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Association between vildagliptin and risk of angioedema, foot ulcers, skin lesions, hepatic toxicity, and serious infections in patients with type 2 diabetes mellitus: A European multidatabase, noninterventional, postauthorization safety study

Rachael Williams[1] | Wolfgang Kothny[2] | Carmen Serban[2] | Sandra Lopez-Leon[3] | Frank de Vries[4,5] | Raymond Schlienger[2]

[1]Clinical Practice Research Datalink, London, UK

[2]Novartis Pharma AG, Basel, Switzerland

[3]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA

[4]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

[5]Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre, Maastricht, The Netherlands

Correspondence
Rachael Williams, Clinical Practice Research Datalink (CPRD), Medicines and Healthcare products Regulatory Agency, 10 South Colonnade, Canary Wharf, London E14 4PU, UK.
Email: rachael.williams@mhra.gov.uk

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Novartis Pharma

Abstract

Objectives: This noninterventional, multidatabase, analytical cohort study explored whether vildagliptin is associated with an increased risk of specific safety events of interest, namely angioedema, foot ulcers, or skin lesions, adverse hepatic events, or serious infections compared with other noninsulin antidiabetic drugs (NIADs) using real-world data from five European electronic healthcare databases.

Design: Patients with type 2 diabetes mellitus aged ≥18 years on NIAD treatment were included between January 2005 and June 2014. Adjusted incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for the outcomes of interest were estimated using negative binomial regression.

Patients: Approximately 2.8% of the included patients (n = 738 054) used vildagliptin at any time during the study, with an average follow-up time of 1.4 years.

Results: The adjusted IRRs (vildagliptin vs. other NIADs) were in the range of 0.87-3.71 (angioedema), 0.73-1.19 (foot ulcers), 0.37-1.18 (skin lesions), 0.24-1.14 (composite of foot ulcer or skin lesions), 0.29-0.55 (serious hepatic events), and 0.59-1.04 (serious infections), with no lower bound of the 95% CIs > 1.

Conclusions: Overall, there was no increased risk of the events of interest in association with vildagliptin use compared with other NIADs.

KEYWORDS

angioedema, dipeptidyl peptidase-4 inhibitors, foot ulcers, hepatic toxicity, serious infections, skin lesions, type 2 diabetes mellitus, vildagliptin

1 | INTRODUCTION

Vildagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor has accumulated extensive efficacy and safety data from various meta-analyses of randomized controlled trials (RCTs), large RCTs, or noninterventional studies.[1] Its glycemic efficacy, reduced risk of hypoglycaemia, weight-neutral effect and favourable benefit-risk profile have made it an attractive treatment option for the management of patients with type 2 diabetes mellitus (T2DM) including those with renal impairment, heart failure, the elderly, or patients fasting during Ramadan.[1-3]

However, there has been an interest in specific safety outcomes that may be associated with DPP-4 inhibitors in general[4-6] as well as with vildagliptin specifically.[1] Findings from a small clinical study reported that decreased DPP-4 activity may increase substance P or bradykinin concentrations, which can potentially increase the risk of angiotensin-converting enzyme (ACE) inhibitor–associated angioedema.[7] Preclinical studies with cynomolgus monkeys reported vildagliptin-related skin lesions located on the distal extremities (including hands, feet, tips of ears, and tail) at high doses.[8] In-vitro studies showed suppression of human lymphocyte proliferation with vildagliptin,[9] which can potentially increase the risk of infections, this however, was not observed in in-vivo immunotoxicity studies.[10] Furthermore, two meta-analyses of RCTs in patients with type 2 diabetes mellitus also suggested an increased risk of all-cause infections (including nasopharyngitis, upper respiratory tract infection, and urinary tract infection) with DPP-4 inhibitors.[11,12] Rare cases of hepatic dysfunction (including hepatitis and elevated transaminases) were reported with vildagliptin use, which were however asymptomatic and nonprogressive.[3]

In this context, the present noninterventional, postauthorization safety study was undertaken by the marketing authorization holder of vildagliptin as part of a commitment to the European Committee for Medicinal Products for Human Use (CHMP),[13] to assess whether vildagliptin is associated with an increased risk of angioedema, foot ulcers, skin lesions, adverse hepatic events, or serious infections compared with other noninsulin antidiabetic drugs (NIADs) in a real-world setting.

2 | MATERIALS AND METHODS

2.1 | Study design

The present multidatabase, population-based, analytical cohort study used data from five European electronic healthcare databases: United Kingdom (UK), Clinical Practice Research Datalink General practice OnLine Database (CPRD GOLD); Germany, IMS Disease Analyzer (IMS DA Germany); France, IMS DA France; Denmark, Odense Pharmaco-Epidemiological Database (OPED); and Sweden, Swedish National Registers (for details, see Table S4).[13]

2.2 | Patients and study assessments

Patients with T2DM (defined as those having at least one prior record of T2DM, and no prior records of type 1 diabetes mellitus or other forms of diabetes) aged ≥18 years prescribed with vildagliptin (as single agent or as fixed-dose combination with metformin) or an NIAD (including biguanides, sulfonylureas, glinides, thiazolidinediones, DPP-4 inhibitors [other than vildagliptin], glucagon-like peptide-1 [GLP-1] analogs, α-glucosidase inhibitors, sodium-glucose co-transporter 2 [SGLT-2] inhibitors, and amylin analogs) on or after 1st January 2005 were included. The index date (start of follow-up) was defined by the date of the first NIAD prescription, thereby including prevalent and incident users. Patients with a history of cancer, HIV/AIDS, and/or history of insulin use prior to index date were excluded.

Patients were followed up from their index date to the earliest of the following: end of study (30th June 2014), patient's transfer out of the database, death, or date of first insulin prescription.

Demographic parameters (age, sex, body mass index [BMI]), NIAD use, specific comorbidities, and diabetes duration were determined using all available data prior to the index date. In addition, comedications of interest recorded within 6 months prior to the index date, representing recent use, were identified. Safety outcomes of interest included recorded incident events for angioedema; foot ulcer and/or skin lesions (as individual outcomes and as composite outcome); adverse hepatic events including serious hepatic events (eg, hepatitis, liver failure, cirrhosis, liver fibrosis, liver necrosis, ascites, hepatic coma, hepatic encephalopathy, portal hypertension), and hepatic enzyme abnormalities (separately as ALT or AST > 3-times upper limit of normal [ULN] together with bilirubin > 2-times ULN; and ALT or AST > 10-times ULN [only in CPRD GOLD]), as well as the composite endpoint of any hepatic toxicity (ie, serious hepatic events or hepatic enzyme abnormalities [only in CPRD GOLD]); and serious infections (defined as sepsis, pneumonia, or meningitis only in CPRD GOLD]). Read or ICD-10 codes were used to identify the outcomes of interest (for details, see Table S1). To focus on incident events (ie, first-time event after start of follow-up), patients with an outcome of interest recorded on or before the start of follow-up were excluded (eg, patients with a prior angioedema event excluded for the angioedema assessment).

2.3 | Statistical analysis

Demographics and other baseline characteristics were descriptively summarized by database and NIAD cohorts. The period of follow-up of patients was divided into periods of NIAD use. Patients could move over time between exposure categories and between NIAD types (vildagliptin, other NIAD); patients using vildagliptin concurrently with other NIADs were included in the vildagliptin cohort. Incidence rates (IRs) with 95% confidence intervals (CIs) for outcomes of interest in current vildagliptin and in current users of other NIADs were calculated per 1000 patient-years (PYs) by dividing the number of patients with an event of interest by the cumulative person-time of current exposure. Age- and sex-adjusted incidence rate ratios (IRRs) with 95% CIs were estimated using negative binomial regression. Statistical significance was assessed using adjusted *P*-values accounting for the false discovery rate (FDR).

TABLE 1 Baseline characteristics at the start of follow-up

Characteristic	CPRD GOLD (UK)		IMS DA (Germany)		IMS DA (France)		OPED (Denmark)		National Regis (Sweden)	
	Vildagliptin N = 1990	NIAD N = 211 327	Vildagliptin N = 13 286	NIAD N = 206 576	Vildagliptin N = 2982	NIAD N = 41 911	Vildagliptin N = 923	NIAD N = 23 725	Vildagliptin N = 569	NIAD N = 254 515
Age, y	59 ± 12	63 ± 14	63 ± 12	65 ± 13	62 ± 11	63 ± 12	61 ± 11	64 ± 13	60 ± 10	65 ± 12
18-39	108 (5.4)	9484 (4.5)	367 (2.8)	5829 (2.8)	65 (2.2)	1082 (2.6)	33 (3.6)	940 (4.0)	15 (2.6)	4270 (1.7)
40-64	1255 (63.1)	101 569 (48.1)	6864 (51.7)	87 379 (42.3)	1721 (57.7)	21 349 (50.9)	516 (55.9)	11 102 (46.8)	372 (65.4)	125 609 (49.4)
≥65	627 (31.5)	100 274 (47.4)	6055 (45.6)	113 368 (54.9)	1196 (40.1)	19 480 (46.5)	374 (40.5)	11 683 (49.2)	182 (32.0)	124 636 (49.0)
Women	842 (42.3)	90 815 (43.0)	5703 (42.9)	98 040 (47.5)	1174 (39.4)	17 765 (42.4)	572 (62.0)	13 700 (57.7)	216 (38.0)	104 933 (41.2)
Men	1148 (57.7)	120 512 (57.0)	7583 (57.1)	108 536 (52.5)	1808 (60.6)	24 146 (57.6)	351 (38.0)	10 025 (42.3)	353 (62.0)	149 582 (58.8)
BMI (kg/m^2)	33 ± 7	31 ± 7	32 ± 6	31 ± 6	–	–	–	–	31 ± 6	30 ± 5
<20	9 (0.5)	2685 (1.3)	32 (0.2)	594 (0.3)	–	–	–	–	3 (0.5)	1460 (0.6)
20-25	165 (8.3)	26 700 (12.6)	486 (3.7)	8308 (4.0)	–	–	–	–	68 (12.0)	42 751 (16.8)
26-29	591 (29.7)	68 791 (32.6)	1541 (11.6)	22 431 (10.9)	–	–	–	–	140 (24.6)	68 748 (27.0)
>30	1222 (61.4)	110 178 (52.1)	2649 (19.9)	32 308 (15.6)	–	–	–	–	249 (43.8)	96 251 (37.8)
Unknown	3 (0.2)	2973 (1.4)	8578 (64.6)	142 935 (69.2)	–		–	–	109 (19.2)	45 305 (17.8)
Diabetes duration, y	4 ± 5	4 ± 5	1 ± 3	1 ± 3	1 ± 1	1 ± 1	2 ± 3	2 ± 3	4 ± 5	4 ± 5
Average follow-up time (y)	1.9	3.9	1.3	2.3	1.3	2.3	1.2	2.8	1.5	4.3
Number of patients on ACE inhibitors (%)	762 (38.3)	86 374 (40.9)	3002 (22.6)	52 447 (25.4)	624 (20.9)	9313 (22.2)	260 (28.2)	7713 (32.5)	123 (21.6)	66 091 (26.0)

Note: Data are expressed as mean ± SD or n (%).

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; CPRD GOLD, Clinical Practice Research Datalink General practice OnLine Database; DA, Disease Analyzer; GP, general practitioner; NIAD, noninsulin antidiabetic drug; OPED, Odense Pharmaco-Epidemiological Database; SD, standard deviation; UK, United Kingdom; y, years.

2.4 | Ethics and good clinical practice

The protocol was endorsed by the Committee for Medicinal Products for Human Use (CHMP), and the study was led by the CPRD Group, with Swedish analyses undertaken by the Karolinska Institute. Further, approvals were obtained from the Independent Scientific Advisory Committee (ISAC; for CPRD 09_069R) and the Danish Health Board.

3 | RESULTS

Of the 738 054 patients included, 20 973 (2.8%) received vildagliptin at any time during the study, with an average follow-up time of 1.4 years, resulting in 28 330 PYs of cumulative current vildagliptin exposure. Table 1 summarizes the demographic characteristics by cohort, with co-medication use and comorbidities presented in Tables S2 and S3. Patients on vildagliptin were younger, had a higher BMI, and shorter follow-up. The percentage of women was generally lower in the vildagliptin cohort (except for Denmark). Otherwise, baseline characteristics were comparable.

3.1 | Angioedema

No evidence was found for an increased risk of angioedema associated with vildagliptin compared with other NIADs, with adjusted IRRs ranging from 0.87 to 3.71 and all 95% CIs crossing the null value

		Vilda Events (IR)	Other NIADs Events (IR)	Adjusted incidence rate ratio (95% CI)
Angioedema	UK CPRD GOLD	6 (1.6)	1247 (1.5)	1.07 (0.47, 2.45)
	Germany IMS DA	15 (0.8)	432 (1.0)	0.87 (0.52, 1.46)
	France IMS DA	7 (1.7)	128 (1.4)	1.25 (0.53, 2.95)
	Denmark OPED	2 (1.7)	40 (0.6)	3.25 (0.60, 17.64)
	Sweden NR	1 (1.2)	316 (0.3)	3.71 (0.52, 26.44)
Foot ulcer	UK CPRD GOLD	11 (3.0)	2478 (3.1)	1.00 (0.55, 1.82)
	Germany IMS DA	360 (20.9)	7903 (18.5)	1.05 (0.92, 1.20)
	France IMS DA	35 (8.6)	549 (6.2)	0.73 (0.22, 2.38)
	Denmark OPED	16 (14.2)	695 (11.1)	1.19 (0.70, 2.02)
	Sweden NR	0	2963	Not estimable
Skin lesion	UK CPRD GOLD	84 (30.5)	17607 (29.1)	1.07 (0.86, 1.33)
	Germany IMS DA	646 (44.8)	16468 (45.9)	0.94 (0.86, 1.03)
	France IMS DA	68 (17.9)	1417 (17.1)	1.04 (0.81, 1.34)
	Denmark OPED	4 (3.4)	187 (2.9)	1.18 (0.44, 3.17)
	Sweden NR	1 (1.2)	3367 (3.3)	0.37 (0.05, 2.60)
Foot ulcer or Skin lesions (composite)	UK CPRD GOLD	89 (32.6)	18621 (31.1)	1.07 (0.87, 1.32)
	Germany IMS DA	834 (60.0)	19900 (57.1)	0.99 (0.91, 1.08)
	France IMS DA	94 (25.2)	1808 (22.2)	1.13 (0.90, 1.42)
	Denmark OPED	18 (16.3)	831 (13.6)	1.14 (0.70, 1.86)
	Sweden NR	1 (1.2)	5104 (5.1)	0.24 (0.03, 1.72)
Serious hepatic events	UK CPRD GOLD	2 (0.5)	1021 (1.3)	0.43 (0.11, 1.71)
	Germany IMS DA	443 (31.0)	12333 (34.2)	0.55 (0.47, 0.65)
	France IMS DA	7 (1.7)	456 (5.1)	0.29 (0.13, 0.63)
	Denmark OPED	1 (0.8)	136 (2.1)	0.36 (0.05, 2.72)
	Sweden NR	0	1910	Not estimable
Serious infections	UK CPRD GOLD	11 (3.1)	4513 (5.7)	0.59 (0.33, 1.07)
	Germany IMS DA	213 (12.4)	6281 (14.8)	0.82 (0.71, 0.95)
	France IMS DA	35 (8.8)	778 (8.9)	0.96 (0.67, 1.37)
	Denmark OPED	17 (15.4)	1103 (18.3)	0.80 (0.50, 1.29)
	Sweden NR	18 (21.8)	21793 (22.4)	1.04 (0.66, 1.65)

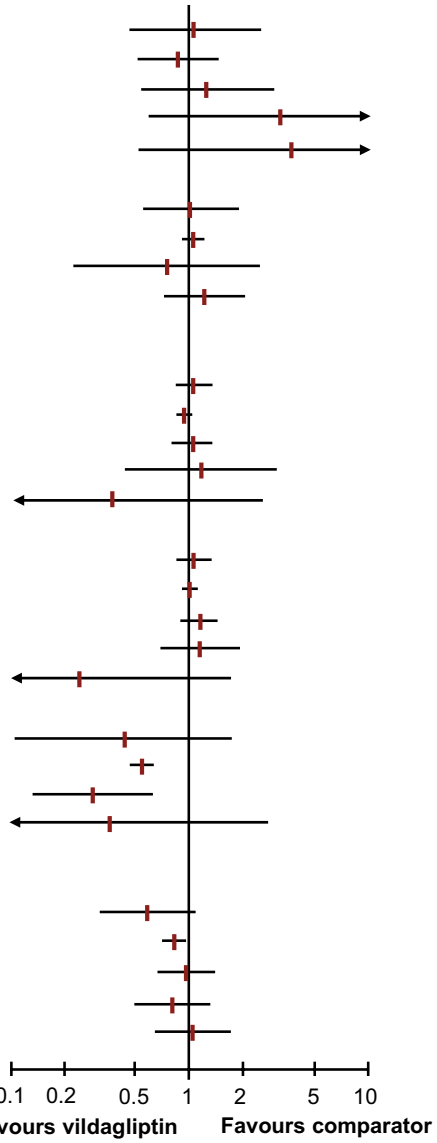

FIGURE 1 Adjusted incidence rate ratios of all safety events for current use of vildagliptin versus other NIAD. CI, confidence interval; CPRD GOLD, Clinical Practice Research Datalink General practice OnLine Database; DA, Disease Analyzer; IR, incidence rate (per 1000 PYs); NIADs, noninsulin antidiabetic drugs (other than vildagliptin); NR, National Registers; OPED, Odense Pharmaco-Epidemiological Database; UK, United Kingdom

of 1, indicating no statistically significant difference between exposure groups (Figure 1). Few subgroup analyses by age (40-64 years) in Sweden and Denmark were suggestive of an increased risk of angioedema with vildagliptin (based on very few cases, 2 in Denmark and 1 in Sweden in the vildagliptin group) with lower bounds of the 95% CIs > 1 but corresponding adjusted *P*-values > 0.05, indicating no statistically significant difference between groups.

3.2 | Foot ulcer

No evidence was identified for an increased risk of foot ulcer associated with use of vildagliptin compared with other NIADs, with adjusted IRRs close to 1 (range: 0.73-1.19) and all 95% CIs crossing 1 (Figure 1). One subgroup analysis in CPRD suggestive of an increased risk was identified in the 18-39 age group (with a single case in the vildagliptin group) but with a corresponding adjusted *P*-value of 1.0.

3.3 | Skin lesion

No evidence for an increased risk was identified for vildagliptin compared with other NIADs for skin lesions, with adjusted IRRs below or close to 1 (range: 0.37-1.18) and all 95% CIs crossing 1 (Figure 1).

3.4 | Foot ulcer or skin lesions (composite)

No evidence for an increased risk was identified for vildagliptin compared with other NIADs for foot ulcers or skin lesions with adjusted IRRs below or close to 1 (range: 0.24-1.14) with 95% CIs crossing 1 (Figure 1). One subgroup analysis in men from IMS DA Germany was suggestive of an increased risk for vildagliptin with a lower bound of the 95% CI crossing 1, but a corresponding adjusted *P*-value of 1.0.

3.5 | Serious hepatic events

No evidence for an increased risk for serious hepatic events was identified for vildagliptin compared with other NIADs, with adjusted IRRs ranging from 0.29 to 0.55; the upper bound of the 95% CI risk estimate from IMS DA Germany and France was below 1 (0.65, and 0.63, respectively; corresponding adjusted *P*-values < 0.05 for both databases) (Figure 1). Various subgroup analyses for vildagliptin based on age and sex in Germany and France also indicated no increased risk of serious hepatic events with corresponding adjusted *P*-values < 0.05. Due to zero cases identified in the vildagliptin group in the Swedish National Registers, no risk estimates were assessed for this database.

3.6 | ALT or AST > 3-times ULN and bilirubin > 2-times ULN (only assessed in CPRD GOLD)

The adjusted IRR for ALT or AST > 3-times ULN and bilirubin > 2-times ULN was not suggestive of an increased risk associated with vildagliptin compared to other NIADs (0.72; 95% CI: 0.42-1.25).

3.7 | ALT or AST > 10-times ULN (only assessed in CPRD GOLD)

The adjusted IRR for ALT or AST > 10-times ULN was 1.61 (95% CI: 0.51-5.08) and not suggestive of an increased relative risk associated with vildagliptin compared with other NIADs. One subgroup analysis in patients aged ≥65 years (based on three cases in the vildagliptin group) was suggestive of an increased risk (however, the corresponding adjusted *P*-value was 1.0).

3.8 | Any hepatic toxicity (composite of serious hepatic events or hepatic enzyme abnormalities [only assessed in CPRD GOLD])

The adjusted IRR for hepatic toxicity was 0.67 (95% CI: 0.40-1.13) and not suggestive of an increased relative risk associated with vildagliptin compared with other NIADs.

3.9 | Serious infections

No evidence for an increased risk for serious infections was identified for vildagliptin compared with other NIADs, with adjusted IRRs close to or below 1 ranging from 0.59 to 1.04 (Figure 1). The relative risk estimates generally favoured vildagliptin (adjusted IRR estimates < 1), except for the Swedish National Registers, but there was no statistical difference between vildagliptin and NIADs as the upper bounds of the 95% CI values for all databases were >1.

4 | DISCUSSION

This noninterventional, multidatabase, postmarketing safety study provides evidence that the use of vildagliptin is not associated with an increased risk of angioedema, foot ulcers, skin lesions, hepatic toxicity, and serious infections when compared to other NIADs under real-world conditions. Some subgroup analyses based on age and sex yielded risk ratios that are suggestive of an increased or decreased risk (ie, with 95% CIs not crossing 1). However, such analyses were generally based on very few cases in association with vildagliptin use, adjustment was generally done only for age and sex, and results for those estimates suggestive of an increased risk did not reach statistical significance based on the adjusted *P*-value. The most likely explanation for such results could be chance findings because of multiple testing.

No evidence of an increased risk of angioedema with vildagliptin exposure was observed. An earlier meta-analysis from phase III RCTs is in line with our results, reporting no association between vildagliptin use and angioedema.[14] No indication of an increased risk of foot ulcers and/or skin lesions was seen in patients exposed to vildagliptin. These results are consistent with a meta-analysis of 38 phase II and phase III clinical trials. The incidence of skin-related adverse events was low with vildagliptin, and similar to that of the comparators (OR = 1.10; 95% CI: 0.80-1.51; *P* = 0.70).[15] In a pooled analysis, similar frequencies of skin-related adverse events were

seen with vildagliptin (12.6%) and comparators (14.4%).[16] In a retrospective cohort study, the incidence of diabetic foot ulcers was similar for vildagliptin in comparison with sulfonylurea (OR = 0.76; 95% CI: 0.57-1.03; $P = 0.07$).[17]

The analyses of the levels of transaminases (ALT or AST) alone or together with bilirubin (assessed only in CPRD GOLD), showed no indication of an increased risk of hepatotoxicity in patients treated with vildagliptin. This is in line with a pooled analysis of 38 RCTs which also showed no evidence of an increased risk for ALT/AST ≥ 3 × ULN accompanied by bilirubin for vildagliptin 50 mg bid relative to comparators (OR = 1.19; 95% CI: 0.29-4.90; $P = 0.999$).[15] Furthermore, a recent meta-analysis of 69 RCTs revealed no association of vildagliptin with elevated hepatic enzymes (OR = 0.61; 95% CI: 0.28-1.36).[18]

Similarly, no indication of an increased risk of serious infections was observed with vildagliptin. Safety data from a meta-analysis reported that the incidence of infections was comparable between vildagliptin and comparator groups.[15] Another meta-analysis including 30 RCTs[19] also showed no increased risk of nasopharyngitis or upper respiratory tract infection in vildagliptin users versus comparators.

4.1 | Strengths and limitations

The broad inclusion/exclusion criteria of the current study done in five European countries allow generalizability of the results as the cohort constitutes a real-world population. Being a noninterventional study, selection or channelling bias cannot be excluded as patients were not randomized. Vildagliptin may have been a preferred treatment choice for patients who were inadequately controlled on other NIADs possibly channelling vildagliptin to a sicker population. Pooling of new and prevalent users might mask the adverse effect as the estimate may be weighted towards prevalent users who provide the majority of person-time. However, prevalent users tend to be depleted of those patients who may previously have developed an adverse event in association with antidiabetic treatment (ie, patients with a prior event would have been discontinued). As the study period corresponds with the launch of vildagliptin in Europe, a higher proportion of vildagliptin exposure time was likely associated with incident use of the medication, compared with the comparator. Potential bias of prevalent use may therefore rather have been to the disadvantage of vildagliptin.

Since the data were derived from electronic healthcare databases and the safety events were not further validated, there is a possibility of misclassification of events. In addition, as these analyses were only adjusted for age and sex, but not for other potential confounding variables (due to the limited number of patients with the outcomes of interest), residual confounding cannot be excluded.

5 | CONCLUSIONS

In conclusion, these safety analyses indicate that vildagliptin is not associated with an increased risk of angioedema, foot ulcer and/or skin lesions, hepatic toxicity, and serious infections when compared with other NIADs under real-world conditions. The current data complement earlier studies and meta-analyses of vildagliptin and add further evidence with respect to the positive safety profile of vildagliptin.

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CONFLICT OF INTEREST

R. W. is an employee of CPRD, London, UK. F. d. V. was a senior epidemiologist at the CPRD, London, UK at the time the study was conducted. W. K., C. S., and R. S. are employees and own shares of Novartis Pharma AG, Basel, Switzerland. S. L. is an employee and shareholder of Novartis Pharmaceuticals Corporation, East Hanover, New Jersey. The project was funded by Novartis Pharma AG.

AUTHORS CONTRIBUTION

All authors assume responsibility for the accuracy of the data interpretation and approved the manuscript for publication. R. W. and F. d. V. contributed to study conception, data collection, and analysis. R. S. contributed to study conception, data analysis, and interpretation of data. S. L. L. contributed on the interpretation of data and critical review of the study. R. W. and R. S. drafted the first version of the manuscript. F. d. V., W. K.,and C. S. helped with the critical review and finalization of the manuscript.

DATA ACCESSIBILITY

The data generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

ORCID

Raymond Schlienger https://orcid.org/0000-0001-5160-0872

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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