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The effect of vildagliptin relative to sulphonylureas in Muslim patients with type 2 diabetes fasting during Ramadan: the VIRTUE study

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SUMMARY

Aims: To assess, in a real-world setting, the effect of vildagliptin compared with sulphonylurea (SU) treatment on hypoglycaemia in Muslim patients with type 2 diabetes mellitus (T2DM) fasting during Ramadan. **Methods:** This multinational, non-interventional study, conducted in Asia and the Middle East, included Muslim adult patients with T2DM who received treatment with vildagliptin or SU as add-on to metformin or monotherapy. During a ~16-week observation period, data were collected up to 6 weeks before and 6 weeks after Ramadan fasting. The primary study objective was to compare the proportion of patients with ≥ 1 hypoglycaemic event (HE) during fasting. **Results:** Of > 1300 patients enrolled in the study, 684 were treated with vildagliptin and 631 with SUs. Significantly fewer patients experienced ≥ 1 HE with vildagliptin compared with those receiving SUs (5.4% vs. 19.8%, respectively; $p < 0.001$); no vildagliptin-treated patients reported a grade 2 HE, vs. 4 SU-treated patients ($p = 0.053$). Mean HbA1c changes from baseline were vildagliptin: –0.24%, SUs: +0.02% ($p < 0.001$). Mean body weight reductions from baseline were vildagliptin: –0.76 kg, SUs: –0.13 kg ($p < 0.001$). A higher proportion of SU-treated patients experienced adverse events (AEs) compared with vildagliptin (22.8% vs. 10.2%). This difference was driven by hypoglycaemia as the most common AE. **Conclusions:** In this real-world study of fasting Muslim patients with T2DM, vildagliptin was associated with significantly fewer hypoglycaemic episodes compared with SU therapy. This outcome is particularly meaningful when viewed in the context of good glycaemic and weight control observed in vildagliptin-treated patients. Vildagliptin was well tolerated in this patient population.

What's known

- Many patients with diabetes fast during Ramadan despite fasting-related complications, including hypoglycaemia.
- Treatment with vildagliptin is associated with a reduced risk of hypoglycaemia compared with sulphonylurea (SU) treatment in patients with type 2 diabetes mellitus; this was observed in earlier studies in UK-based Muslim patients who fasted during Ramadan.

What's new

- To our knowledge, this is the largest study published to date assessing the relative benefit of dipeptidyl peptidase-4 inhibitor treatment in Muslim patients fasting during Ramadan.
- Treatment with vildagliptin is associated with a lower incidence of hypoglycaemic events compared with SU treatment during Ramadan fasting in a large representative cohort of Muslim patients.

Background

The global prevalence of diabetes is worryingly high and continues to grow, particularly in the emerging economies (1), including those with large Muslim populations. According to the International Diabetes Federation, four of the world's top 10 countries for the highest prevalence of diabetes are in the Middle East and North Africa region (2). Indeed, in 2012, 34 million people (one in nine adults) had diabetes in this region, and this number is expected to increase to almost 60 million by 2030 (2).

Of an estimated 1.57 billion Muslims worldwide, more than 50 million people with diabetes fast during the lunar-based month of Ramadan (3,4), a period when adult Muslims abstain from food, water, or use of oral medications between dawn and sunset for between 29 and 30 days each year. In people with diabetes, the pattern of daytime fasting and night-time meals, together with the use of anti-diabetic treatment, increases the risk of complications, including hypoglycaemia (3–5), which has a negative impact on morbidity, mortality and quality of life (6). The effect of fasting during Ramadan in patients with diabetes was examined in the Epidemiology of Diabetes and Ramadan study, which reported a significant 7.5-fold increase in the risk of severe hypoglycaemic events (HEs) in the overall population during Ramadan, compared with previous months (7). Although the consensus from religious and medical leaders is that Muslims with diabetes are generally not obliged to fast (8), a sig-

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Disclosures

Dr Monira Al-Arouj: Has received investigator fees related to conduct of the VIRTUE study; has received consultancy fees for advisory/speaker engagements for Novartis and its affiliates.
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nificant number will choose to fast nonetheless (3,7).

Given the growing global challenge of diabetes and fasting during Ramadan, as well as the considerable associated clinical consequences, a consensus document was developed by members of the American Diabetes Association (3). These recommendations advocate a holistic approach to the management of patients who fast, incorporating patient education, guidance on nutrition, frequent monitoring of glycaemia and individualised treatment plans. While there is no clear consensus on the most appropriate oral antihyperglycaemic treatment for fasting patients with type 2 diabetes mellitus (T2DM), use of oral medications associated with a low risk of hypoglycaemia is advocated whilst caution is advised with the use of agents associated with a higher risk in this regard, e.g. sulphonylureas (SUs).

Dipeptidyl peptidase-4 (DPP-4) inhibitors are an established treatment class in T2DM. Vildagliptin, a potent and selective DPP-4 inhibitor that improves glycaemic control by increasing α- and β-cell responsiveness to glucose, has been shown to reduce the risk of hypoglycaemia when compared with SUs (9,10). Moreover, a recent observational study of 72 fasting UK Muslim patients with T2DM (VECTOR), reported lower rates of hypoglycaemia with vildagliptin compared with gliclazide during Ramadan, thus indicating its potential suitability as an anti-diabetic treatment during fasting (11).

The encouraging results from the VECTOR study (11) and other exploratory research (12), together with the sizeable number of Muslim patients who undertake fasting worldwide (3,7), prompted the need for a large, multinational study of vildagliptin treatment in type 2 diabetic patients fasting during Ramadan. This study, VildagliptIn expeRience compared wiTh sulphonylUreas obsErved (VIRTUE) during Ramadan, was therefore undertaken to assess the relative effectiveness and safety of vildagliptin compared with SU treatment in a large, real-world population of patients from the Middle East and Asia.

Methods

Study design and patient population

This was a multicentre, post-authorisation, prospective study conducted in countries in the Middle East and Asia. As VIRTUE was conducted as a non-interventional study, in accordance with the definition applied by the European Medicines Agency (Directive 2001/20/EC), study-specific patient visits, tests and monitoring were not imposed, and only data originating from routine clinical practice were collected.

Male and female Muslim patients aged ≥ 18 years diagnosed with T2DM for ≥ 12 months prior to the start of Ramadan fasting and treated with vildagliptin or SU as add-on to metformin or as monotherapy (as per routine care and in compliance with the locally approved prescribing information) for ≥ 4 weeks and < 3 years prior to the start of fasting were eligible for inclusion in the study. In addition, patients were required to have baseline HbA1c ≤ 8.5%, measured within 6 weeks of study entry, and the intention to fast during Ramadan. Patients with contraindications to the medications of interest were excluded from the study, as were those requiring three or more oral anti-diabetic therapies or insulin therapy at the time of study entry. Use of any investigational drugs at the time, or within 30 days or five half-lives, of enrolment was also prohibited. Written informed consent to the collection and use of data was obtained from all participants, and the study was performed in accordance with the guidelines for Good Pharmacoepidemiological Practices, national requirements and regulations, in line with the ethical principles laid down in the Declaration of Helsinki.

During the observational period of approximately 16 weeks, data from at least two routine clinical visits were recorded: the baseline visit, occurring up to 6 weeks prior to the start of fasting, and a final visit within 6 weeks after the end of the Ramadan fasting period. Data were also collected from any additional patient visits occurring during the fasting period.

Outcome assessments

The primary study objective was to assess the proportion of patients with at least one HE during the fasting period in patients treated with vildagliptin and metformin dual therapy or vildagliptin monotherapy (where approved for this indication), and in patients treated with SU and metformin dual therapy or SU monotherapy. Patients were provided with an optional diary for recording hypoglycaemia-related symptoms and blood glucose levels, if measured. HEs were categorised by investigators as grade 1 (mild), defined as any reported symptoms by the patient and/or any blood glucose measurement < 3.9 mmol/l (70 mg/dl), and grade 2 (severe), defined as the need for third-party assistance. Secondary objectives included an assessment of changes in body weight and HbA1c from pre-fasting baseline, treatment adherence (proportion of patients from each cohort who did not miss more than 20% of the prescribed medication doses during Ramadan), and overall safety [as assessed by adverse event (AE) and serious AE (SAE) monitoring].

Statistical analyses

Data from identical protocols across 10 countries (Bangladesh, Egypt, India, Indonesia, Kuwait, Lebanon, Oman, Pakistan, Saudi Arabia and the United Arab Emirates), conducted under one umbrella protocol, were pooled for this report. As conduct of the study in Malaysia ($n = 80$) was inconsistent with the protocol, results were not included in this pooled analysis. Data from these patients will be the subject of a separate country analysis/report. The primary study variable was analysed using a two-sided Fisher's exact test performed on data from all patients who received one dose of the medication of interest at the beginning of Ramadan and had at least one efficacy assessment after the start of fasting [primary analysis set, (PAS)]. Apart from HbA1c assessments (PAS), other assessments were performed on the safety population, consisting of all patients who received at least one dose of the medication of interest at the beginning of Ramadan and had a least one safety assessment. HbA1c and body weight data were analysed using the last observation carried forward approach. Data analysis was performed by DATAMAP GmbH, Freiburg, Germany using SAS® Release 9.3 (SAS Institute Inc, Cary, NC).

Results

Patient disposition

Of 1333 patients enrolled into the study, 684 received treatment with vildagliptin and 631 received SU treatment; 18 patients did not receive medications of interest and were therefore excluded from subsequent analysis. Overall, 668 patients in the vildagliptin cohort (97.7%) and 620 patients in the SU cohort (98.3%) completed the study. Of the 16 patients in the vildagliptin cohort who discontinued, 15 (2.2%) were lost to follow-up and one patient (0.1%) died. Of the 11 patients receiving SU treatment who discontinued, 10 were lost to follow-up (1.6%) and one patient (0.2%) withdrew because of an unsatisfactory therapeutic effect.

All patients included in the study were from Asia (Pakistan 18.3%, India 8.2%, Bangladesh 7.5%, and Indonesia 3.2%) and the Middle East (Lebanon 24.5%, Egypt 19.1%, United Arab Emirates 10.1%, Oman 4.1%, Saudi Arabia 3.0%, and Kuwait 2.3%). Patient demographics and baseline characteristics were broadly similar between the two treatment groups (Table 1); mean patient age was 49.6 years, 58.7% of patients were male, mean body weight was 80.7 kg, mean body mass index was 29.0 kg/m^2, and the mean baseline HbA1c was 7.4%. There were small between-group variations in the proportion of patients aged ≥ 65 years (5.4% in the vildagliptin group and 10.9% in the SU group) and in the mean duration of T2DM (3.41 and 4.45 years in the vildagliptin and SU groups, respectively). At the start of Ramadan, the majority of patients were receiving dual therapy with metformin; 90.7% ($n = 607/669$) in the vildagliptin cohort and 86.7% ($n = 541/624$) in the SU cohort. Patients fasted for mean (SD) of 28.5 (3.86) days in the vildagliptin cohort and 28.6 (3.27) days in the SU cohort.

Table 1 Patient demographics and baseline characteristics (safety set)

Variable	Vildagliptin (n = 669)	Sulphonylurea (n = 624)
Age (years), mean (SD)	48.0 (10.9)	51.3 (10.7)
Age group, n (%)		
< 65 years	633 (94.6)	556 (89.1)
Gender, n (%)		
Male	386 (57.7)	373 (59.8)
Race, n (%)		
Caucasian	205 (30.6)	181 (29.0)
Black	8 (1.20)	6 (1.0)
Asian	289 (43.2)	286 (45.8)
Other	167 (25.0)	151 (24.2)
Weight (kg), mean (SD)	82.2 (15.7)	79.0 (16.3)
BMI (kg/m^2), mean (SD)	29.37 (5.16)	28.58 (5.13)
T2DM duration (years), mean (SD)	3.41 (3.18)	4.45 (4.27)
Baseline HbA1c (%), mean (SD)	7.34 (0.79)	7.44 (0.85)

BMI, body mass index; HbA1c, haemoglobin A1c; SD, standard deviation; T2DM, type 2 diabetes mellitus.

Frequency of HEs

For the primary study end-point, significantly fewer patients experienced ≥ 1 HE with vildagliptin ($n = 36/669$, 5.4%) compared with those receiving SUs ($n = 123/621$, 19.8%) [OR (95% CI) = 0.23 (0.156; 0.340), $p < 0.001$] (Figure 1A). No patients reported a grade 2 (severe) HE with vildagliptin compared with four patients receiving SUs ($p = 0.053$) (Figure 1B). The majority of patients experiencing hypoglycaemia during fasting reported a single HE [30 patients (4.5%) in the vildagliptin group and 109 patients (17.6%) in the SU group]. Overall, six patients (0.9%) experienced more than one HE in the vildagliptin group compared with 14 (2.3%) in the SU group.

A large proportion of reported HEs were confirmed by a corresponding low blood glucose measurement. Half of the 5.4% of patients reporting a HE in the vildagliptin cohort (2.7%) and almost two-thirds of the 19.8% of patients in the SU cohort with a HE (12.9%) had an accompanying blood

glucose measurement of < 3.9 mmol/l (70 mg/dl). Finally, a descriptive analysis found that a smaller proportion of patients experienced ≥ 1 HE with vildagliptin (n = 36/669, 5.4%) when compared with commonly used individual SU drug types: glimepiride (n = 63/351, 17.9%), gliclazide (n = 38/198, 19.2%), glibenclamide (n = 21/66, 31.8%) and glipizide (n = 1/8, 12.5%).

HbA1c and body weight changes

At the end of the study, the mean change in HbA1c from prefasting baseline levels was –0.24% in the vildagliptin group compared with +0.02% in the SU group (–0.26% between-treatment difference; p < 0.001) (Figure 2). Furthermore, weight changes pre- to post-Ramadan were –0.76 kg with vildagliptin compared with –0.13 kg with SUs, representing a mean between-treatment difference of –0.63 kg (p < 0.001) (Figure 3).

Adherence and medication changes

Treatment adherence during Ramadan was high, with a low and similar number of missed doses [mean (SD)] in the vildagliptin cohort [0.7 (3.36)] and the SU cohort [0.8 (2.66)]. Changes to diabetes medication were infrequent and more common in the SU-treated cohort than in the vildagliptin cohort; 9.9% of patients treated with vildagliptin had medication changes in preparation for Ramadan compared with 20.2% of patients in the SU cohort. Furthermore, 1.8% of patients in the vildagliptin cohort required medication changes during Ramadan compared with 4.6% in the SU cohort. Overall, few patients stopped the medication of interest [vildag-

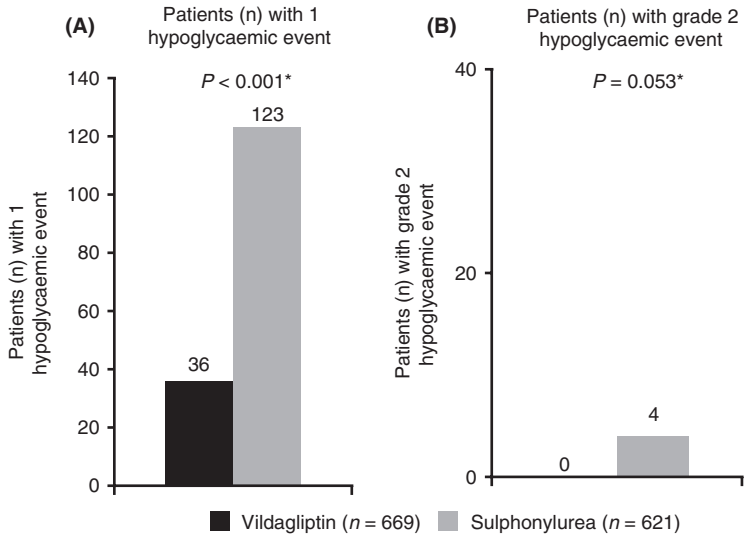

Figure 1 Number of patients with hypoglycaemic events (HEs) during Ramadan fasting. Includes patients with a postbaseline assessment of HEs. *Fishers exact test

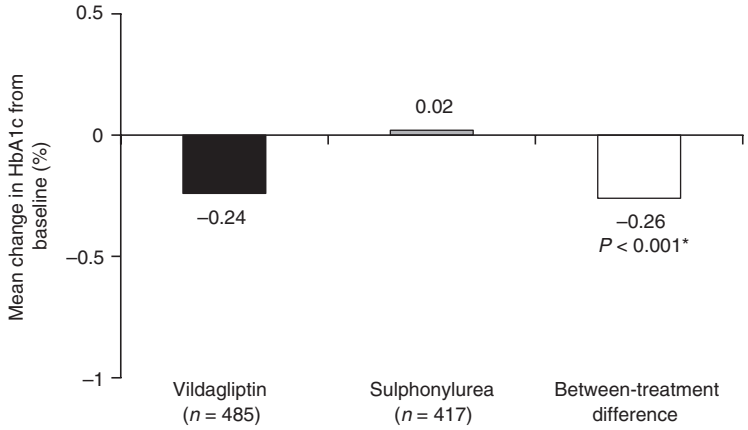

Figure 2 Mean change in HbA1c pre- to post-Ramadan in vildagliptin and SU cohorts. Primary analysis set of patients with both pre- and post-Ramadan HbA1c measurements. *Two sample t-test. Last observation carried forward

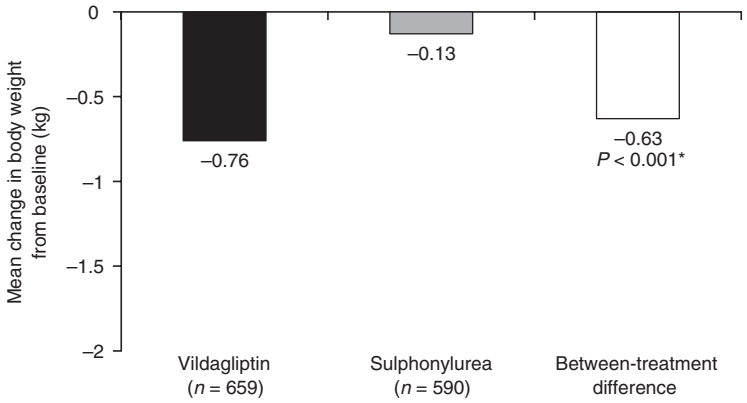

Figure 3 Mean change in body weight pre- to post-Ramadan in vildagliptin and SU cohorts. Patients with both pre- and post-Ramadan body weight measurements. *Two-sample *t*-test. Last observation carried forward

Table 2 Daily dose of diabetes medication at the start and the end of Ramadan fasting (safety set)

	Vildagliptin (n = 669)				Sulphonylurea (n = 624)			
	Start of Ramadan		End of Ramadan		Start of Ramadan		End of Ramadan	
	n*	Median dose (mg)	n*	Median dose (mg)	n*	Median dose (mg)	n*	Median dose (mg)
Metformin	604	1700.0	599	1700.0	536	1500.0	538	1500.0
Vildagliptin	665	100.0	664	100.0				
Glibenclamide					61	5.0	60	5.0
Gliclazide					195	60.0	196	60.0
Glimepiride					343	2.0	341	2.0
Glipizide					5	10.0	5	10.0

*Patients with dosage information provided for the medication of interest.

liptin: 1 (0.1%); SU: 4 (0.6%)] or had dose reductions during Ramadan [vildagliptin: 4 (0.6%); SU: 13 (2.1%)]. The median daily dose of the respective treatment of interest was the same at the beginning and end of Ramadan (Table 2).

Safety and tolerability

A higher proportion of SU-treated patients experienced AEs compared with patients treated with vildagliptin (22.8% vs. 10.2%, respectively; Table 3). This difference was driven by hypoglycaemia, which was reported as the most common AE, followed by pyrexia, nausea and vomiting (Table 3). The majority of AEs were mild in severity. Seven patients experienced SAEs, five of these were in the SU cohort (a transient ischaemic attack in one patient and hypoglycaemia in four patients). In the vildagliptin cohort, one patient experienced a myocardial infarction (resulting in death) and one had viral hepatitis. All non-hypoglycaemic SAEs were considered to be unrelated to the medication of interest.

Discussion

To our knowledge, this is the largest study to date assessing the relative benefit of DPP-4 inhibitor treatment in Muslim patients with T2DM fasting during Ramadan. Overall, over 1300 Muslim patients with T2DM were observed in routine clinical practice in 10 countries in Asia and the Middle East around the Ramadan fasting period.

The results of this observational study showed a significant and clinically relevant ~3.5-fold lower incidence of HEs with vildagliptin compared with SU treatment during Ramadan fasting in this large representative cohort of Muslim patients. This positive result is noteworthy in that it was achieved without episodes of severe hypoglycaemia in the vildagliptin

Table 3 Adverse events (safety set) occurring in ≥ 0.3% of any treatment cohort

	Vildagliptin n (%)	Sulphonylurea n (%)
Any adverse event	68 (10.2)	142 (22.8)
Hypoglycaemia	35 (5.2)	123 (19.7)
Pyrexia	8 (1.2)	8 (1.3)
Nausea	6 (0.9)	2 (0.3)
Vomiting	6 (0.9)	1 (0.2)
Diarrhoea	5 (0.7)	2 (0.3)
Abdominal pain	4 (0.6)	0 (0.0)
Headache	3 (0.4)	1 (0.2)
Abdominal discomfort	2 (0.3)	1 (0.2)
Asthenia	2 (0.3)	0 (0.0)
Restlessness	2 (0.3)	0 (0.0)
Hyperhidrosis	2 (0.3)	0 (0.0)
Peptic ulcer	0 (0.0)	2 (0.3)

cohort, and is consistent with findings from previous vildagliptin research undertaken in this patient population (11,12). Related to this end-point, a descriptive analysis assessing the usage of individual SUs and the frequency of HEs with these SUs is particularly interesting; the data suggest a preference for the use of glimepiride and gliclazide (approximately three quarters of the latter appeared to receive the modified release formulation of gliclazide), as opposed to glibenclamide, presumably as a consequence of the higher incidence of HEs reported previously with glibenclamide (13–15). Reassuringly, vildagliptin appeared to be associated with a lower incidence of HEs regardless of the individual SU employed; it is not immediately apparent as to why this consistent effect was not observed in studies with other DPP-4 inhibitors (14,16).

Vildagliptin improves glycaemic control primarily by the enhancement of pancreatic islet function (9). Blocking degradation of the incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), increases plasma levels of these peptides (17) and thereby increases the sensitivity and responsiveness of β- and α-cells to glucose (18). The low risk of hypoglycaemia associated with vildagliptin treatment (9,10) is likely to relate to the fact that GLP-1 enhancement of insulin secretion and inhibition of glucagon secretion are glucose dependent (19). Furthermore, evidence suggests that the low hypoglycaemic potential of vildagliptin relates to the ability to prevent or counteract hypoglycaemia through increased levels of intact (active) GIP (17), which stimulate glucagon secretion under hypoglycaemic conditions (20,21). The favourable HE outcomes observed in our study can therefore be reasonably explained by the mechanistic considerations described in the aforementioned research.

Vildagliptin treatment was associated with a modest, but significant reduction in HbA1c from baseline compared with SU treatment. This finding is not inconsistent with other vildagliptin studies conducted in fasting patients with T2DM (11,22). Whilst the magnitude of effect is smaller in this study, compared with the result observed in VECTOR (11), this is not unexpected given that patients in this study had a lower HbA1c at baseline and large differences in HbA1c would not be expected given the short study duration. In the VECTOR study (11), the difference in HbA1c was, at least in part, explained by treatment adherence differences between the two study arms; by comparison, in our study, adherence was high and similar for both treatment groups. An approximate characterisation of the magnitude of HbA1c reduction observed compared with other DPP-4 inhibitor studies in a similar population was not possible as this data does not appear to have been collected (16).

Small reductions in body weight from pre-fasting baseline were observed in both cohorts, with slightly greater reductions being observed with vildagliptin relative to SU treatment. The short study duration makes it difficult to draw more definitive conclusions from this result.

Considering all the data from VIRTUE as a whole, this study reaffirms previous evidence (derived principally from UK-based research (11,12)) indicating that vildagliptin treatment is associated with a lower incidence of HEs in comparison with SUs during fasting, but does so in a large cohort of patients from the Middle East and Asia who represent the majority of Muslim patients who fast during Ramadan. These encouraging hypoglycaemia data are particularly noteworthy when viewed in the context of good glycaemic and weight control observed in the vildagliptin patient cohort.

There are limitations to this study that deserve mention. Firstly, as this was an observational study, there are of course inherent limitations and bias that accompany reports of observational study work. Conversely, such research has enabled collection of real-world data from a patient cohort in a more naturalistic setting than could be achieved in a randomised, interventional clinical trial. Also in support of the reliability of the data, is the observation that reported results are in line with other vildagliptin-related research in this patient population. Finally, it should also be highlighted that the large size of this study (made feasible by undertaking this research in a non-interventional manner) increases the robustness of the findings and potentially improves generalisability

to the broader population of Muslim patients who fast. Another limitation is that, in line with the non-interventional nature of the study, reported HEs did not require mandatory confirmation with blood glucose measurements, which can potentially overestimate the number of events. Again, it is reassuring to observe that many investigators did collect these data as part of usual practice. In this regard, approximately half of all patients reporting HEs in the vildagliptin cohort and almost two-thirds in the SU cohort had accompanying blood glucose measurement values below 3.9 mmol/l (70 mg/dl). A final limitation relates to HbA1c and body weight data, which were reported in large number, but not for all patients; presumably this reflects differences in routine clinical practice by physicians across the various participating countries in the course of this observational study.

Conclusions

Vildagliptin therapy was associated with significantly fewer patients experiencing hypoglycaemia compared with SU therapy in this large representative cohort of fasting Muslim patients with T2DM. This outcome is particularly meaningful when viewed in the context of good glycaemic and weight control observed in vildagliptin-treated patients who fasted in this study. Vildagliptin was well-tolerated in this patient population.

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Authors' contributions

SH, SD and MYK were involved in the concept and design of the study. All authors were involved in data collection, analysis and/or interpretation of the results, as well as the critical revision and approval of the article.

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