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Effectiveness and tolerability of second-line therapy with vildagliptin vs. other oral agents in type 2 diabetes: A real-life worldwide observational study (EDGE)

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SUMMARY

Aim: Real-life studies are needed to confirm the clinical relevance of findings from randomised controlled trials (RCTs). This study aimed to assess the effectiveness and tolerability of vildagliptin add-on vs. other oral antihyperglycaemic drugs (OADs) added to OAD monotherapy in a real-life setting, and to explore the advantages and limitations of large-scale 'pragmatic' trials. **Methods:** EDGE was a prospective, 1-year, worldwide, real-life observational study in which 2957 physicians reported on the effects of second-line OADs in 45,868 patients with T2DM not reaching glycaemic targets with monotherapy. Physicians could add any OAD, and patients entered either vildagliptin or (pooled) comparator cohort. The primary effectiveness and tolerability end-point (PEP) evaluated proportions of patients decreasing $HbA_{1c} > 0.3\%$, without hypoglycaemia, weight gain, peripheral oedema or gastrointestinal side effects. The most clinically relevant secondary end-point (SEP 3) was attainment of end-point $HbA_{1c} < 7\%$ without hypoglycaemia or $\geq 3\%$ increase in body weight. **Results:** In this large group of T2DM patients, a second OAD was added at mean HbA_{1c} of $8.2 \pm 1.3\%$, with no baseline HbA_{1c} difference between cohorts. Second-line OAD therapy attained the PEP in the majority of patients, with higher attainment in those prescribed a vildagliptin-based regimen. The adjusted odds ratio was 1.49 (95% CI: 1.42, 1.55; $p < 0.001$). In patients with baseline $HbA_{1c} \geq 7\%$, SEP 3 was achieved by 35% of patients on a vildagliptin-based combination and by 23% of those receiving comparator combinations. The adjusted odds ratio was 1.96 (95% CI: 1.85, 2.07; $p < 0.001$). Safety events were reported infrequently and safety profiles of vildagliptin and other OADs were consistent with previous data. **Conclusion:** EDGE demonstrates that in a 'real-life' setting, vildagliptin as second OAD can lower HbA_{1c} to target without well-recognised OAD side effects, more frequently than comparator OADs. In addition, EDGE illustrates that conducting large-scale, prospective, real-life studies poses challenges but yields valuable clinical information complementary to RCTs.

What's known

Randomised controlled clinical trials (RCTs) have established that vildagliptin is efficacious and well tolerated when used as second-line therapy in patients with inadequate glycaemic control while receiving monotherapy with other oral agents (or insulin). For example, when added to metformin, vildagliptin lowers HbA_{1c} by approximately 1% and has similar or more favourable safety and tolerability profiles as/than comparator agents. While RCTs have strong internal validity, the external validity (generalisability) of such findings requires a large non-interventional study.

What's new

The present prospective, 1-year, worldwide, observational study of more than 45,000 patients seen in normal clinical practice demonstrated that vildagliptin was highly effective and well tolerated, thus confirming results from a host of RCTs. Conduct of this study was challenging because of the large number of physicians involved and because of the observational nature of the study (open label, not randomised). Furthermore, although no incentive was offered, and physicians were to select the second-line oral therapy for patients prior to enrolling them in the study, the new agent, vildagliptin, was overrepresented by approximately 2 : 1. Baseline data confirmed the previously reported high prevalence of insufficient glycaemic control globally: 'failure' of first-line monotherapy was recognised, with physicians adding a second oral agent, at a mean HbA_{1c} of 8.2%.

Introduction

Type 2 diabetes mellitus (T2DM) is a progressive disease, for which combination therapies of diverse glucose-lowering drugs in addition to lifestyle interventions are needed to keep patients in good glycaemic control (1). This requires early recognition of failure of first-line therapy in order to keep HbA_{1c} within boundaries suggested by guidelines (1) and prevent long-term complications, as shown by the United Kingdom Prospective Diabetes Study (UKPDS) (2–4). The recent American Diabetes Association/European Association for the Study of Diabetes position statement suggests that choices should be made on the basis of effectiveness, tolerability, long-term safety, cost and patients' preferences, needs and values (1). However, most efficacy and tolerability data arise from randomised controlled clinical trials

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Disclosure

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(RCTs) that are criticised as not representing real clinical life, where the profile of the patient rather than a random choice will trigger the selection of the second-line therapy.

Despite the scientific rigour with which RCTs must be conducted, or perhaps because of such rigour, RCTs provide limited useful information about the effectiveness of a drug in the real world. Accordingly, there is an increasing call for pragmatic trials (5–7), conducted in a real-world setting, without stringent inclusion/exclusion criteria and other properties that limit generalisability of results. The present report describes a prospective, 1-year, real-life observational study conducted globally on the effectiveness and tolerability of the dipeptidyl peptidase-IV (DPP-4) inhibitor, vildagliptin, added to monotherapy with an oral antidiabetes drug (OAD), compared with any two-OAD combinations without any DPP-4 inhibitor (pooled). Physicians were invited to enrol patients with T2DM not reaching desired glucose control using one OAD at the moment when a second glucose-lowering agent was considered. Data were collected at baseline (BL) and at any time point in the next 12 months, with a required reporting at 12 months.

This large-scale real-life study sought to assess effectiveness (HbA_{1c} lowering of > 0.3%) and tolerability [absence of oedema, hypoglycaemia, significant body weight increase (≥ 5%) or discontinuation because of gastrointestinal side effects] of vildagliptin combinations vs. all other OAD two-agent combinations. EDGE also aimed to explore the advantages and limitations of large real-life studies.

Methods

Study design

EDGE (Effectiveness of Diabetes control with vildaGliptin and vildagliptin/mEtformin) was a 1-year, prospective, observational cohort study including 45,868 patients from 2957 centres in 27 countries from Europe, Central and Latin America, Asia and Middle East (Table S1). First patient/first visit occurred on 04 September 2008 and final patient/final visit occurred on 23 May 2011.

Adult patients (aged > 18 years) with T2DM and inadequate glycaemic control while receiving OAD monotherapy with a sulphonylurea (SU), metformin, thiazolidinedione (TZD), glinide, or α-glucosidase inhibitor (AGI), and for whom a second OAD was considered were eligible. Patients who were planned to initiate a DPP-4 inhibitor other than vildagliptin, or an incretin mimetic/analogue, or who required three or more OADs at study entry were excluded, as were patients changed from one OAD or OAD class to another at the time of study entry. Patients who were using insulin at the time of study entry and patients with a history of hypersensitivity to any of the study drugs or drugs of similar chemical classes were excluded.

Participants were required to provide written or oral informed consent (per country regulations) to have data collected and agree to follow all local medication labelling or prescribing requirements of their new OAD. Physicians chose glucose-lowering treatment for their patients at their discretion. To ensure non-interventional status, patient enrolment was agreed after the treatment decision was made. Suitable patients fell into one of two cohorts (vildagliptin or comparator). The term index therapy is used to represent the combination treatment initiated at enrolment. For any index therapy, a fixed dose combination, when available, was allowed.

Data collection

Demography (age, gender, race, height, ethnicity), body weight, medical history, creatinine to estimate the glomerular filtration rate (GFR) by the modification of Diet in Renal Disease (MDRD) method (8), date of diagnosis of T2DM, antidiabetes medications taken prior to study entry, newly initiated add-on OAD (second component of index medication), other medications (by class), most recent HbA_{1c} test date and result, and any other laboratory test dates and results were collected at BL during a routine office visit. After 12 months, the final data collected included body weight, changes to newly initiated index OAD, most recent HbA_{1c} test data and result, other laboratory test dates and results, adverse events (AEs) and serious AEs (SAEs) and study completion status. Interim assessments could occur at any time between BL and final study data collection, or early termination. Laboratory testing was performed on patients in line with normal medical practice and/or as defined by local prescribing information and/or at a time period judged appropriate by the physician. Because of the 'real-world' nature of the study, central laboratories were not used.

In keeping with the non-interventional observational design employed, monitoring was conducted only at centres with high enrolment (~5% of centres). However, physicians were requested to maintain source documents for each patient, including signed informed consent forms.

Effectiveness and tolerability end-points

Combined end-points, weighing effectiveness and tolerability were considered. The primary end-point (PEP) was defined as the proportion of patients having a treatment response (as defined by regulatory

agencies (9,10): HbA_{1c} reduction from BL to month 12 end-point > 0.3%) and no tolerability findings [peripheral oedema, hypoglycaemic event, discontinuation because of a gastrointestinal (GI) event, or weight gain ≥ 5%]. This cut-off for 'significant' weight gain was based on NIH guidelines (11,12). Hypoglycaemia was defined as symptoms suggestive of hypoglycaemia that resolved promptly on the administration of oral carbohydrate (including mild and severe events). Patients who could not be categorised as a success or failure (e.g. because of missing HbA_{1c} or body weight data at 12 month end-point) were considered non-evaluable. Non-evaluable patient data were considered failures in calculation of the odds ratio (OR) for success. The main analysis of the PEP utilised the per protocol (PP) population; data were censored if patient changed index therapy.

Secondary effectiveness end-points

There were three SEPs, listed below. SEP 1: treatment response without any of the following tolerability findings; peripheral oedema, hypoglycaemic event, discontinuation because of GI event, or weight gain ≥ 3% at 12 months; SEP 2: treatment response without ≥ 3% weight gain at 12 months or hypoglycaemic event; SEP 3: in patients with BL $HbA_{1c} \geq 7.0\%$, attainment of target HbA_{1c} level of < 7.0% at month 12 end-point, without ≥ 3% weight gain at 12 months or hypoglycaemic event.

Secondary safety end-points

This study also aimed to assess the safety profile of vildagliptin add-on dual therapy and the fixed dose combination of vildagliptin/metformin relative to comparator OAD dual therapy in a real-world setting with a focus on identified and potential risks described in the vildagliptin risk management plan. Specific attention was also given to hepatic safety under the supervision of an external vildagliptin Hepatic Adjudication Committee.

Sample size/power calculation

The sample size was calculated as driven by the critical secondary objective of SAE profile, which requires a very large sample size, and was also assessed for adequacy for the primary objective of treatment response. The overall sample size required to detect at least a two-fold increased risk of SAEs occurring with a frequency of ≥ 1/1000 person-years with a power of ≥ 80% (two-sided α set at 0.05) would be 23,511 patients followed up for 12 months in each cohort. Actual enrolment into the study was not balanced, with approximately two patients accrued in the vildagliptin cohort for every patient in comparison cohort (2 : 1 ratio). The proportion of responders (percentage of patients experiencing HbA_{1c} decrease of more than 0.3%) was assumed to be in the range of 50–60%, based on prior clinical study data. Power for detecting a treatment response was assessed considering the 2 : 1 ratio between cohorts, with 45,000 subjects, to be about 51%, 85% and 97%, respectively, for a true difference of 1%, 1.5% and 2%, respectively.

Analysis of primary and secondary effectiveness and tolerability end-points

The probability of success was analysed using a multivariable logistic regression model to calculate ORs with 95% confidence intervals (CIs). The covariates used were BL HbA_{1c}, BL BMI, race, region, age, gender, duration of T2DM, background OAD at study entry and 'patient type' (determined by underlying or comorbid conditions). The OR expresses odds in favour of success with vildagliptin or vildagliptin/metformin relative to odds in favour of success with comparator OADs. Propensity score (PS) methodology was used to overcome the potential of imbalance in the distribution of observed (and unobserved) covariates between the vildagliptin add-on dual therapy or vildagliptin/metformin arm and the comparator OAD dual therapy arm (13,14). The OR *per se* is unaffected by imbalances in sample size. Accordingly, the adjusted OR is an unbiased estimate of treatment effect not affected by difference in covariate or difference in allocation. The selection of confounders/covariates was based on clinical judgment, with input from the Steering Committee and statistical inference. Statistical tests were kept at a minimum to avoid multiplicity, and were predefined in the protocol.

Additional analyses

Blood HbA_{1c} levels were measured during clinic visits at the discretion of the physician, and these data were summarised by time window. The changes from BL to end of study in HbA_{1c} and body weight were also calculated, although statistical significance between cohorts was not assessed.

Ethics

The protocol for EDGE was approved by all local Independent Review Boards (IRBs) or Ethics Committees.

Results

Patient populations and baseline characteristics

Patients in whom it was not possible to retrieve adequate source documentation for the informed consent were excluded from the analysis. Thus, the

enrolled population comprised 45,868 patients with documented informed consent, but 2046 patients (1317 in the vildagliptin and 729 in the comparator cohort plus 31 without cohort assigned) were excluded because of inadequate source documentation or problems with quality/accuracy of data entry (Table 1). The Intention-to-Treat (ITT) population, used for BL demographics and safety analyses, comprised 28,442 patients newly receiving dual therapy including vildagliptin and 15,349 patients receiving a new non-DPP-4 inhibitor OAD added to prior monotherapy. The PP population was a subset of the ITT population used for the analyses of effectiveness end-points. This population, defined by the lack of protocol deviations, comprised 28,061 patients receiving vildagliptin, and 15,294 receiving a comparator. Tables S2A and S2B detail the reasons for discontinuation and protocol deviations.

Table 2 summarises baseline characteristics of the ITT population. Mean age of participants was 57.8 years and was similar in both cohorts. There were more male than female participants, and most patients were of Caucasian or Asian ethnicity. Mean BMI was 29 kg/m^2 and mean HbA_{1c}, 8.2%, both with large standard deviations, indicating the very heterogeneous population included in this study, based primarily on regional and ethnic differences. For example, the average HbA_{1c} was 7.9 $\pm$ 1.3% in Europe, 7.7 $\pm$ 1.3% in East Asia, 8.6 $\pm$ 1.1% in India, 8.5 $\pm$ 1.2% in the Middle East and 8.5 $\pm$ 1.7% in Latin America.

There were also clear imbalances between cohorts in baseline BMI (higher in vildagliptin than comparator cohort) and race, with vildagliptin cohort more predominantly Caucasian and comparator cohort more predominantly Asian. Such differences suggest that these factors influenced the physicians' choice of second-line therapy.

Mean duration of diabetes was 5.5 $\pm$ 5.3 years, with 58.4% of patients having diabetes diagnosis less than 5 years prior to study, but also 15.2% having greater than 10 years disease duration. Some grade of renal impairment was present in 50.9% of patients, predominantly categorised as mild. The vast majority of participants had one or more underlying or co-morbid conditions, the most common being cardiovascular disease which was present in a slightly higher percentage of the vildagliptin than comparator cohort (75.5% vs. 69.9%). All other reported underlying conditions were present in fewer than 10% of patients in either cohort, but again, the prevalence was slightly higher in vildagliptin than comparator cohort.

Table 1 Patient populations and flow

Enrolled*	**45,868**	
No cohort assignment	31	
	Vildagliptin Cohort	**Comparator Cohort**
Assigned to	29,759	16,078
No adequate source documentation at site; lack of quality & accuracy of data entry	1317	729
ITT†	28,442	15,349
Patients completed	24,504	14,114
Patients discontinued	3938	1235
Patients with $\geq$ 1 protocol deviation	381	55
Per protocol‡	28,061	15,294

*The enrolled population includes all patients who gave documented informed consent.
†The Intent-to-treat (ITT) population is a subset of the enrolled population and includes all patients who were assigned to new treatment at study start. Sites and/or patients identified with quality and compliance findings, irregular data were excluded from the ITT analysis population.
‡The per protocol (PP) population is a subset of the ITT population. The PP population was used for the analyses of effectiveness end-points. Patients with the following deviations at baseline assessment were excluded from the per protocol population:
- patients receiving DPP-4 inhibitors at baseline or within 1 month prior to baseline;
- patients receiving GLP-1 mimetics/analogues at baseline or within 1 month prior to baseline; patients receiving insulin at baseline;
- patients receiving only newly initiated monotherapy or more than two oral antidiabetic medications at baseline;
- drug-naive patients at baseline (patients not taking any diabetic medication prior to baseline);
- patients who swapped from one oral antidiabetic medication or class to another at baseline;
- patients receiving investigational drug at baseline or 30 days prior to baseline or 5 half-lives prior to baseline;
- patients receiving more than one oral antidiabetic medication prior to baseline.

Table S3 reports index therapies in the ITT population by cohort. Most patients were receiving monotherapy with metformin prior to entering the study (81.5%). In the vildagliptin cohort, 24,854 (87.5%) of patients received vildagliptin added to metformin and 2936 (10.3%) received vildagliptin added to SU. In comparator cohort, 10,779 (70.3%) of patients received prior metformin monotherapy and 3833 (25%) of patients received prior SU monotherapy.

Table 2 Demographic and patient baseline characteristics (ITT Population)

Characteristic Mean ± SD or n (%*)	Vildagliptin N = 28,442	Comparator N = 15,349	Total N = 43,791
Mean age (years)	57.9 ± 11.8	57.6 ± 11.7	57.8 ± 11.8
Age group ≥ 65 years	8542 (30.0)	4375 (28.5)	12,917 (29.5)
Gender			
Male	15,623 (54.9)	8367 (54.5)	23,990 (54.8)
Female	12,819 (45.1)	6982 (45.5)	19,801 (45.2)
Race			
Caucasian	14,454 (50.8)	6461 (42.1)	20,915 (47.8)
Black	137 (0.5)	86 (0.6)	223 (0.5)
Asian	7813 (27.5)	6307 (41.1)	14,120 (32.2)
Native American	318 (1.1)	60 (0.4)	378 (0.9)
Pacific islander	6 (0.0)	1 (0.0)	7 (0.0)
Other	5714 (20.1)	2434 (15.9)	8148 (18.6)
Region			
East Asia	1661 (5.8)	740 (4.8)	2401 (5.5)
Europe	15,582 (54.8)	6491 (42.3)	22,073 (50.4)
Latin America	3065 (10.8)	781 (5.1)	3846 (8.8)
Middle East	2513 (8.8)	2266 (14.8)	4779 (10.9)
India	5621 (19.8)	5071 (33.0)	10,692 (24.4)
Mean BMI (kg/m^2)	29.3 ± 5.3	28.4 ± 4.8	29.0 ± 5.1
BMI group: n (%)			
BMI < 25	5234 (19.0)	3494 (23.7)	8728 (20.6)
BMI 25–< 30	11,928 (43.2)	6757 (45.8)	18,685 (44.1)
BMI 30–< 35	6899 (25.0)	3213 (21.8)	10,112 (23.9)
BMI ≥ 35	3525 (12.8)	1292 (8.8)	4817 (11.4)
Missing	856 (3.0)	593 (3.9)	1449 (3.3)
Mean baseline HbA_{1c} (%)	8.2 ± 1.3	8.2 ± 1.3	8.2 ± 1.3
HbA_{1c} group: n (%)			
HbA_{1c} ≤ 8.0%	14,670 (54.4)	7831 (53.3)	22,501 (54.1)
HbA_{1c}> 8.0–9.0%	7001 (26.0)	4117 (28.0)	11,118 (26.7)
HbA_{1c} ≥ 9.0%	5275 (19.6)	2733 (18.6)	8008 (19.2)
Missing	1496 (5.3)	668 (4.4)	2164 (4.9)
Mean duration of T2DM (years)	5.5 ± 5.4	5.4 ± 5.2	5.5 ± 5.2
Duration of T2DM group: n (%)			
< 5	16,454 (57.9)	9114 (59.4)	25,568 (58.4)
5–< 10	7539 (26.5)	4007 (26.1)	1156 (26.4)
≥ 10	4446 (15.6)	2228 (14.5)	6674 (15.2)
Missing	3 (0.0)	0 (0.0)	3 (0.0)
Renal impairment group (eGFR)[†]			
Normal	7470 (49.8)	3893 (47.8)	11,363 (49.1)
Mild	6579 (43.9)	3695 (45.3)	10,274 (44.4)
Moderate	876 (5.8)	511 (6.3)	1387 (6.0)
Severe	72 (0.5)	52 (0.6)	124 (0.5)
Missing	13,445 (47.3)	7198 (46.9)	20,643 (47.1)

Table 2 Continued

Characteristic Mean ± SD or n (%*)	Vildagliptin N = 28,442	Comparator N = 15,349	Total N = 43,791
Underlying conditions (patient 'type')‡			
Cardiovascular disease	21,467 (75.5)	10,722 (69.9)	32189 (73.5)
Pulmonary disease	1328 (4.7)	550 (3.6)	1878 (4.3)
Liver disease	1503 (5.3)	559 (3.6)	2062 (4.7)
Diabetes complications	2209 (7.8)	1146 (7.5)	3355 (7.7)
Mixed/inflammatory/skin disease	2615 (9.2)	1018 (6.6)	3633 (8.3)

*Percentage (%) calculated as percentage of total available observations; percentage for missing values reported as percentage of total population N.
†eGFR (MDRD, ml/min/1.73 m^2): > 80 = normal, ≥ 50 to ≤ 80 = mild, ≥ 30 to < 50 = moderate, < 30 = severe renal impairment.
‡Patients can belong to multiple types.
CVD patient–Any of the following medical conditions present: Myocardial Infarction, Angina Pectoris, Ischaemic Heart Disease, Transient Ischaemic Attack, Stroke, Peripheral Vascular Disease, Hypertension, Dyslipidaemia, Hyperlipidaemia, Congestive Heart Failure, Impaired Renal Function or Oedema or any of the following drugs received: Aspirin and other Antiplatelet Drug, Anticoagulants, ACE Inhibitors, ARBS, Calcium Channel Blockers, Beta Blockers, Other Antihypertensive Agents, Thiazide/Loop diuretics, Other diuretics, Statins, Fibrates, Digoxin, Nitrates or Anti Arrhythmics.
Pulmonary patient–Any of the following medical conditions present: Chronic Obstructive Pulmonary Disease or Asthma or any of the following drugs received: Medications for Obstructive Airway Disorders or Systemic corticosteroids.
Liver patient–Any of the following medical conditions present: Hepatic Steatosis, Viral Hepatitis, Alcoholic Fatty Liver, Jaundice or Alcoholism.
Diabetic patient–Any of the following medical conditions present: Skin Ulcer, Diabetic Nephropathy, Hypoglycaemia, Diabetic Neuropathy or Diabetic Retinopathy.
Mix/inflammatory/skin patient–Any of the following medical conditions present: Skin Blister, Skin Infection, Skin Lesion, Skin Rash, Drug Allergy, Angioedema or Myalgia or any of the following drugs received: Antidepressants, Gonadotropins, Hormones (i.e., oral contraceptives, hormone replacement therapies, etc.) or Non-steroidal Anti-inflammatory Agent.

Primary and secondary end-points

Table 3 reports analyses of the PEP and SEPs. For all end-points, a benefit for vildagliptin-treated patients was observed, with 55.4% of vildagliptin-treated patients reaching the PEP of a decrease in HbA_{1c} > 0.3%, without peripheral oedema, ≥ 5% increase in body weight, hypoglycaemia or discontinuation because of GI side effects. The PEP was reached in 51.3% of comparator-treated patients, resulting in an OR of 1.18 (95% CI: 1.13, 1.22). As predefined in the protocol, PEP was adjusted for potential confounders such as age, BL HbA_{1c}, BL BMI, gender, region, comorbidities and cotreatments, and the OR rose to 1.49 (95% CI: 1.42, 1.55; p < 0.001). For PEP, there was an imbalance in the number and percentages of non-evaluable patients [7631 (27.2%) of vildagliptin- and 3569 (23.3%) of comparator-treated patients]. Since non-evaluable patients were considered failures, the ORs likely underestimate effectiveness and tolerability of vildagliptin. As indicated in Table 3, a similar advantage for vildagliptin-based therapies was seen for all SEPs, with special interest for SEP 3. This end-point (reaching HbA_{1c}< 7% after 12 months without weight gain of ≥ 3% or hypoglycaemia) may be considered the most clinically relevant. Here, 35.1% of vildagliptin-treated patients reached SEP 3, vs. 23.2% for comparator, resulting in an adjusted OR of 1.96 (95% CI: 1.85, 2.07, p < 0.001).

Figure 1 illustrates HbA_{1c} time course in both cohorts, with final HbA_{1c} changes at 12 months of −1.19% (95% CI: −1.21%, −1.18%) in vildagliptin-treated patients and −0.99% (95% CI: −1.01%, −0.97%) in comparator-treated patients (analysis not prespecified in protocol). Baseline body weight (mean ± SEM) was 81.4 ± 0.5 kg in the vildagliptin cohort and 77.9 ± 0.1 kg in the comparator cohort. The change from BL to end-point in body weight was −1.6 ± 0.03 kg with vildagliptin, and −0.3 ± 0.03 kg with comparator.

Safety analysis

Table S4 summarises AEs that occurred during study, listed by primary system organ class (SOC). The percentage of patients with any reported AE in any SOC was similar in vildagliptin (5.3%) and comparator cohorts (5.7%). The most affected categories per standardised MedDRA queries (broad search) were gastrointestinal non-specific inflammation and dysfunctional conditions (1.3% with vildagliptin, 1.16% with comparator), hyperglycaemia/new onset diabetes

Table 3 Primary and secondary efficacy and tolerability end-points (PP population)

	Success rate vildagliptin N = 28,061	Non-evaluable vildagliptin	Success rate comparator N = 15,294	Non-evaluable comparator	OR unadjusted (95%CI)	Adjusted OR (95% CI)	p-value
Primary end-point (PEP) Decrease HbA_{1c} > 0.3%, no hypoglycaemia, no significant weight gain (≥ 5%), no discontinuation for GI events, no peripheral oedema	15,536 (55.4)	7631 (27.2)	7852 (51.3)	3562 (23.3)	1.18 (1.13, 1.22)	1.49 (1.42, 1.55)	< 0.001
Secondary end-point 1 (SEP 1) Decrease HbA_{1c} > 0.3%, no hypoglycaemia, no weight gain (≥ 3%), no discontinuation for GI events, no peripheral oedema	15,066 (53.7)	7584 (27.0)	7170 (46.9)	3543 (23.2)	1.31 (1.26, 1.37)	1.64 (1.57, 1.72)	< 0.001
Secondary end-point 2 (SEP 2) Decrease in HbA_{1c} > 0.3% from BL to EOS without ≥ 3% weight gain or hypoglycaemia	15,071 (53.7)	7635 (27.2)	7177 (46.9)	3568 (23.3)	1.31 (1.26, 1.36)	1.64 (1.57, 1.72)	< 0.001
Secondary end-point 3 (SEP 3) In patients with BL HbA_{1c} > 7%, HbA_{1c} < 7% at EOS without hypoglycaemia or weight gain ≥ 3%	8027 (35.1)	4695 (20.5)	2940 (23.2)	2076 (16.4)	1.79 (1.70, 1.88)	1.96 (1.85, 2.07)	< 0.001

GI, gastrointestinal; BL, baseline; EOS, End of Study.

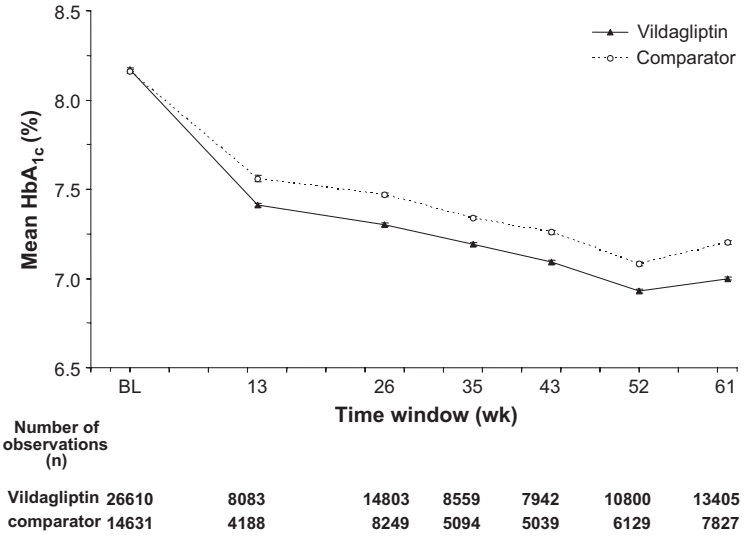

Figure 1 Time course of mean (± SEM) HbA_{1c} over ≥ 52 weeks of observation of large cohorts of patients with T2DM receiving vildagliptin and another OAD (solid line, filled triangles) or dual OAD, non-DPP-4 inhibitor combination therapy (dashed line, open circles). The numbers of observations available in each cohort, for each time window are provided below the figure.

mellitus (0.53% with vildagliptin, 1.60% with comparator) and acute pancreatitis (0.65% with vildagliptin, 0.44% with comparator).

Table S5 summarises SAEs. Overall, 178 cases were reported in the vildagliptin cohort (0.63%) and 65 in comparator cohort (0.42%). Forty-one cardiac disorders were reported in the vildagliptin cohort (0.14%) and 10 in comparator cohort (0.07%). Twenty-seven neoplasms were reported with vildagliptin (0.09%) and 25 with comparator (0.16%). Seventeen cases of hepatobiliary disorder (of which 10 were cholecystitis or cholelithiasis) were reported in the vildagliptin

cohort (0.06%) and 5 in comparator cohort (0.03%). Forty-six (0.16%) and 30 deaths (0.20%) were reported in the vildagliptin and comparator cohort, respectively.

Hypoglycaemia was reported by 72 patients (0.3%) in the vildagliptin cohort, with a total of 82 hypoglycaemic events, and by 180 patients (1.2%) in comparator cohort, with a total of 217 hypoglycaemic events. In the vildagliptin cohort, ten patients required third party assistance vs. 24 patients in comparator cohort.

Overall, liver function test abnormalities were infrequent. With vildagliptin, 411 of 9508 evaluable patients (4.3%) had bilirubin above ULN vs. 190 of 4691 (4.1%) patients receiving comparator(s). Four of 9334 (0.0%) of evaluable patients in the vildagliptin cohort had ALT $\geq 3 \times$ ULN and bilirubin $\geq 2 \times$ ULN vs. none (0.0%) of 4620 evaluable patients in comparator cohort. These cases (three pancreatic cancers and one alcoholic intoxication) were adjudicated and none were suspected to be related to study drug.

Discussion

In recent years, pleas to perform real-life studies to complement data on efficacy and safety of new drugs gathered from RCTs, have become louder, but reports on large, real-life treatment studies remain scarce. A notable finding of EDGE was the confirmation of the global high prevalence of suboptimal glycaemic control in patients with T2DM in real life (mean baseline HbA_{1c} was 8.2%), despite the worldwide efforts to create awareness of the importance of good glycaemic control in prevention of diabetic complications (15). Many factors may contribute to this suboptimal glucose control, like poor patient adherence to lifestyle modification advice or limited access to healthcare services or personnel, but also failure to monitor and intensify therapy may contribute. Indeed, it is unlikely that maximal doses of comparator OADs were always utilised, due at least in part to concern about potential side effects. Thus, the fact that vildagliptin does not need to be titrated may have contributed to its greater success.

Inadequate glycaemic control is present worldwide, but specific regions appear more problematic, such as India, Latin America and the Middle East. Increasing efforts will be needed to implement guidelines, since evidence that early, tight glycaemic control improves outcomes is overwhelming, as indicated by the long-term data from UKPDS (4).

Once the second agent was added, more than half of all patients successfully reached the PEP (treatment response, i.e., decrease in $HbA_{1c} > 0.3\%$, without peripheral oedema, hypoglycaemia, discontinuation because of GI side effects or $\geq 5\%$ increase in body weight). This composite end-point was chosen on the basis of the balanced decisions that clinicians need to make when choosing a glucose-lowering agent, namely the combination of efficacy [as defined by regulatory agencies (9,10)] and most common side effects. This composite decision-making is also acknowledged by the recent ADA-EASD guidelines, where efficacy and side effects, emphasising hypoglycaemia and weight gain in particular, are suggested to weigh in on the decision on which drug to choose. In the present composite primary end-point, we included additionally the most common side effect of TZD drugs and metformin, namely peripheral oedema and GI side effects, respectively. When limiting to the side effects emphasized in the ADA-EASD guidelines, and a more clinically acceptable therapeutic target, the proportion of patients (with baseline $HbA_{1c} \geq 7\%$) reaching $HbA_{1c} < 7\%$ after 12 months without weight gain $\geq 3\%$ or hypoglycaemia (SEP 3) was 35.1% with vildagliptin and 23.2% with comparator (adjusted OR = 1.96, 95% CI: 1.42,1.55; $p < 0.001$). Because non-evaluable patients were considered failures, the ORs likely underestimate effectiveness and tolerability of vildagliptin. This result is consistent with those from a *post hoc* analysis of RCTs of dual therapy with vildagliptin or glimepiride added to metformin, where the proportion of patients at target without hypoglycaemia or weight gain was 32.3% and 21.9% in vildagliptin and glimepiride group, respectively (16). Furthermore, HbA_{1c} reduction with addition of vildagliptin to prior monotherapy ($\Delta = -1.19\%$) was similar to those seen in RCTs (17–21) in patients with comparable baseline HbA_{1c} levels.

A strength of EDGE is the large sample size, clearly indicating the enthusiasm and interest of both patients and healthcare professionals to be part of such an undertaking. Here, however, also lies an important weakness, as patients were not only recruited in specialised centres, by experienced clinical researchers but also by doctors working in routine care, not accustomed to filling in data reports or being monitored by clinical research associates. To ensure quality of the data, we monitored high-recruiting centres, applied automatic data checks at data entry and queried inconsistent data. However, selecting only experienced clinical research physicians would not have been representative of the overall physician population, but this choice itself also impacted the overall results. A total of 2046 patients had to be excluded because of poor quality data, with physicians refusing to respond to queries asked before the database lock. Importantly, this led to missing effectiveness data, with 25% of the 12 month HbA_{1c} values missing. Such a percentage would be

unacceptable in an RCT, but it is in line with other real-life studies (22), some of which report even higher percentages of missing data (23).

Underreporting also occurred for safety events, as suggested by the low overall AE rate. In typical RCTs, there is a systematic and proactive search for AEs, which are reported on dedicated forms. Generally, in a 1-year RCT, the prevalence of AEs exceeds 60% or 70%. In this study, the detection and reporting of AEs were based on the voluntary reporting scheme which is the most widely used method to identify AEs for new drugs in clinical practice (24). One systematic review estimated that only 6% of all AEs are reported to the national spontaneous reporting system (25). It could be argued that physicians are more likely to report more serious events, particularly if known relation to the drug or causality can be inferred. In this study, SAEs were overall balanced between the two cohorts. Slight imbalances were seen in the cardiac and neoplasm SAEs but it is difficult to draw conclusion with such small numbers of events, especially in the context of a non-randomised study. However, overall the present safety/tolerability findings are in line with RCTs of vildagliptin showing no safety signals related to cardio- or cerebrovascular, pancreatitis, hepatic, immune system or skin-related disorders (26–28).

A final major limitation is the open nature of the trial, allowing doctors to select any drug, again aimed at reflecting real life. Unfortunately, although great care was taken in communicating to the participating physicians that their choice should only be guided by their clinical judgment, and no incentive was offered to promote selection of any agent, an important imbalance in treatment arms was present, clearly favouring the novel drug of the sponsoring company (29,759 patients on vildagliptin vs. 16,078 patients on comparator drugs). However, this may not reflect physician drug selection, but represents the number of patients agreeing to have their data collected (i.e., to be followed more closely) and factors other than the desire to explore the potential of new drugs may have driven the choice, as indicated by the imbalance in BMI and race also observed between treatment cohorts. To take into account this potential bias, propensity scoring was used to adjust the odds ratio.

Real-life studies are deemed necessary to complement information retrieved with RCTs. Randomised trials and real-life studies both have limitations and should be seen as complementary (7). It is important to understand the strengths and weaknesses of both approaches and trade-off between internal and external validity. The lack of randomisation, the choice of the investigators, the lack of a centralised laboratory, the lack of intensive monitoring–all characteristics applying to clinical practice–increase the generalisability and external validity of such studies, but at the expense of internal validity.

In conclusion, EDGE demonstrated in a real-life setting that T2DM patients in whom second-line oral glucose-lowering therapy is initiated, vildagliptin can succeed in lowering HbA_{1c} to < 7%, without weight gain, hypoglycaemia or peripheral oedema in a higher proportion than comparator OADs, with no differences in the reported number of AEs or SAEs. This information is consistent with data from RCTs with vildagliptin. Additionally, the EDGE study illustrates the strengths and limitations of real-world studies performed on a global scale.

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Author contributions

All authors had full access to all data, and take responsibility for the integrity of the data and accuracy of analyses. All provided input to the study design, data collection, data interpretation and preparation of the manuscript. CM and AHB co-chaired the steering committee.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Regions, countries, number of centres and patients participating in EDGE.

Table S2A. Number and reasons for discontinuations by cohort (ITT population).

Table S2B. Deviations from protocol requiring exclusion from the PP population by cohort.

Table S3. Index medication (ITT population).

Table S4. Adverse events by primary System Organ Class (SOC) and cohort (ITT population).

Table S5. Serious adverse events by SOC and cohort (ITT population).

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