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ORIGINAL RESEARCH

Assessing the general safety and tolerability of vildagliptin: value of pooled analyses from a large safety database versus evaluation of individual studies

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Anja Schweizer[1]
Sylvie Dejager[2]
James E Foley[3]
Wolfgang Kothny[3]

[1]Novartis Pharma AG, Basel, Switzerland; [2]Novartis Pharma SAS, Rueil-Malmaison, France; [3]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

Aim: Analyzing safety aspects of a drug from individual studies can lead to difficult-to-interpret results. The aim of this paper is therefore to assess the general safety and tolerability, including incidences of the most common adverse events (AEs), of vildagliptin based on a large pooled database of Phase II and III clinical trials.

Methods: Safety data were pooled from 38 studies of ≥12 to ≥104 weeks' duration. AE profiles of vildagliptin (50 mg bid; N = 6116) were evaluated relative to a pool of comparators (placebo and active comparators; N = 6210). Absolute incidence rates were calculated for all AEs, serious AEs (SAEs), discontinuations due to AEs, and deaths.

Results: Overall AEs, SAEs, discontinuations due to AEs, and deaths were all reported with a similar frequency in patients receiving vildagliptin (69.1%, 8.9%, 5.7%, and 0.4%, respectively) and patients receiving comparators (69.0%, 9.0%, 6.4%, and 0.4%, respectively), whereas drug-related AEs were seen with a lower frequency in vildagliptin-treated patients (15.7% vs 21.7% with comparators). The incidences of the most commonly reported specific AEs were also similar between vildagliptin and comparators, except for increased incidences of hypoglycemia, tremor, and hyperhidrosis in the comparator group related to the use of sulfonylureas.

Conclusions: The present pooled analysis shows that vildagliptin was overall well tolerated in clinical trials of up to >2 years in duration. The data further emphasize the value of a pooled analysis from a large safety database versus assessing safety and tolerability from individual studies.

Keywords: type 2 diabetes, dipeptidyl peptidase-4, edema, safety, vildagliptin

Introduction

Vildagliptin is an orally effective dipeptidyl peptidase-4 (DPP-4) inhibitor that has been studied in a large clinical program as monotherapy and combination therapy.[1] It binds covalently to the catalytic site of DPP-4, eliciting prolonged enzyme inhibition. This raises intact glucagon-like peptide-1(GLP-1) levels both after meal ingestion and in the fasting state. By increasing concentrations of active GLP-1, vildagliptin improves β- and α-cell sensitivity to glucose.[2] This results in glucose-sensitive modulation of insulin and glucagon secretion, improving both fasting and postprandial glycemia, with a low risk for hypoglycemia and no weight gain.

Areas of potential safety concern related to type 2 diabetes (T2DM) itself (ie, cardiovascular and hepatic safety), as well as potential safety concerns specific to DPP-4 inhibitors (ie, immune system, skin, and pancreatitis), have been analyzed

Correspondence: Anja Schweizer
Novartis Pharma AG, Postfach,
CH-4002 Basel, Switzerland
Tel + 41 61 3243530
Fax + 41 61 3247487
Email anja.schweizer@novartis.com

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previously for vildagliptin based on a large pooled database, with no increased risks identified versus comparators.[3,4] However, other safety aspects, such as general safety and tolerability, including incidences of most common specific adverse events (AEs), have so far been reviewed in the literature from individual studies only.[1,5,6] Although this is often the only possible approach early in the development of a new drug, such data from single and often relatively small studies are less reliable than analyses from larger datasets. Furthermore, specific design features, study duration, sample size, and, in particular, the comparator chosen for individual studies can influence the AE reporting rates in a specific study, which needs to be weighed against the overall experience in a clinical trial program. For example, one issue that arose from an individual study with vildagliptin was related to edema. In contrast to other studies, Bolli et al,[7] in a trial comparing vildagliptin and pioglitazone as add-on therapy with metformin, reported peripheral edema as the most common AE for vildagliptin with an incidence even somewhat higher than for the thiazolidinedione (TZD) itself.

Based on these considerations, it was of interest to assess the general safety and tolerability of vildagliptin, as well as the specific risk of edema-related AEs with vildagliptin treatment, using the previously described large pooled database of vildagliptin Phase II and III clinical studies.[4] We report here the results of these new pooled safety analyses.

Methods

Populations

The safety analyses are based on the previously reported pool of 38 Phase II and Phase III studies that used vildagliptin as monotherapy or in combination with metformin, TZDs, sulfonylureas (SUs), or insulin for ≥12 weeks up to ≥104 weeks.[4]

For the analysis of overall AEs, AEs by system organ class (SOC) or preferred term (PT), serious AEs (SAEs), discontinuations due to AEs, and deaths, as well as edema-related AEs, the "all studies (excluding open-label) safety population", which excludes open-label studies in order to minimize reporting bias, was used. Supplementary Table 1 briefly describes each of the studies included in this pooled dataset.

Peto odds ratios (ORs) were additionally calculated for edema-related AEs, as a single study had previously reported a higher incidence with vildagliptin.[7] Calculation of ORs requires a comparator; thus, calculation of ORs and the resulting Forest plot for edema-related AEs used data pooled from all controlled studies excluding open-label trials. This population is termed "all controlled studies (excluding open-label) safety population" (see Supplementary Table 1 for details).

In addition to being analyzed in the all studies (excluding open-label) safety population, confirmed hypoglycemic episodes (as defined in this article) were also assessed in monotherapy (monotherapy [excluding open-label] safety population), which was deemed more appropriate considering that the risk of hypoglycemia is influenced by antidiabetic background therapy. Confirmed hypoglycemia is thus not reflected under the most common AEs in the all studies (excluding open-label) safety population in Table 1. The monotherapy (excluding open-label) safety population includes 21 studies (see Supplementary Table 1 for details on the contributing studies).

Assessments

All AEs were recorded and assessed by the investigator as to the severity and possible relationship to the study medication. This included laboratory abnormalities if considered an AE by the investigator. All laboratory assessments were performed by central laboratories (for details, see Ligueros-Saylan et al[4]).

Confirmed hypoglycemia was defined as symptoms suggestive of low blood glucose confirmed by self-monitored blood glucose measurement <3.1 mmol/L plasma glucose equivalent.

Standardization of terms

AEs were encoded in all studies using the Medical Dictionary for Regulatory Activities (MedDRA, Version 12.1) system. This is a medically validated terminology database developed by the International Conference on Harmonization. Within the MedDRA, AEs are grouped by SOC, eg, "cardiac disorders" or "gastrointestinal disorders". Within an SOC, specific AEs are identified by PT. The PTs included in the analysis of edema-related AEs are allergic edema, generalized edema, local swelling, localized edema, edema, peripheral edema, pitting edema, skin edema, skin swelling, and swelling.

Data analysis

For AEs, SAEs, discontinuations due to AEs, and deaths, incidences were calculated as number of patients with an event divided by the number of patients in the treatment group. For edema-related AEs (as defined previously), exposure-adjusted incidences were additionally calculated as number of patients having events per 100 subject-year exposure (SYE), defined as 100×(number of patients with an event divided by the total exposure time in years).

To further compare edema-related AEs between vildagliptin and comparators, for each trial, Peto OR and the corresponding 95% confidence interval (CI) were calculated. The pooled estimate was obtained using a fixed-effect model and presented in a forest plot. An OR below unity is indicative of a treatment effect favoring vildagliptin. Correction for continuity using the inverse of the opposite arm size was used when zero events occurred.[8] This correction causes less bias than the standard continuity correction of 0.5 when the sizes of the treatment arms are unbalanced.[9]

Safety data of vildagliptin 50 mg bid (the highest approved and most commonly used dosage of the drug) are reported along with pooled safety data of all comparators (active or placebo) from the safety populations.

Ethics and good clinical practice

All study participants provided written informed consent. All protocols were approved by the independent ethics committee/institutional review board at each study site or country. All studies were conducted using good clinical practice and in accordance with the Declaration of Helsinki.

Results

Exposure and demography

As detailed in Ligueros-Saylan et al,[4] in the all studies (excluding open-label) safety population, 6116 patients received vildagliptin 50 mg bid (representing 7313.6 SYE) and 6210 patients received any comparator (representing 6512.7 SYE). The comparators group included placebo (23.7%), SUs (41.7%), metformin (18.8%), TZDs (12.3%), and acarbose (3.5%).

The mean duration of exposure was 62.4 weeks with vildagliptin 50 mg bid and 54.7 weeks with comparators (Table 1). This allows for direct comparisons between the two groups and provides a conservative estimate, as the slightly longer exposure with vildagliptin tends to favor the comparator group.

The demographic and baseline characteristics of patients in the all studies (excluding open-label) safety population have also been described previously.[4] In brief, the population studied was representative of a broad spectrum of T2DM patients, with a mean age, body mass index, glycosylated hemoglobin A, fasting plasma glucose, and duration of T2DM of approximately 56 years, 31.4 kg/m^2, 8.1%, 9.8 mmol/L, and >4 years, respectively, and with nearly one-third of patients having some degree of renal insufficiency (glomerular filtration rate [Modification of Diet in Renal Disease] ≤80 mL/min per 1.73 m^2).

Table 1 Adverse event (AE) summary and most common AEs (all studies [excluding open-label] safety population)

n (%)	Vildagliptin 50 mg bid	Comparators[a]
	N = 6116	N = 6210
Mean exposure (weeks)	**62.4**	**54.7**
AEs	**4225 (69.1)**	**4228 (69.0)**
Drug-related AEs	**961 (15.7)**	**1349 (21.7)**
Serious AEs	**545 (8.9)**	**557 (9.0)**
Discontinuations due to AEs[b]	**347 (5.7)**	**400 (6.4)**
Deaths	**24 (0.4)**	**23 (0.4)**
Most common AEs (occurring in ≥3% of patients in either group):		
Nasopharyngitis	577 (9.4)	528 (8.5)
Headache	431 (7.0)	371 (6.0)
Dizziness	390 (6.4)	460 (7.4)
Back pain	356 (5.8)	321 (5.2)
Diarrhea	345 (5.6)	418 (6.7)
Upper respiratory tract infection	317 (5.2)	254 (4.1)
Bronchitis	297 (4.9)	278 (4.5)
Hypertension	297 (4.9)	315 (5.1)
Influenza	290 (4.7)	282 (4.5)
Arthralgia	289 (4.7)	236 (3.8)
Nausea	247 (4.0)	268 (4.3)
Pain in extremity	217 (3.5)	238 (3.8)
Fatigue	210 (3.4)	253 (4.1)
Cough	206 (3.4)	210 (3.4)
Urinary tract infection	204 (3.3)	185 (3.0)
Asthenia	198 (3.2)	306 (4.9)
Tremor	184 (3.0)	471 (7.6)
Edema peripheral	180 (2.9)	219 (3.5)
Hyperhidrosis	169 (2.8)	422 (6.8)

Notes: [a]Comparators = placebo plus active comparators; [b]Only AEs that caused the study drug to be permanently discontinued are included.

Overall safety and tolerability

Tables 1 and 2 report AE profiles for vildagliptin 50 mg bid and comparators in the all studies (excluding open-label) safety population.

Overall AEs, SAEs, discontinuations due to AEs, and deaths were all reported with a similar frequency in patients receiving vildagliptin (69.1%, 8.9%, 5.7%, and 0.4%, respectively) and patients receiving comparators (69.0%, 9.0%, 6.4%, and 0.4%, respectively), and drug-related AEs were seen with a lower frequency in vildagliptin-treated patients (15.7% vs 21.7% with comparators) (Table 1).

When the reported AEs were analyzed by SOC (Table 2), the incidences with vildagliptin and comparators were also similar overall. The four SOCs with the highest incidence of AEs were infections and infestations (35.3% for vildagliptin vs 32.4% for comparators), gastrointestinal disorders (23.5% vs 22.4%), musculoskeletal and

Table 2 Adverse events (AEs) by system organ class (SOC) (all studies [excluding open-label] safety population)

n (%)	Vildagliptin 50 mg bid	Comparators[a]
	N = 6116	N = 6210
Mean exposure (weeks)	**62.4**	**54.7**
AEs by SOC:		
Blood and lymphatic system disorders	125 (2.0)	114 (1.8)
Cardiac disorders	375 (6.1)	375 (6.0)
Congenital, familial, and genetic disorders	12 (0.2)	13 (0.2)
Ear and labyrinth disorders	189 (3.1)	221 (3.6)
Endocrine disorders	40 (0.7)	32 (0.5)
Eye disorders	368 (6.0)	356 (5.7)
Gastrointestinal disorders	1440 (23.5)	1393 (22.4)
General disorders/administration site conditions	884 (14.5)	1069 (17.2)
Hepatobiliary disorders	102 (1.7)	99 (1.6)
Immune system disorders	63 (1.0)	63 (1.0)
Infections and infestations	2162 (35.3)	2014 (32.4)
Injury, poisoning, and procedural complications	595 (9.7)	522 (8.4)
Investigations	368 (6.0)	427 (6.9)
Metabolism and nutrition disorders	476 (7.8)	706 (11.4)
Musculoskeletal and connective tissue disorders	1374 (22.5)	1313 (21.1)
Benign, malignant, and unspecified neoplasms	149 (2.4)	144 (2.3)
Nervous system disorders	1320 (21.6)	1474 (23.7)
Pregnancy, puerperium and perinatal conditions	2 (0.0)	8 (0.1)
Psychiatric disorders	480 (7.8)	474 (7.6)
Renal and urinary disorders	291 (4.8)	255 (4.1)
Reproductive system and breast disorders	241 (3.9)	220 (3.5)
Respiratory, thoracic and mediastinal disorders	601 (9.8)	570 (9.2)
Skin and subcutaneous tissue disorders	769 (12.6)	893 (14.4)
Social circumstances	12 (0.2)	3 (0.0)
Surgical and medical procedures	18 (0.3)	11 (0.2)
Vascular disorders	475 (7.8)	484 (7.8)

Note: [a]Comparators = placebo plus active comparators.

connective tissue disorders (22.5% vs 21.1%), and nervous system disorders (21.6% vs 23.7%). Of note, there were no imbalances between vildagliptin and comparators in the overall reporting rates under the cardiac (6.1% with vildagliptin vs 6.0% with comparators), hepatobiliary (1.7% vs 1.6%), skin (12.6% vs 14.4%), and vascular (7.8% in both groups) SOCs. The most notable difference was observed in the metabolism/nutrition SOC, with incidences of 7.8% for vildagliptin and 11.4% for comparators, which were mainly due to hypoglycemia.

Overall, there were no appreciable trends in SAEs reported, and the majority of SAEs were scattered across many different SOCs. The primary SOC with the highest incidence of SAEs was cardiac disorders, with no imbalance between vildagliptin (1.7%) and comparators (1.9%). The only other SOCs with an incidence of SAEs ≥ 1% were infections and infestations (1.5% with vildagliptin 50 mg bid vs 1.4% with comparators); benign, malignant, and unspecified neoplasms (including cysts and polyps) (1.2% vs 1.1%); nervous system disorders (1.1% vs 1.0%); and gastrointestinal disorders (1.0% vs 0.9%).

There were no meaningful imbalances across the treatment groups in the incidence of AEs leading to discontinuation in any SOC. The SOC with the highest incidence of AEs leading to discontinuation was gastrointestinal disorders (1.2% with vildagliptin vs 1.4% with comparators).

A summary of the most commonly (≥3% in either group) reported specific AEs for vildagliptin 50 mg bid and comparators is also provided in Table 1. All of the individual AEs were reported with a low frequency of <10%. The most common AEs across treatment groups were nasopharyngitis (9.4% with vildagliptin vs 8.5% with comparators), dizziness (6.4% vs 7.4%), headache (7.0% vs 6.0%), and diarrhea (5.6% vs 6.7%). The incidences of the most commonly reported AEs were overall similar between vildagliptin and comparators. The most notable differences were lower incidences with vildagliptin of tremor (3.0% vs 7.6%) and hyperhidrosis (2.8% vs 6.8%). Furthermore, confirmed hypoglycemia was reported less frequently with vildagliptin (1.7%) than with comparators (5.8%). Hypoglycemia was additionally assessed in a pooled monotherapy population, which was deemed more appropriate than the assessment in the overall pooled dataset, considering that the risk of hypoglycemia is influenced by antidiabetic background therapy. In the pooled monotherapy safety population, confirmed hypoglycemic events were reported in 0.5% of patients treated with vildagliptin versus 0.3% treated with placebo and 0.6% treated with all comparators (the comparator group consisted of 38.3% metformin, 20.7% placebo, 17.9% SU, 7.2% acarbose, and 15.9% TZD).

Edema

As depicted in Figure 1, there was no evidence of an increased risk of edema-related AEs with vildagliptin 50 mg bid relative to comparators. The Peto OR for vildagliptin 50 mg bid was 0.72 (95% CI 0.59–0.88), indicating a statistically significant risk reduction versus the comparator group.

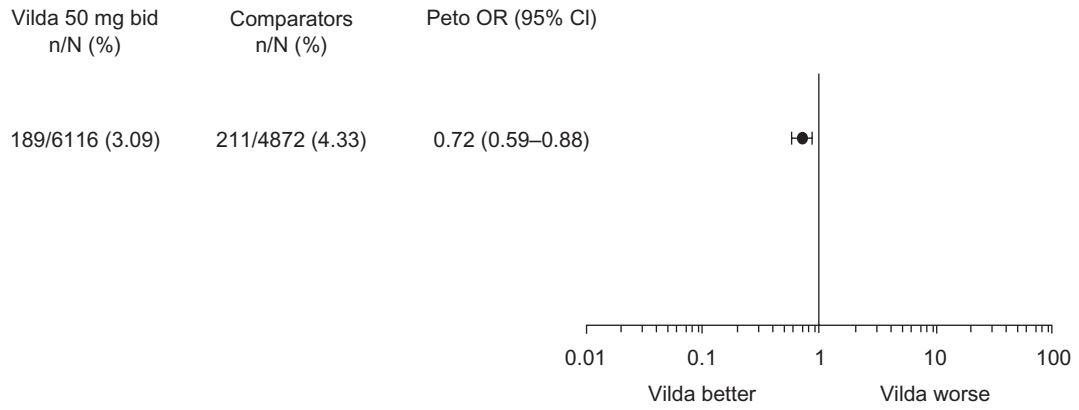

Figure 1 Incidences and Peto odds ratio (OR) for edema-related adverse events with vildagliptin 50 mg bid versus comparators (placebo and active comparators) in the all controlled studies (excluding open-label) safety population.
Abbreviation: Vilda, vildagliptin

The overall incidence of any edema-related AE was low in both treatment groups (Table 3). The unadjusted and SYE-adjusted incidences of any edema-related AEs were lower for vildagliptin than for comparators (Table 1). The most commonly reported edema-related AE was peripheral edema, and for this AE the incidence was also lower with vildagliptin (2.9%, 2.46 events per 100 SYE) than with comparators (3.5%, 3.36 events per 100 SYE). For all other specific edema-related AEs, the SYE-adjusted incidences with vildagliptin were the same as or lower than with comparators.

Discussion

The present paper has evaluated in a large pooled database safety aspects of the DPP-4 inhibitor vildagliptin that were previously assessed only from individual study results. Although the latter approach represents generally a good approach to judging the efficacy of a drug, it has considerable limitations when assessing safety and tolerability and can lead to difficult-to-interpret or even misleading results. On the one hand, sample sizes of individual trials are often too small to reliably assess whether any imbalances observed in individual AEs reflect a true excess over the comparator treatment studied or rather a chance finding. On the other hand, the study duration, the safety surveillance measures, and, in particular, the comparator chosen for individual studies can influence the AE reporting rates in a specific study. Another complication arises if the results of an individual study are extrapolated as being representative for the overall safety of a drug, as happens in the literature, especially if pooled data are not available.

Table 3 Edema-related adverse events (AEs) (all studies [excluding open-label] safety population)

	Vildagliptin 50 mg bid	Comparators[a]
	N = 6116	N = 6210
	n (%)	
	Subject-year exposure adjusted	
Any edema-related AE	**198 (3.2)**	**242 (3.9)**
	2.71	**3.72**
Generalized edema	2 (0.0)	2 (0.0)
	0.03	0.03
Local swelling	1 (0.0)	1 (0.0)
	0.01	0.02
Edema	10 (0.2)	9 (0.1)
	0.14	0.14
Peripheral edema	180 (2.9)	219 (3.5)
	2.46	3.36
Pitting edema	9 (0.1)	12 (0.2)
	0.12	0.18
Skin swelling	0 (0.0)	1 (0.0)
	0.00	0.02

Note: [a]Comparators = placebo plus active comparators.

For vildagliptin, a higher incidence of peripheral edema, for example, was observed in a study that compared the drug with the TZD pioglitazone, for which edema is a known side effect.[7] In contrast, the new pooled analysis presented here did not confirm an increased incidence of edema-related events with vildagliptin but rather showed a statistically significant risk reduction versus the comparator group (OR = 0.72). Peripheral edema specifically occurred at an incidence rate of 2.46 events per 100 SYE with vildagliptin 50 mg bid versus 3.36 events per 100 SYE with comparators. Of note, only 12% of patients in the comparator group were treated with TZDs. Another study reported an imbalance with vildagliptin versus comparator treatment for the AE of hypertension.[10] In contrast, hypertension was well balanced when analyzed in the large pooled dataset (4.9% with vildagliptin vs 5.1% with comparators). These examples clearly highlight the value and importance of pooled safety analyses.

The safety of vildagliptin versus all comparators was previously assessed with regard to organs, systems, or tissues of particular interest in T2DM and areas of potential concern with DPP-4 inhibitors.[4] The meta-analyses indicated that vildagliptin was not associated with an increased risk of hepatic events or hepatic enzyme elevations indicative of drug-induced liver injury, pancreatitis, skin-related toxicity, or infections. In line with these results, the data presented here did not show any imbalances between vildagliptin and comparators for AEs in the SOCs of hepatobiliary disorders, skin and subcutaneous tissue disorders and infection and infestations.

The present pooled analysis further shows a general safety profile of vildagliptin 50 mg bid in clinical trials of up to >2 years in duration that was very similar to that of comparators regarding the overall incidences of AEs, SAEs, discontinuations due to AEs, and deaths. This also holds true when AEs were analyzed by SOCs or the most common AEs were evaluated. The only notable differences were for confirmed hypoglycemia and the likely hypoglycemia-related AEs of tremor and hyperhidrosis, for which lower incidences were observed with vildagliptin than with comparator treatment, mainly due to the use of SUs as a comparator in several studies (representing >40% of the comparator group). Because hypoglycemia incidences are largely influenced by antidiabetic background therapy, it is important to review hypoglycemia rates for specific treatment regimens. The overall safety population used for the present safety analyses consists of a broad range of studies with different treatment regimens, including add-on to insulin; thus, the frequency of confirmed hypoglycemia was also assessed in a pooled monotherapy safety population. Of the patients treated with vildagliptin monotherapy, 0.5% reported confirmed hypoglycemic episodes, which is very similar to the rate found with placebo (0.3%).

Taken together, the present pooled analysis provides a more comprehensive and reliable assessment of the general safety and tolerability of vildagliptin than can be obtained by extracting safety data from individual studies only.

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Declaration

All authors are employees of Novartis.

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Supplementary material

Table S1 Vildagliptin studies contributing to safety analyses

Study no.	Study description	Phase/ population	Randomized patients*	Treatment duration**	Publication***
Monotherapy					
1	Placebo-controlled dose-ranging study in drug-naïve T2DM patients (HbA_{1c} 6.8%–10%)	II/a,b,c	279	12 weeks	1
2	Uncontrolled 40-week extension to Study 1	II/a,c	141	52 weeks	Not available
3	Placebo-controlled low-dose efficacy/safety study in drug-naïve T2DM patients (HbA_{1c} 6.8%–11%)	II/a,b,c	100	12 weeks	2
4	Placebo-controlled dose-ranging study (efficacy/safety) in drug-naïve T2DM patients (HbA_{1c} 7.5%–10%)	III/a,b,c	632	24 weeks	3
5	Uncontrolled 28-week extension to Study 4	III/a,c	440	52 weeks	NCT00138541
6	Placebo-controlled long-term efficacy/safety study in drug-naïve T2DM patients with mild hyperglycemia (HbA_{1c} 6.2%–7.5%)	III/a,b,c	306	52 weeks	4,5
7	Placebo-controlled 52-week extension to Study 6	III/a,b,c	131	104 weeks	6
8	Active-controlled (metformin) long-term efficacy/safety study in drug-naïve T2DM patients (HbA_{1c} 7.5%–11%)	III/a,b,c	780	52 weeks	7
9	Active-controlled (metformin) 52-week extension to Study 8	III/a,b,c	463	104 weeks	8
10	Active-controlled (gliclazide) long-term efficacy/safety study in drug-naïve T2DM patients (HbA_{1c} 7.5%–11%)	III/a,b,c	1092	104 weeks	9
11	Active-controlled (acarbose) efficacy/safety study in drug-naïve T2DM patients (HbA_{1c} 7.5%–11%)	III/a,b,c	661	24 weeks	10
12	Active-controlled (rosiglitazone) efficacy/safety study in drug-naïve T2DM patients (HbA_{1c} 7.5%–11%)	III/a,b,c	786	24 weeks	11
13	Active-controlled (rosiglitazone) 80-week extension to Study 12	III/a,b,c	598	104 weeks	12
14	Active-controlled (pioglitazone) dose regimen comparison study in drug-naïve T2DM patients (HbA_{1c} 9%–11%)	III/a,b,c	273	12 weeks	NCT00101673
15	Placebo-controlled efficacy/safety study in patients with IGT	III/a,b,c	179	12 weeks	13
16	Placebo-controlled mechanistic study (β-cell function) in drug-naïve T2DM patients with mild hyperglycemia ($HbA_{1c} \leq 7.5\%$)	III/a,b,c	89	52 weeks	NCT00260156
17	Placebo-controlled dose-ranging study (efficacy/safety) in drug-naïve T2DM patients (HbA_{1c} 7.5%–10%)	III/a,b,c	354	24 weeks	14
18	Active-controlled (metformin) efficacy/safety study in drug-naïve elderly (≥65 years) T2DM patients (HbA_{1c} 7%–9%)	III/a,b,c	335	24 weeks	15
Combination therapy with metformin					
19	Placebo-controlled dose-selection study in patients inadequately controlled by metformin (HbA_{1c} 7.0%–9.5%)	II/a,b	132	12 weeks	16
20	Placebo-controlled 40-week extension to Study 19	II/a,b	71	52 weeks	16
21	Placebo-controlled efficacy/safety study in T2DM patients inadequately controlled with metformin (HbA_{1c} 7.5%–11%)	III/a,b	544	24 weeks	17
22	Uncontrolled 28-week extension to Study 21	III/a	417	52 weeks	NCT00138515
23	Active-controlled (glimepiride) long-term efficacy/safety study in T2DM patients treated with metformin ($HbA_{1c} > 6.5\%$–8.5%)	III/a,b	3118	≥104 weeks	18,19
24	Active-controlled (gliclazide) long-term efficacy/safety study in T2DM patients inadequately controlled with metformin (HbA_{1c} 7.5%–11%)	III/a,b	1007	52 weeks	20
25	Active-controlled (pioglitazone) long-term efficacy/safety study in T2DM patients inadequately controlled with metformin (HbA_{1c} 7.5%–11%)	III/a,b	576	52 weeks	21,22
26	Placebo-controlled efficacy/safety study in T2DM patients inadequately controlled with metformin (HbA_{1c} 7.5%–11%) to compare a.m. vs p.m. dosing regimens	III/a,b	370	24 weeks	23
27	Efficacy/safety study in T2DM patients treated with metformin (HbA_{1c} 6.5%–9%) to compare vildagliptin as add-on to metformin vs uptitration of metformin	III/a,b,c****	914	24 weeks	24
28	Efficacy/safety study of initial fixed combination therapy of vildagliptin and metformin in drug-naïve T2DM patients (HbA_{1c} 7.5%–11%)	III/a,b,c****	1179	24 weeks	25

(*Continued*)

Table S1 (*Continued*)

Study no.	Study description	Phase/ population	Randomized patients*	Treatment duration**	Publication***
Combination therapy with TZD					
29	Placebo-controlled efficacy/safety study in T2DM patients inadequately controlled by TZD (HbA_{1c} 7.5%–11%)	III/a,b	463	24 weeks	26
30	Uncontrolled 28-week extension to Study 29	III/a	312	52 weeks	NCT00138554
31	Initial combination (vildagliptin/pioglitazone) efficacy/safety study in drug-naïve T2DM patients (HbA_{1c} 7.5%–11%)	III/a,b,c****	607	24 weeks	27
Combination therapy with SU					
32	Placebo-controlled efficacy/safety study in T2DM patients inadequately controlled by SU (HbA_{1c} 7.5%–11%)	III/a,b	515	24 weeks	28
33	Uncontrolled 28-week extension to Study 32	III/a	332	52 weeks	NCT00138580
Combination therapy with insulin					
34	Placebo-controlled efficacy/safety study in T2DM patients treated with insulin (HbA_{1c} 7.5%–11%)	III/a,b	296	24 weeks	29
35	Uncontrolled 28-week extension to Study 34	III/a	200	52 weeks	30

Notes: *For extension studies: patients who entered extension; **For extension studies: duration of core + extension study. ***ClinicalTrials.gov identifier number is provided if data are not yet published; ****Monotherapy arms only. Population a = all studies (excluding open-label) safety population. Population b = all controlled studies (excluding open-label) safety population; Population c = monotherapy (excluding open-label) safety population.

Abbreviations: HbA_{1c}, glycosylated hemoglobin A; IGT, impaired glucose tolerance; SU, sulfonylurea; T2DM, type 2 diabetes; TZD, thiazolidinedione.

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