c ≤7.0%		27 (24.3)	60 (54.1)	<0.001		34 (20.9)	84 (51.5)	<0.001

FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; PPG: postprandial plasma glucose; SD: standard deviation.

The 0.8% reduction in HbA1c observed in a patient population with a baseline level of 7.8% was consistent with the reductions observed in other prospective real-life studies of patients with similar mean baseline HbA1c (7.8%) treated with vildagliptin and metformin, including the PROVIL study (0.9%); the VILDA study and a post-hoc analysis of the EDGE study (0.7%, in both)[10,33,34]. The slightly greater reduction (1.1%) in HbA1c observed in a large RCT of patients with a mean baseline HbA1c of 8.4% was reported to be related to the higher baseline HbA1c and the study design, which ensured better compliance with treatment[35].

We found that the percentage of patients with HbA1c ≤7.0% increased 2.4-fold, from 22.1% to 52.6%, after 6 ± 1 months of vildagliptin and metformin treatment. This was similar to changes from 22.1% to 54.0%, previously reported[27]. Moreover, the percentage of patients with HbA1c ≤6.5% increased 3.1-fold, from 10.7% to 33.6%, similar to that from ~7.0% to ~25% observed in the PROVIL study[10].

The mean change in FPG concentration at 6 months in this study was equivalent to the 0.95 mmol/L decrease reported in a previous RCT with similar baseline FPG[36]. In contrast, the change in FPG versus baseline (−17.0 mg/dL [−0.94 mmol/l]) in the GALATA trial was below changes observed in several other real-life studies and RCTs (approximately −30 mg/dL [−1.66 mmol/l])[10,39]. The high percentage of patients in our study (65%) with relatively low baseline mean FPG concentration (139.6 mg/dL [7.75 mmol/l]) compared to the above mentioned studies (160.4 to 178.2 mg/dL [8.90 to 9.89 mmol/l]) may explain the disparity among results. The decrease (35.7 mg/dL [1.98 mmol/l]) in PPG from baseline (217.7 mg/dL [12.1 mmol/L]) was also slightly lower than those reported in RCTs[35,36], in which the baseline PPGs were around 13 mmol/L. Overall, the HbA1c, FPG and PPG results supported findings showing that treatment-associated reductions in levels of glycemia are dependent on baseline irrespective of drug class[40]. Additionally the effectiveness of vildagliptin in lowering HbA1c was consistent across different subgroups including baseline HbA1c (≤8% vs. 8–10% vs. ≥10%) levels, age (>65 vs. ≤65 years) and BMI (<30 vs. ≥30 kg/m^2), indicating that the vildagliptin and metformin combination is a valuable

Table 6. Summary of adverse events.

	Vildagliptin + Metformin ($n = 665$)
Patients with at least 1 AE, *n* (%)	71 (10.7)
System organ class, *n* (%)	
Gastrointestinal disorders	29 (4.4)
Investigations	19 (2.9)
General disorders and administration site conditions	14 (2.1)
Endocrine disorders	13 (2)
Nervous system disorders	10 (1.5)
Skin and subcutaneous tissue disorders	9 (1.4)
Eye disorders	6 (0.9)
Cardiac disorders	4 (0.6)
Psychiatric disorders	3 (0.5)
Renal and urinary disorders	2 (0.3)
Respiratory, thoracic and mediastinal disorders	2 (0.3)
Metabolism and nutrition disorders	1 (0.2)
Pregnancy, puerperium and perinatal conditions	1 (0.2)
Vascular disorders	1 (0.2)
Serious or other significant events, *n* (%)	
Death[a]	2 (0.3)
Pregnancy	1 (0.2)
Adverse events	$n = 136$
Severity, *n* (%)	
Mild	72 (52.9)
Moderate	33 (24.3)
Severe	4 (2.9)
Not evaluated by the investigator	27 (19.9)
Relationship to study drug, *n* (%)	
Not suspected	67 (49.3)
Suspected	69 (50.7)

AE: adverse event.
[a]Death due to accident ($n = 1$) and cerebral hemorrhage ($n = 1$).

treatment option for broad T2DM populations with different patient characteristics.

This study had several limitations. First, due to its observational nature, there is a likelihood of patient inclusion bias. Second, the lack of interventions based on timing and number of follow-up visits, in accordance with the observational nature of this study, resulted in relatively limited follow-up data and a non-uniform frequency of patient visits. However, this was overcome by post hoc repeated measures variance analysis, which included the covariance effects of study center, follow-up duration and follow-up number of visits. Limiting our ability to attribute the efficacy regarding improved glycemic control exclusively to the vildagliptin and metformin regimen, lack of a control group is another limitation without which the level of evidence of the study would increase. However, given the single-arm cohort design of the study, efficacy conclusions were based on change in the efficacy parameters from baseline to the end of follow-up period in a 'real-life' setting. Additionally, we were unable to monitor factors such as diet, exercise and drug adherence, all of which could have affected diabetes control and have been frequently underestimated and underreported in routine daily practice. However, by providing data in a heterogeneous population consisting of 665 T2DM patients at 39 centers distributed throughout Turkey under real-life conditions, this trial is suggested to be a valuable source of information about the safety and effectiveness of vildagliptin and metformin, which may be applicable to the daily practice of DM management, besides making a contribution to the literature.

Conclusion

The findings of the GALATA study on the real-life experience of adult Turkish T2DM patients suggest a good overall safety/tolerability profile for vildagliptin and metformin treatment along with significantly improved glycemic control over 6 months irrespective of baseline HbA1c, age and BMI.

Transparency

Declaration of funding
The study was funded by Novartis Pharmaceuticals Turkey.

Declaration of financial/other relationships
G.A. has disclosed that he has received sponsorship from Novartis and research grants from Novartis and Novo Nordisk; he is on Astra Zeneca's Advisory Board and is a consultant to Eli Lilly; he is also on the Speakers' Bureau of AstraZeneca, BMS and Merck. L.K. has disclosed that she has received sponsorship and research grants from Novartis. F.A. has disclosed that she has received research grants from Novartis, Boehringer Ingelheim and Novo Nordisk. H.S.D. has disclosed that she has received sponsorship from Novartis, and has received research grants from Novartis and Sanofi Aventis; she is also on the Speakers' Bureau of Astra Zeneca. E.T. has disclosed that he has received research grants from Novartis, and is a consultant to Novartis and Astra Zeneca. I.B.A. and E.U. have disclosed that they are employees of Novartis.

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