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ORIGINAL RESEARCH ARTICLE

Safety of Sitagliptin in Elderly Patients with Type 2 Diabetes: A Pooled Analysis of 25 Clinical Studies

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Abstract

Objective The aim of this study was to evaluate the safety and tolerability of sitagliptin 100 mg/day in elderly patients with type 2 diabetes.

Design A post hoc pooled analysis of 25 randomized, double-blind, parallel group clinical studies with results available as of 1 December 2011.

Setting Multicenter, international clinical trials.

Subjects Patients with type 2 diabetes aged 65 years or older.

Interventions Patients were randomized to sitagliptin 100 mg/day ($n = 1{,}261$) or a comparator ($n = 1{,}185$) for 12 weeks to 2 years.

Main Outcome Measures In each study, investigators reported serious and non-serious adverse events that occurred during the study, and serious adverse events occurring within 14 days following the last dose of study drug. This analysis used patient-level data from each study to assess the exposure-adjusted incidence rates of specific adverse events that occurred following initiation of study drug.

Results Summary measures of adverse events overall were similar between the sitagliptin and non-exposed (active comparator or placebo) groups, except for higher incidences of deaths and drug-related adverse events in the non-exposed group. Incidence rates of specific adverse events were generally similar between the two groups, with the exception of hypoglycemia. A lower incidence rate of hypoglycemia was observed in the sitagliptin group compared with the non-exposed group [7.0 vs. 14.3 per 100 patient-years; difference −7.6 (95 % CI −11.2 to −4.3]), primarily due to greater use of sulfonylureas in the non-exposed group.

Conclusions In this pooled safety analysis of elderly patients with type 2 diabetes, treatment with sitagliptin 100 mg/day was generally well tolerated for up to 2 years.

Key Points

An analysis of the safety and tolerability of sitagliptin in type 2 diabetes patients ≥65 years of age was conducted using patient-level data from 25 double-blind, randomized clinical studies.

The exposure-adjusted incidence rates of adverse events were generally similar between sitagliptin-treated and control groups.

A lower incidence rate of hypoglycemia was observed in the sitagliptin group compared with the control group, primarily due to greater use of sulfonylureas in the control group.

In studies of up to 2 years in duration, sitagliptin was well-tolerated in older patients with type 2 diabetes.

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1 Introduction

The prevalence of type 2 diabetes increases with advancing age, with approximately one-third of US adults ≥65 years of age having either diagnosed or undiagnosed disease [1–3]. Given that the worldwide population of adults ≥65 years of age is expected to more than double from 2000 to 2030 [4], the number of elderly patients with type 2 diabetes is expected to continue to rise. Elderly adults with type 2 diabetes are at a greater risk for comorbidities and mortality compared with non-diabetic elderly subjects [5–7].

Management of type 2 diabetes in the elderly is often challenging because of pre-existing or co-morbid conditions such as impaired renal or cardiovascular function and the presence of geriatric syndromes [8–11]. Furthermore, antihyperglycemic treatment options may be limited in this population because of potential side effects or contraindications. For example, metformin is associated with increased gastrointestinal side effects and is contraindicated in patients with moderate to severe renal impairment [12]; increasing age is associated with a decline in renal function, which may partially explain the decrease in metformin use in the elderly [13, 14]. Sulfonylureas and insulin are associated with an increased risk of hypoglycemia [12], which may be exacerbated in elderly patients who may have reduced hypoglycemia awareness [15]. Thiazolidinediones (TZDs) are associated with fluid retention, peripheral edema, and an increased risk of congestive heart failure [16]. In addition, TZDs may increase the risk of bone fractures, and rosiglitazone has been implicated in an increased risk of cardiovascular events [17]. Therefore, there is a need for safe and well-tolerated antihyperglycemic treatments in elderly patients with type 2 diabetes.

Among the newer modalities for treating type 2 diabetes are the incretin-based therapies, including dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RA). In clinical trials, these agents have been shown to be generally well tolerated, with a low risk of hypoglycemia [18]. GLP-1RAs have been shown to be more effective in glucose lowering compared with the DPP-4 inhibitors, but they have a higher incidence of gastrointestinal side effects and require injection for administration [19, 20]. However, unlike the older agents, there is less long-term safety experience with the incretin-based agents, especially in elderly patients with type 2 diabetes.

In a prior pooled analysis of 25 double-blind, randomized clinical trials of up to 2 years in duration, the DPP-4 inhibitor sitagliptin was shown to be generally well tolerated in a broad range of patients with type 2 diabetes [21]. In a phase III study of patients ≥65 years of age with type 2 diabetes, sitagliptin monotherapy improved fasting and postprandial glycemic control and measures of β-cell function, and was generally well tolerated over 24 weeks, with incidences of hypoglycemia and gastrointestinal adverse events similar to placebo [22]. To further evaluate the safety and tolerability of sitagliptin 100 mg/day in elderly patients, we have re-analyzed data from the 25 studies referred to above, focusing on the data from patients ≥65 years of age.

2 Methods

This post hoc analysis used a pooled population of patients ≥65 years of age ($N = 2{,}446$) drawn from all 25 multicenter, US or multinational, double-blind, parallel-group studies conducted by Merck & Co., Inc., in which patients were randomized to receive sitagliptin 100 mg/day ($n = 1{,}261$) or a comparator ($n = 1{,}185$) for at least 12 weeks and up to 2 years (the duration of the longest studies) and for which results were available as of 1 December 2011 (see the Appendix for a complete listing of the studies). Each protocol was reviewed and approved by appropriate ethical review committees and authorities for each clinical site. All patients were to have provided written informed consent.

The studies evaluated sitagliptin as monotherapy, initial combination therapy with either metformin or pioglitazone, or add-on combination therapy with other antihyperglycemic agents, including metformin, pioglitazone, a sulfonylurea (with and without metformin), insulin (with and without metformin), or metformin with rosiglitazone or pioglitazone. Patients not receiving sitagliptin (i.e. the non-exposed group) received placebo, metformin, pioglitazone, a sulfonylurea (with and without metformin), insulin (with and without metformin), or metformin with rosiglitazone or pioglitazone. From each contributing study, the pooling was conducted by including those portions that had parallel treatment groups with concurrent exposures to sitagliptin 100 mg/day (primarily administered as 100 mg once daily) or other treatments (either placebo or active comparator). Studies conducted only in Japan were excluded from all analyses as a lower starting dose of sitagliptin has been separately developed in Japan. The pooling also excluded patients who received sitagliptin at doses less than 100 mg/day due to a creatinine clearance <50 mL/min (i.e. moderate to severe renal insufficiency). In addition, studies in which metformin was used as either background therapy or as an active comparator excluded patients whose creatinine clearance was <60 mL/min or whose serum creatinine level was ≥1.4 mg/dL (males) or ≥1.3 mg/dL (females)

due to the contraindications for metformin use in this population with renal impairment.

Investigators reported adverse events (serious and non-serious) that occurred during the conduct of the study. Furthermore, all serious adverse events occurring within 14 days following the last dose of blinded study drug were to have been reported. This pooled analysis used patient-level data from each study to assess the incidence rates of specific adverse events that occurred following initiation of double-blind study drug. These events were encoded in a uniform manner using the Medical Dictionary for Regulatory Activities (MedDRA version 14.1), in which terms for specific adverse events that are alike or pertain to the same organ system are categorized by System Organ Class (SOC). To account for potential differences between groups in duration of exposure to treatment, reports of adverse events are expressed as exposure-adjusted incidence rates (numbers of patients with events per 100 patient-years). These analyses were based upon the time to the first (incident) event, calculated as follows: incident event rate = 100 × (total number of patients with ≥1 event during eligible exposure period per total patient-years of exposure). The incident event rate per 100 patient-years is referred to as the 'incidence rate' throughout the manuscript. For patients for whom an event was reported, the patient-years of exposure were calculated as the time from the first dose of sitagliptin (or comparator) at randomization to the time that the first post-randomization event occurred. For patients without an event, the patient-years of exposure were calculated as the time from the first dose to 14 days after the last dose of study medication (i.e. sitagliptin or comparator).

Most of the studies in this analysis included open-label glycemic rescue therapy. Glycemic rescue therapies included metformin, a thiazolidinedione, a sulfonylurea, or an insulin dose increase (in the add-on to insulin study), and were to have been initiated based upon progressively stricter, protocol-specified hyperglycemic criteria. When initiated, glycemic rescue therapy was added to the ongoing, blinded study medication to which patients had been randomized. The primary analysis in this pooled population used all reported events, including those with an onset after the initiation of glycemic rescue therapy, unless otherwise specified. Differences between treatment groups and the associated 95 % confidence intervals (CI) were calculated using the Miettinen and Nurminen method [23], stratified by study. No statistical adjustments were performed for multiple comparisons. All analyses were performed using SAS Version 9.1 (SAS Institute, Cary, NC, USA).

Hypoglycemia was a prespecified adverse event of interest for most studies in this analysis. Hypoglycemia was based upon investigator assessment of clinical symptoms, without the requirement for a concurrent glucose determination. In contrast to the general analysis of adverse events, the analysis of hypoglycemia excluded data following initiation of glycemic rescue therapy to avoid the confounding influence of medications that could cause hypoglycemia. An additional analysis of hypoglycemia was performed that included only those studies and portions of studies that did not include a sulfonylurea or insulin as a comparator agent or as background therapy, to characterize the incidence rate of hypoglycemia with sitagliptin relative to comparators not generally associated with an increased risk for hypoglycemia (i.e. metformin and pioglitazone, as well as placebo). This additional analysis also excluded data that occurred after initiation of glycemic rescue therapy.

3 Results

3.1 Patient Characteristics and Exposure

At baseline, patients in the entire cohort were ≥65 years of age (55 % male), with a mean age of 69 years (range 65–91 years; 10 % ≥75 years of age), a mean body mass index of 30 kg/m^2, a median duration of diabetes of 5 years, and a mean HbA1c of 8.1 %. The entire cohort was 76 % White, 9 % Asian, and 3 % Black. At baseline, 22 % of patients had a history of cardiovascular disease, and 91 % had additional cardiovascular risk factors besides type 2 diabetes and cardiovascular disease, including hypertension (72 %), history of dyslipidemia/hypercholesterolemia (58 %), and history of smoking (39 %). There were no meaningful differences between treatment groups in these baseline characteristics.

In this pooled analysis of studies 12 weeks to 2 years in duration, the cumulative patient exposure was 984 patient-

Table 1 Patient disposition

	Sitagliptin 100 mg	Non-exposed
Randomized, *N*	1,261	1,185
Discontinued [*n* (%)]	343 (27.2)	341 (28.8)
Reason for discontinuation [*n* (%)]		
Adverse event	65 (5.2)	55 (4.6)
Lack of efficacy[a]	92 (7.3)	89 (7.5)
Lost to follow-up	10 (0.8)	19 (1.6)
Protocol violation	17 (1.3)	23 (1.9)
Withdrawal of consent	76 (6.0)	81 (6.8)
Other reasons[b]	83 (6.5)	74 (6.3)

[a] Includes patients not meeting the protocol-specified, progressively stricter glycemic rescue criteria and/or not meeting the investigator's expectations of glycemic improvement

[b] Includes physician decision, patient moved, site terminated, and other

Table 2 Adverse event summary

	No. of patients with ≥1 event/patient-years follow-up time (100 patient-years incidence rate)		Difference in rates between sitagliptin and non-exposed (95 % CI)[b]
	Sitagliptin 100 mg	Non-exposed	
Patients in population	1,261	1,185	
With one or more adverse events	726/503 (144.2)	687/441 (155.6)	−12.1 (−28.1 to 3.7)
With drug-related adverse events[a]	146/893 (16.4)	198/745 (26.6)	−11.0 (−15.8 to −6.4)[d]
With serious adverse events	102/937 (10.9)	104/843 (12.3)	−1.5 (−4.8 to 1.7)
With serious drug-related adverse events[a]	3/984 (0.3)	2/885 (0.2)	0.0[c]
Who died	2/984 (0.2)	8/885 (0.9)	−0.7 (−1.6 to −0.0)[d]
Discontinued due to an adverse event	61/978 (6.2)	52/881 (5.9)	0.2 (−2.2 to 2.4)
Discontinued due to a drug-related adverse event	15/983 (1.5)	18/884 (2.0)	−0.6 (−1.9 to 0.7)
Discontinued due to a serious adverse event	31/981 (3.2)	18/884 (2.0)	1.0 (−0.6 to 2.5)
Discontinued due to a serious drug-related adverse event	2/984 (0.2)	0/885 (0.0)	0.2[c]

CI confidence interval

[a] As determined by the investigator

[b] Between-group difference and 95 % CI based on stratified analysis. Positive differences indicate that the incidence rate for the sitagliptin group is higher than the incidence rate for the non-exposed group. '0.0' and '−0.0' represent rounding for values that are slightly greater and slightly less than zero, respectively

[c] 95 % CIs were not computed for events that occurred in fewer than four patients in both groups because the CIs would necessarily have included 0

[d] 95 % CI around the difference in incidence rates excludes 0

years for the sitagliptin group and 885 patient-years for the non-exposed group. The proportions of patients discontinuing treatment were 27 % in the sitagliptin group and 29 % in the non-exposed group, with generally similar reasons for discontinuations in the two treatment groups (Table 1).

3.2 Safety and Tolerability

The sitagliptin and non-exposed groups were generally similar in terms of summary measures of adverse events (Table 2). However, there was a higher incidence of death and drug-related adverse events in the non-exposed group (Table 2). Two patients died in the sitagliptin group, one due to multiple injuries related to traumatic accident and one due to an accidental drowning. Eight patients died in the non-exposed group due to cancer ($n = 2$), suicide ($n = 2$), acute myocardial infarction ($n = 1$), hemorrhagic stroke ($n = 1$), hepatic/renal failure ($n = 1$), and unknown cause ($n = 1$). The difference in drug-related adverse events was primarily due to the greater incidence of hypoglycemia in the non-exposed group.

When adverse events were summarized by SOC, there were two SOC categories (Infections and Infestations, and Metabolism and Nutrition Disorders) for which the 95 % CI for the between-group difference in incidence rate excluded 0, with a higher incidence rate in the non-exposed group (Table 3). The between-group difference in the incidence rate in the Infections and Infestations SOC was primarily due to a collectively higher incidence rate of nasopharyngitis, upper respiratory tract infection, urinary tract infection, and herpes zoster in the non-exposed group (Table 4). The between-group difference in the incidence rate in the Metabolism and Nutrition Disorders SOC was primarily due to a higher incidence rate of hypoglycemia in the non-exposed group (discussed below).

The incidence rates of specific adverse events with at least one incident event per 100 patient-years in either group are listed in Table 4. The most commonly reported adverse events (i.e. ≥5 incident events per 100 patient-years in either group) were hypoglycemia, diarrhea, nasopharyngitis, upper respiratory tract infection, and urinary tract infection. For specific adverse events in which the 95 % CI around the between-group difference in incidence rates excluded 0, there were six adverse events (allergic rhinitis, arthropod bite, atrial fibrillation, dental caries, rotator cuff syndrome, and sinus congestion) reported at a higher incidence rate in the sitagliptin group and seven adverse events (blood glucose decreased, head injury, herpes zoster, hypoglycemia, otitis media, peripheral neuropathy, and thermal burn) reported at a higher incidence rate in the non-exposed group (Table 5). Incidence rates for all specific gastrointestinal-related adverse events were similar between the two groups.

For hypoglycemia, the analysis excluded data after initiation of glycemic rescue therapy. The incidence rates of

Table 3 Summary of adverse events by SOC

SOC category	Number of patients with ≥1 event/ patient-years follow-up time (100 patient-years incidence rate)		Difference in rates between sitagliptin and non-exposed (95 % CI)[a]
	Sitagliptin 100 mg	Non-exposed	
Blood and lymphatic system disorders	14/975 (1.4)	6/883 (0.7)	0.6 (−0.4 to 1.7)
Cardiac disorders	61/950 (6.4)	57/858 (6.6)	−0.5 (−2.9 to 1.9)
Congenital, familial and genetic disorders	1/984 (0.1)	1/885 (0.1)	0.0[b]
Ear and labyrinth disorders	21/970 (2.2)	23/871 (2.6)	−0.6 (−2.2 to 0.8)
Endocrine disorders	4/981 (0.4)	7/881 (0.8)	−0.5 (−1.4 to 0.3)
Eye disorders	35/964 (3.6)	37/866 (4.3)	−0.8 (−2.7 to 1.1)
Gastrointestinal disorders	217/847 (25.6)	192/756 (25.4)	−0.5 (−5.6 to 4.5)
General disorders and administration site conditions	80/933 (8.6)	80/838 (9.5)	−1.4 (−4.3 to 1.5)
Hepatobiliary disorders	10/980 (1.0)	7/882 (0.8)	0.2 (−0.8 to 1.1)
Immune system disorders	6/980 (0.6)	9/880 (1.0)	−0.5 (−1.6 to 0.3)
Infections and infestations	306/795 (38.5)	316/695 (45.5)	−6.9 (−13.6 to −0.2)[c]
Injury, poisoning and procedural complications	91/920 (9.9)	83/837 (9.9)	−0.0 (−3.1 to 3.0)
Investigations	127/920 (13.8)	121/823 (14.7)	−0.8 (−4.4 to 2.8)
Metabolism and nutrition disorders	92/935 (9.8)	142/768 (18.5)	−8.8 (−12.7 to −5.1)[c]
Musculoskeletal and connective tissue disorders	175/877 (20.0)	160/788 (20.3)	−1.0 (−5.4 to 3.4)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	35/969 (3.6)	27/872 (3.1)	0.3 (−1.4 to 2.1)
Nervous system disorders	122/907 (13.4)	117/823 (14.2)	−1.0 (−4.6 to 2.5)
Psychiatric disorders	41/961 (4.3)	35/866 (4.0)	0.5 (−1.4 to 2.5)
Renal and urinary disorders	36/961 (3.7)	35/864 (4.0)	−0.5 (−2.4 to 1.4)
Reproductive system and breast disorders	24/968 (2.5)	29/866 (3.3)	−0.9 (−2.6 to 0.7)
Respiratory, thoracic and mediastinal disorders	86/932 (9.2)	77/838 (9.2)	−0.3 (−3.2 to 2.6)
Skin and subcutaneous tissue disorders	89/938 (9.5)	59/850 (6.9)	2.5 (−0.2 to 5.2)
Surgical and medical procedures	1/984 (0.1)	1/885 (0.1)	−0.0[b]
Vascular disorders	56/947 (5.9)	59/847 (7.0)	−1.0 (−3.5 to 1.4)

SOC System Organ Class, *CI* confidence interval

[a] Between-group difference and 95 % CI based on stratified analysis. Positive differences indicate that the incidence rate for the sitagliptin group is higher than the incidence rate for the non-exposed group. '0.0' and '−0.0' represent rounding for values that are slightly greater and slightly less than zero, respectively

[b] 95 % CIs were not computed for events that occurred in fewer than four patients in both groups because the CIs would necessarily have included 0

[c] 95 % CI around the difference in incidence rates excludes 0

hypoglycemia were 7.0 per 100 patient-years in the sitagliptin group and 14.3 in the non-exposed group (difference in rate −7.6 [95 % CI −11.2 to −4.3]). The difference observed for hypoglycemia adverse events was mainly due to the use of a sulfonylurea as a comparator agent in two studies, as well as a study in which patients were switched from placebo to a sulfonylurea during a double-blind continuation period (see Appendix). To account for the use of a sulfonylurea as a comparator agent or the use of a sulfonylurea or insulin as background therapy, a separate pooled analysis of hypoglycemia was conducted in which the confounding effects of these agents were removed. In this analysis, which compared sitagliptin to either placebo or antihyperglycemic agents not known to increase rates of hypoglycemia when used by themselves or together (i.e. metformin or a thiazolidinedione), the incidence rates of hypoglycemia were 5.2 per 100 patient-years in the sitagliptin group ($n = 890$) and 3.8 in the non-exposed group ($n = 810$) [difference in rate 1.5 (95 % CI −1.3 to 4.4)].

4 Discussion

This pooled analysis of 25 double-blind, randomized clinical studies included the data of approximately 2,500 elderly patients treated with sitagliptin 100 mg/day or a

Table 4 Adverse events with at least one incident event per 100 patient-years in one or both groups

Adverse events by SOC	Number of patients with ≥1 event/ patient-years follow-up time (100 patient-years incidence rate)		Difference in rates between sitagliptin and non-exposed (95 % CI)[a]
	Sitagliptin 100 mg	Non-exposed	
Cardiac disorders			
Atrial fibrillation	15/977 (1.5)	4/884 (0.5)	1.1 (0.2 to 2.3)
Coronary artery disease	5/982 (0.5)	9/882 (1.0)	−0.6 (−1.7 to 0.2)
Ear and labyrinth disorders			
Vertigo	12/976 (1.2)	6/881 (0.7)	0.4 (−0.5 to 1.5)
Eye disorders			
Cataract	5/980 (0.5)	9/879 (1.0)	−0.4 (−1.5 to 0.4)
Gastrointestinal disorders			
Abdominal pain[b]	34/965 (3.5)	38/863 (4.4)	−1.2 (−3.2 to 0.6)
Constipation	27/970 (2.8)	16/871 (1.8)	0.9 (−0.5 to 2.4)
Diarrhea	56/948 (5.9)	66/849 (7.8)	−2.1 (−4.7 to 0.3)
Dyspepsia	25/966 (2.6)	16/873 (1.8)	0.8 (−0.6 to 2.3)
Gastritis	14/977 (1.4)	14/877 (1.6)	−0.1 (−1.3 to 1.2)
Gastroesophageal reflux disease	16/974 (1.6)	9/880 (1.0)	0.5 (−0.7 to 1.6)
Nausea	23/968 (2.4)	21/868 (2.4)	−0.1 (−1.7 to 1.4)
Vomiting	13/974 (1.3)	10/880 (1.1)	0.2 (−1.0 to 1.3)
General disorders and administration site conditions			
Fatigue	18/975 (1.8)	21/873 (2.4)	−0.7 (−2.2 to 0.7)
Peripheral edema	25/967 (2.6)	28/874 (3.2)	−0.5 (−2.2 to 1.1)
Infections and infestations			
Bronchitis	34/964 (3.5)	33/866 (3.8)	−0.2 (−2.1 to 1.6)
Cellulitis	5/980 (0.5)	9/879 (1.0)	−0.5 (−1.5 to 0.4)
Cystitis	7/981 (0.7)	9/884 (1.0)	−0.3 (−1.4 to 0.6)
Gastroenteritis	14/977 (1.4)	13/875 (1.5)	0.0 (−1.2 to 1.2)
Herpes zoster	4/982 (0.4)	11/877 (1.3)	−0.9 (−1.9 to −0.0)
Influenza	30/970 (3.1)	31/865 (3.6)	−0.6 (−2.4 to 1.2)
Nasopharyngitis	55/948 (5.8)	59/852 (6.9)	−1.0 (−3.5 to 1.4)
Pharyngitis	8/980 (0.8)	11/880 (1.2)	−0.3 (−1.4 to 0.7)
Pneumonia	14/973 (1.4)	15/879 (1.7)	−0.3 (−1.6 to 0.9)
Sinusitis	22/974 (2.3)	15/879 (1.7)	0.4 (−1.0 to 1.8)
Upper respiratory tract infection	68/940 (7.2)	72/843 (8.5)	−1.3 (−4.0 to 1.3)
Urinary tract infection	41/963 (4.3)	45/862 (5.2)	−1.1 (−3.3 to 0.9)
Injury, poisoning, and procedural complications			
Contusion	16/976 (1.6)	11/881 (1.2)	0.3 (−0.8 to 1.5)
Investigations			
Blood glucose decreased	6/979 (0.6)	15/876 (1.7)	−1.1 (−2.3 to −0.1)
Blood glucose increased	14/980 (1.4)	16/880 (1.8)	−0.1 (−1.4 to 1.2)
Blood uric acid increased	11/980 (1.1)	6/883 (0.7)	0.5 (−0.4 to 1.6)
Creatinine renal clearance decreased	17/979 (1.7)	12/882 (1.4)	0.3 (−0.9 to 1.5)
Metabolism and nutrition disorders			
Hyperglycemia	9/981 (0.9)	16/879 (1.8)	−0.9 (−2.1 to 0.2)
Hypoglycemia[c]	65/947 (6.9)	110/785 (14.0)	−7.5 (−10.9 to −4.3)
Musculoskeletal and connective tissue disorders			
Arthralgia	37/965 (3.8)	32/865 (3.7)	0.2 (−1.7 to 2.0)
Back pain	40/963 (4.2)	29/869 (3.3)	0.8 (−1.0 to 2.7)
Muscle spasms	13/976 (1.3)	13/878 (1.5)	−0.1 (−1.3 to 1.1)

Table 4 continued

Adverse events by SOC	Number of patients with ≥1 event/ patient-years follow-up time (100 patient-years incidence rate)		Difference in rates between sitagliptin and non-exposed (95 % CI)[a]
	Sitagliptin 100 mg	Non-exposed	
Musculoskeletal pain	10/978 (1.0)	13/877 (1.5)	−0.6 (−1.8 to 0.5)
Osteoarthritis	21/971 (2.2)	26/871 (3.0)	−1.0 (−2.6 to 0.5)
Pain in extremity	28/967 (2.9)	17/877 (1.9)	0.7 (−0.8 to 2.3)
Nervous system disorders			
Dizziness	30/969 (3.1)	15/879 (1.7)	1.3 (−0.1 to 2.8)
Headache	31/968 (3.2)	35/867 (4.0)	−0.9 (−2.8 to 0.9)
Paraesthesia	12/977 (1.2)	9/883 (1.0)	0.3 (−0.9 to 1.3)
Sciatica	12/977 (1.2)	6/884 (0.7)	0.6 (−0.4 to 1.6)
Psychiatric disorders			
Depression	15/978 (1.5)	11/880 (1.3)	0.4 (−0.8 to 1.6)
Insomnia	15/974 (1.5)	11/878 (1.3)	0.3 (−0.9 to 1.4)
Reproductive system and breast disorders			
Benign prostatic hyperplasia	9/980 (0.9)	9/878 (1.0)	−0.0 (−1.1 to 1.0)
Respiratory, thoracic, and mediastinal disorders			
Cough	32/967 (3.3)	25/866 (2.9)	0.1 (−1.6 to 1.8)
Oropharyngeal pain	10/973 (1.0)	10/879 (1.1)	−0.2 (−1.3 to 0.9)
Skin and subcutaneous tissue disorders			
Rash	11/978 (1.1)	9/880 (1.0)	0.1 (−1.0 to 1.1)
Vascular disorders			
Hypertension	31/965 (3.2)	26/869 (3.0)	0.3 (−1.4 to 2.0)

SOC System Organ Class, *CI* confidence interval

[a] Between-group difference and 95 % CI based on stratified analysis. Positive differences indicate that the incidence rate for the sitagliptin group is higher than the incidence rate for the non-exposed group. '0.0' and '−0.0' represent rounding for values that are slightly greater and slightly less than zero, respectively

[b] Abdominal pain includes abdominal pain, upper and lower abdominal pain, and abdominal and epigastric discomfort

[c] For this adverse event, see text for the results of the analysis which excludes data after initiation of glycemic rescue therapy

non-sitagliptin treatment for up to 2 years. Overall, treatment with sitagliptin was generally well tolerated in these patients. The exposure-adjusted incidence rates of adverse events were generally similar between treatment groups. These findings are consistent with smaller pooled analyses evaluating the DPP-4 inhibitors vildagliptin and alogliptin in elderly subjects [24, 25]. Collectively, these results suggest that DPP-4 inhibitors are generally well tolerated when used by elderly patients with type 2 diabetes.

Certain antihyperglycemic therapies (e.g. sulfonylurea or insulin) are associated with a greater risk of hypoglycemia. Hypoglycemia is an undesirable side effect and may limit treatment effectiveness, especially in elderly patients [26, 27]. In this analysis, the incidence rate of hypoglycemia was lower in the sitagliptin group compared with that in the non-exposed group. Use of a sulfonylurea as a comparator agent in some studies accounts primarily for this difference in hypoglycemia as well as the greater incidence of drug-related adverse events overall in the non-exposed group. In a separate analysis excluding the influence of sulfonylurea and insulin, the incidence of hypoglycemia was similar between groups. This is consistent with a clinical trial in 206 elderly patients which showed that the risk of hypoglycemia with sitagliptin monotherapy was similar compared with placebo in this population [22]. However, an increase in hypoglycemia has been reported when sitagliptin is added to sulfonylurea or insulin therapy [28, 29]. Thus, clinicians should understand the differences in risk of hypoglycemia associated with sitagliptin when used alone or with other antihyperglycemic agents.

Gastrointestinal intolerance related to medicines is an important factor to consider for elderly patients [11]. Metformin, α-glucosidase inhibitors, and GLP-1RAs are commonly associated with gastrointestinal side effects [12, 30]. In head-to-head clinical studies, the incidence of gastrointestinal-related adverse events was lower with sitagliptin treatment compared with these agents [19, 20, 31, 32]. In the present analysis, the incidences of gastrointestinal-related adverse events were similar in the sitagliptin group and the non-exposed group.

Table 5 Adverse events for which the 95 % CI around the difference in incidence rates excludes 0

Adverse events (alphabetized)	Number of patients with ≥1 event/ patient-years follow-up time (100 patient-years incidence rate)		Difference in rates between sitagliptin and non-exposed (95 % CI)[a]
	Sitagliptin 100 mg	Non-exposed	
Sitagliptin > non-exposed			
Allergic rhinitis	7/980 (0.7)	1/885 (0.1)	0.7 (0.1 to 1.6)
Arthropod bite	7/979 (0.7)	0/885 (0.0)	0.7 (0.1 to 1.5)
Atrial fibrillation	15/977 (1.5)	4/884 (0.5)	1.1 (0.2 to 2.3)
Dental caries	7/980 (0.7)	1/885 (0.1)	0.6 (0.0 to 1.5)
Rotator cuff syndrome	7/979 (0.7)	1/884 (0.1)	0.6 (0.0 to 1.5)
Sinus congestion	9/978 (0.9)	0/885 (0.0)	0.8 (0.2 to 1.7)
Non-exposed > sitagliptin			
Blood glucose decreased	6/979 (0.6)	15/876 (1.7)	−1.1 (−2.3 to −0.1)
Head injury	0/984 (0.0)	4/882 (0.5)	−0.5 (−1.2 to −0.0)
Herpes zoster	4/982 (0.4)	11/877 (1.3)	−0.9 (−1.9 to −0.0)
Hypoglycemia[b]	65/947 (6.9)	110/785 (14.0)	−7.5 (−10.9 to −4.3)
Otitis media	1/983 (0.1)	6/882 (0.7)	−0.6 (−1.5 to −0.1)
Peripheral neuropathy	2/982 (0.2)	8/881 (0.9)	−0.8 (−1.7 to −0.1)
Thermal burn	0/984 (0.0)	5/883 (0.6)	−0.6 (−1.4, −0.1)

CI confidence interval

[a] Between-group difference and 95 % CI based on stratified analysis. Positive differences indicate that the incidence rate for the sitagliptin group is higher than the incidence rate for the non-exposed group. '0.0' and '−0.0' represent rounding for values that are slightly greater and slightly less than zero, respectively

[b] For this adverse event, see text for the results of the analysis which excludes data after initiation of glycemic rescue therapy

The incidence rate for the Infections and Infestations SOC was higher in the non-exposed group than in the sitagliptin group. The specific adverse events of nasopharyngitis, upper respiratory tract infection, urinary tract infection, and herpes zoster were the main contributors to the overall difference in this SOC. These results are consistent with those from a recent meta-analysis of published studies of marketed DPP-4 inhibitors showing no increased risk of infection-related adverse events [33] and in contrast to findings from earlier meta-analyses that reported an increased risk for infections overall and for the specific infections of nasopharyngitis, upper respiratory tract infection, and urinary tract infection [34, 35].

Patients with type 2 diabetes have an increased mortality risk compared to their non-diabetic counterparts. Although the number of deaths was small in the present analysis, the incidence of death in the sitagliptin group was lower compared with the non-exposed group. Older patients also have a greater risk of experiencing a cardiovascular event. The present analysis showed no difference between groups in the overall evaluation of the Cardiac Disorders SOC. In this SOC, there were two adverse events (one in each group) with an incidence rate ≥1 event per 100 patient-years: atrial fibrillation, with a higher rate in the sitagliptin group; and coronary artery disease, with a numerically higher rate in the non-exposed group. An analysis of major adverse cardiovascular events (MACE) was not performed in this pooled elderly cohort because of the limited number of events. However, the cardiovascular safety of sitagliptin is presently being assessed in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), which enrolled over 14,000 patients ≥50 years of age with type 2 diabetes and documented cardiovascular disease and is anticipated to have a substantial proportion of the randomized population ≥65 years of age [36].

The following limitations of the present pooled analysis should be considered when interpreting the findings. The data are from patients included in randomized, controlled clinical studies of up to 2 years in duration, and these patients may not be fully representative of those who use sitagliptin in the general population. For example, the studies that comprised this pooled analysis did not include patients with recent cardiovascular events or with estimated glomerular filtration rates below 50 mL/min. Additionally, many of the studies that included metformin use had an upper age limit of 78 years, thus limiting the proportion of patients in the higher age range. Multiple comparisons were made without an adjustment for multiplicity, which may increase the chance for spurious findings. The analysis of hypoglycemia was based on symptomatic

events, without requiring corroborating blood glucose measurements; this could potentially overestimate incidence rates, or alternatively could underestimate rates in view of the tendency for older patients to have reduced symptomatic responses to reductions in blood glucose. A strength of this pooled analysis is the use of patient-level data for nearly 2,500 patients ≥65 years of age, although this population size may be too small to identify rare events.

5 Conclusion

In this post hoc analysis of data in elderly patients with type 2 diabetes treated with sitagliptin or comparator for up to 2 years, treatment with sitagliptin 100 mg/day was generally well tolerated, with a low incidence of hypoglycemia.

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Conflicts of interest All authors are employed by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., the manufacturer of sitagliptin, and may have company stock or stock options.

Author contributions Elizabeth M. Round, Samuel S. Engel, Gregory T. Golm, Keith D. Kaufman, and Barry J. Goldstein conceived the design for the analyses. Gregory T. Golm performed the statistical analyses. All authors were involved in the interpretation of the analyses, drafting the manuscript or revising it critically for important intellectual content, and approving the final manuscript.

Appendix

See Table 6.

Table 6 Studies and treatment arms included in the analysis

Study	Study design	Sitagliptin 100 mg/day group[b] ($N = 1,261$)	n	Non-exposed group[b] ($N = 1,185$)	n	References[a]
P010: twice-daily dose-range finding	106-week active-controlled period	Sitagliptin 50 mg bid switched to sitagliptin 100 mg qd	18	Glipizide	22	[37]
P014: once-daily dose-range finding	12-week placebo-controlled period and 94-week active-controlled period	Sitagliptin 100 mg qd	19	Placebo (12 weeks) switched to metformin (94 weeks)	20	[38]
		Sitagliptin 50 mg bid switched to sitagliptin 100 mg qd	20			
P019: placebo-controlled add-on to pioglitazone study	24-week placebo-controlled period	Sitagliptin 100 mg qd	42	Placebo	44	[39]
P020: placebo-controlled add-on to metformin study	24-week placebo-controlled period and 80-week active-controlled period	Sitagliptin 100 mg qd	77	Placebo (24 weeks) switched to glipizide	32	[40]
P021: placebo-controlled monotherapy study	24-week placebo-controlled period	Sitagliptin 100 mg qd	29	Placebo	44	[41]
P023: placebo-controlled monotherapy study	18-week placebo-controlled period and 36-week active-controlled period	Sitagliptin 100 mg qd	38	Placebo (18 weeks) switched to pioglitazone (36 weeks)	21	[42]
P024: active-controlled add-on to metformin study	104-week active-controlled period	Sitagliptin 100 mg qd	120	Glipizide	123	[43, 44]
P035: placebo-controlled add-on to glimepiride, alone or in combination with metformin study	24-week placebo-controlled period and 30-week active-controlled period	Sitagliptin 100 mg qd	47	Placebo (24 weeks) switched to pioglitazone (30 weeks)	50	[28]
P036: placebo- and active-controlled study of initial combination use of sitagliptin and metformin	24-week placebo-controlled period; 80-week active-controlled period	Sitagliptin 100 mg qd	29	Placebo (24 weeks) switched to metformin (80 weeks)	22	[45–47]
		Sitagliptin 50 mg bid + metformin 500 mg bid	30	Metformin 500 mg bid	26	
		Sitagliptin 50 mg bid + metformin 1,000 mg bid	17	Metformin 1,000 mg bid	21	

Table 6 continued

Study	Study design	Sitagliptin 100 mg/day group[b] ($N = 1,261$)	*n*	Non-exposed group[b] ($N = 1,185$)	*n*	References[a]
P040: placebo-controlled monotherapy study	18-week placebo-controlled period	Sitagliptin 100 mg qd	32	Placebo	15	[48]
P047: placebo-controlled monotherapy study in elderly patients	24-week placebo-controlled period	Sitagliptin 100 mg qd	91	Placebo	92	[22]
P049: active-controlled monotherapy study	24-week active-controlled period	Sitagliptin 100 mg qd	129	Metformin	109	[31]
P051: placebo-controlled add-on to insulin, alone or in combination with metformin study	24-week placebo-controlled period	Sitagliptin 100 mg qd	81	Placebo	68	[29]
P052: placebo-controlled add-on to metformin and rosiglitazone study	54-week placebo-controlled period	Sitagliptin 100 mg qd	22	Placebo	14	[49]
P053: placebo-controlled add-on to metformin study	30-week placebo-controlled period	Sitagliptin 100 mg qd	11	Placebo	18	[50]
P061: placebo- and active-controlled mechanism of action factorial study	12-week placebo-controlled period	Sitagliptin 100 mg qd	3	Pioglitazone	4	[51]
		Sitagliptin 100 mg qd + pioglitazone	1	Placebo	2	
P064: active-controlled study of initial combination use of sitagliptin and pioglitazone	54-week active-controlled period	Sitagliptin 100 mg qd + pioglitazone	23	Pioglitazone	31	[52, 53]
P066: active-controlled study of combination use of sitagliptin/metformin FDC	32-week active-controlled period	Sitagliptin 50 mg + metformin 1,000 mg bid (FDC)	39	Pioglitazone 45 mg qd	32	[54]
P068: active-controlled study of sitagliptin and combination use of sitagliptin/metformin FDC	40-week active-controlled period	Sitagliptin 100 mg qd switched to sitagliptin 50 mg + metformin 1,000 mg bid (FDC)	19	Pioglitazone 15 mg qd titrated up to 45 mg qd	29	[55]
P074: placebo-controlled add-on to metformin study	24-week placebo-controlled period	Sitagliptin 100 mg qd	26	Placebo	36	[56]
P079: active-controlled study of initial combination use of sitagliptin/metformin FDC	44-week active-controlled period	Sitagliptin 50 mg + metformin 1,000 mg bid (FDC)	49	Metformin 1,000 mg bid (FDC)	48	[57, 58]
P102: active-controlled study of initial combination use of sitagliptin and pioglitazone	54-week active-controlled period	Sitagliptin 100 mg qd	20			[59]
		Sitagliptin 50 mg bid + pioglitazone 15 mg qd	27	Pioglitazone 15 mg qd	24	
		Sitagliptin 50 mg bid + pioglitazone 30 mg qd	27	Pioglitazone 30 mg qd	30	
		Sitagliptin 50 mg bid + pioglitazone 45 mg qd	29	Pioglitazone 45 mg qd	35	
P128: placebo-controlled add-on to metformin and pioglitazone study	26-week placebo-controlled period	Sitagliptin 100 mg qd	24	Placebo	31	[60]
P801: placebo- and active-controlled add-on to metformin study	18-week placebo-controlled period	Sitagliptin 100 mg qd	17	Rosiglitazone 8 mg qd	17	[61]
				Placebo	13	
P803: active-controlled add-on to metformin study	30-week active-controlled period	Sitagliptin 100 mg qd	105	Glimepiride	112	[62]

qd once daily, *bid* twice daily, *FDC* fixed-dose combination tablet

[a] References are for the initial phases of the studies that had extension or continuation phases, unless a reference is provided for the results beyond the initial phase

[b] This column reflects the blinded treatment(s) to which patients were randomized. For studies identified in column 1 as 'add-on' studies, all patients also received the active therapy indicated in column 1 as open-label

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