Safety of Sitagliptin in Patients with Type 2 Diabetes and Chronic Kidney Disease: Outcomes from TECOS

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ABSTRACT

Aims: To characterize the incidence of diabetes-associated complications and assess the safety of sitagliptin in participants with chronic kidney disease (CKD) in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS).

Materials and methods: For participants with baseline eGFR measurements (n=14,528), baseline characteristics and safety outcomes were compared for the CKD cohort (eGFR <60 mL/min per 1.73 m^2) versus those without CKD. Within the CKD cohort, the same analyses were performed comparing sitagliptin- and placebo-assigned participants. Baseline characteristics were summarized for all participants, and serious adverse events were analyzed in those who received at least one dose of study medication. Adverse events of interest and diabetes complications were summarized for the intention-to-treat population.

Results: CKD was present in 3324 (23%) participants at entry into TECOS. The mean (SD) age for this CKD cohort was 68.8 (7.9) years, mean diabetes duration was 13.7 (9.0) years, and 62% were men. Incidences of serious adverse events, malignancy, bone fracture, severe hypoglycemia and most categories of diabetes complications were higher in the CKD cohort compared with those without CKD. Over ~2.8 median years' follow-up, CKD participants assigned to sitagliptin had similar rates of diabetic eye disease, diabetic neuropathy, renal failure, malignancy, bone fracture, pancreatitis and severe hypoglycemia as placebo-assigned participants.

Conclusions: Participants in TECOS with CKD had higher incidences of serious adverse events and diabetes complications than those without CKD. Treatment with sitagliptin was generally well tolerated with no meaningful differences observed in safety outcomes between those with CKD assigned sitagliptin or placebo.

INTRODUCTION

Chronic kidney disease (CKD) is a well-recognized complication of long-standing diabetes, and is a major factor contributing to the morbidity and mortality of this condition. Despite advances in preventive treatment strategies, such as dietary protein restriction, intensified glycemic control, improved blood pressure management and modulation of the renin-angiotensin system, CKD remains a common co-morbidity for patients with type 2 diabetes. In the DEMAND study,[1] a global (33-country) cross-sectional analysis of over 24,000 patients with diabetes, 22% of the participants had renal insufficiency, defined as an estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2. More recently, an electronic medical records database study in the US[2] comprising approximately 1.4 million patients with type 2 diabetes over the 2014-2015 time frame showed that 28% of this population had an eGFR <60 mL/min per 1.73 m^2. There also appears to be a disproportionate increase in the prevalence of CKD associated with diabetes, beyond the increased global prevalence of diabetes, driven in part by the changing global epidemiology of diabetes and in particular by an increased diabetes prevalence amongst ethnic groups that have a higher risk of diabetic complications.[3]

Treatment guidelines for the management of hyperglycemia in type 2 diabetes continue to emphasize personalized therapy, balancing the benefits of improved glycemic control with the risks related to adverse effects of glucose-lowering medications.[4] These considerations are particularly relevant for patients with CKD, who may be at greater risk for, or more susceptible to, severe consequences from such adverse effects. Metformin use has traditionally been limited in patients with CKD, primarily related to concerns about lactic acidosis; recent scholarly reviews have challenged the evidence base for this restriction, and regulatory agencies are revisiting the use of metformin in patients with moderate renal insufficiency, potentially at reduced doses.[5-7] Concern regarding hypoglycemia limits the use of many sulfonylurea and non-sulfonylurea insulin secretagogues, although short-acting agents such as glipizide and gliclazide are generally considered to be acceptable in this population. SGLT-2 inhibitors, whose mechanism of action is based on the SGLT-2 transporter in the kidney, have limited glycemic efficacy in patients with CKD. In contrast to these concerns, dipeptidyl peptidase-4 (DPP-4) inhibitors have been

found to improve glycemia in patients with renal insufficiency, including patients on dialysis, and are well-tolerated in randomized clinical trials of up to 1 year in duration.[8-10] However, longer-term data regarding the safety and tolerability of DPP-4 inhibitors are limited.

Sitagliptin, an orally administered DPP-4 inhibitor, prolongs the action of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), leading to improved glycemic control in patients with type 2 diabetes. The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) was a randomized, double-blind, placebo-controlled trial that assessed the impact of sitagliptin on cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease. Almost one quarter of the 14,671 participants had CKD, defined as an eGFR <60 mL/min per 1.73 m^2, providing an opportunity to examine placebo-controlled outcomes over a median follow-up period of 3.0 years. TECOS demonstrated that impaired kidney function was associated with worse cardiovascular outcomes and that sitagliptin had no clinically significant impact on either cardiovascular or CKD outcomes, irrespective of baseline eGFR.[11] Here we describe a broad range of safety outcomes in this vulnerable population.

METHODS

The design, protocol, and primary results of TECOS (NCT00790205) have been published previously.[12,13] The study was designed and run independently by the Duke Clinical Research Institute and the University of Oxford Diabetes Trials Unit in an academic collaboration with the sponsor, Merck Sharp & Dohme. The protocol was approved by the ethics committees associated with all participating trial sites, and all participants provided written informed consent for trial participation.

Briefly, 14,671 participants from 38 countries were enrolled between December 2008 and July 2012. Eligible participants were ≥50 years old (with no upper age limit) with type 2 diabetes, atherosclerotic cardiovascular disease, and glycated hemoglobin (HbA1c) values of 6.5–8.0% (48–64 mmol/mol) on stable dose mono- or dual-combination therapy with metformin, pioglitazone, or sulfonylurea, or insulin (with or without metformin). Study participants were randomized in a double-

blind fashion to either sitagliptin or placebo at doses appropriate for their eGFR. Patients with an eGFR <30 mL/min per 1.73 m^2 were not eligible. During follow-up, treatment for type 2 diabetes and its comorbidities was provided by usual care providers based on local guidelines. The addition of any glucose-lowering agent was permitted, with the exception of a GLP-1 receptor agonists or open-label DPP-4 inhibitor. Use of rosiglitazone was discouraged. Data regarding use of concomitant medications, occurrence of severe hypoglycemia (hypoglycemia requiring the assistance of another individual), death, hospitalization, cardiovascular events and interventions, expected clinical events including diabetes complications, serious adverse events (SAEs), and adverse events resulting in study drug discontinuation were recorded at all visits. Adverse events that were included in the expected clinical events list, or that were considered to be potential cardiovascular endpoints, were not subject to expedited reporting and are not included in the SAE analyses. Events that were included in the clinical events list can be found in the Supplementary Appendix. All reported events of death, myocardial infarction, stroke, hospitalization for unstable angina or heart failure, acute pancreatitis and cancer (other than non-melanoma skin cancers) were adjudicated by an independent committee masked to randomized treatment assignment. Adjudicated event definitions have been published previously.[13]

The present analysis compares baseline characteristics and safety in the cohort of participants with CKD (eGFR <60 mL/min per 1.73 m^2) versus those without CKD (eGFR ≥ 60 mL/min per 1.73 m^2), and then within the CKD cohort similarly compares participants assigned to sitagliptin versus those assigned to placebo. Baseline characteristics for continuous variables are summarized as mean ±1 standard deviation or median and interquartile range (IQR), and categorical variables as count (percentage). The duration of intention-to-treat (ITT) follow-up in the study, and the duration of follow-up on study drug, are provided as median and IQR. SAEs were analyzed in the all-patients-as-treated population, which consists of all randomized patients who received at least one dose of study therapy. Adverse events of interest and diabetes complications summaries are presented for the ITT population. Safety events were analyzed as binary variables indicating whether the event occurred during the follow-up period. Summary statistics for each CKD cohort and each treatment group among CKD patients are

presented as percentage and 95% confidence intervals of patients with events, and risk difference between groups. Miettinen-Nurminen confidence intervals are given for the risk difference between CKD and no CKD, and between sitagliptin and placebo. The CIs for percentage of patients with events were estimated through the Wilson score method. No adjustments were made to levels of statistical significance for multiple testing.

Within the CKD cohort, repeated-measures analysis of variance was used to test for eGFR differences between sitagliptin and placebo over 4 years. The model included baseline eGFR, allocated treatment, time of assessment and region. Values for eGFR over the course of the study are plotted at each visit with mean and I-bars drawn to one standard deviation. Data were analyzed with SAS version 9.4.

RESULTS

Of 14,671 TECOS randomized participants, 14,528 (99%) in the ITT population had a documented baseline eGFR value and were included in these analyses. There were 3324 (23%) in the CKD cohort and 11,204 (77%) in the non-CKD cohort. For the CKD cohort, median (IQR) duration of follow-up was 2.8 (2.2, 3.6) years and median study drug exposure was 2.4 (1.9, 3.3) years. For the non-CKD cohort, median (IQR) duration of follow-up was 3.0 (2.3, 3.7) years and median study drug exposure was 2.7 (2.1, 3.5) years.

Comparison of participants with or without CKD

Key baseline demographic and anthropometric characteristics are depicted in Table 1. CKD participants tended to be older and had a longer diabetes duration. By definition, the mean eGFR was lower in the CKD cohort. Other baseline characteristics, including HbA1c, blood pressure, and lipid parameters, did not differ meaningfully between the two cohorts.

SAEs, categorized by System Organ Class and occurring at a frequency of ≥1% in ≥1 cohort, are shown in Table 2. The incidence of reported SAEs in the CKD and non-CKD cohorts was 14.3% and 12.2%, respectively, with the most common category for both cohorts being neoplasms. Slightly higher

incidences were observed in the CKD cohort compared with the non-CKD cohort across all System Organ Class categories, but with no evident imbalances for specific adverse events (data not shown).

The incidence of investigator-reported diabetic complications was generally higher in the CKD cohort (Table 3). Renal failure events were observed in 3.4% *vs.* 0.9% of the CKD and non-CKD cohorts respectively, with a modest decrease in mean eGFR over time in the non-CKD but not the CKD cohort (Figure 1A). Other investigator-reported diabetic complications that occurred more frequently in the CKD cohort included amputation, gangrene, any hospitalization due to complications of diabetes and infections.

Adverse events of interest are displayed in Table 4. Severe hypoglycemia was observed in 3.3% of the CKD cohort *vs.* 1.7% of the non-CKD cohort. Bone fractures and overall malignancies were also more common in the CKD cohort (3.5% *vs.* 2.3% and 4.7% *vs.* 3.6%, respectively). The incidence of pancreatic-related events, *i.e.* pancreatitis and pancreatic malignancy, were similar in the two cohorts.

Comparison within the CKD cohort of the sitagliptin and placebo groups

Key baseline demographic and anthropometric characteristics are depicted in Table 1, and were well balanced between the two treatment groups.

SAEs categorized by System Organ Class, occurring at a frequency of ≥1% in ≥1 treatment group, are shown in Table 2. The incidence of reported SAEs in the sitagliptin and placebo groups was 13.8% *vs.* 14.7%, respectively. For all System Organ Class categories, the 95% confidence intervals around the difference in risk of SAEs between treatment groups included zero. The most common category in both treatment groups was neoplasms (4.8% and 6.0% in the sitagliptin and placebo groups, respectively). For all other System Organ Class categories, the absolute difference in incidences was < 1%.

The incidences of investigator-reported diabetic complications are displayed in Table 3 and were generally similar between the sitagliptin and placebo groups with none that were significantly different. In regard to complications related to renal function, microalbuminuria was reported in 7.7% of the sitagliptin

group and 9.1% of the placebo group, and renal failure in 3.3% and 3.6%, respectively. As shown in Figure 1B, CKD participants assigned to sitagliptin had a marginally lower eGFR during the trial compared with those allocated to placebo (-1.62 [-2.37, -0.87] mL/min per 1.73 m^2); a similar difference was observed in the per protocol population (-1.70 [-2.46, -0.94] mL/min per 1.73 m^2).

Adverse events of interest in the CKD cohort are displayed in Table 4. Similar incidences of these events were observed in the two treatment groups.

DISCUSSION

With the increasing prevalence and longevity of patients with both type 2 diabetes and CKD, the need for long-term data on the safety of glucose-lowering therapies in this population has become increasingly compelling. DPP-4 inhibitors have been demonstrated to be efficacious and generally well-tolerated in patients with CKD, but most clinical trials involving CKD patients have been conducted for ≤1 year and have not focused specifically on the more vulnerable population of patients who are at high cardiovascular risk. This further analysis of the TECOS data examines safety outcomes in a type 2 diabetes population with existing cardiovascular disease, looking specifically at those with CKD allocated to sitagliptin or placebo with 9641 person-years' follow-up over a median of 3.0 years.

The incidence of cardiovascular events was higher in the TECOS CKD cohort compared with the non-CKD cohort, as reported previously.[11] A similar pattern was evident with respect to the general safety assessments reported here, with a trend to higher incidences of SAEs, malignancy, bone fracture, severe hypoglycemia and most categories of investigator-reported diabetic complications. While impairment in renal function *per se* may be contributing to some of these observations, differences in the CKD cohort baseline characteristics may also have contributed to different incidences of these safety endpoints. It is noteworthy that the CKD cohort, compared with the non-CKD cohort, was older, had a longer duration of diabetes, had a higher proportion of women, and had a higher proportion of insulin use at baseline.

Within the CKD cohort, the sitagliptin and placebo groups were well-balanced with regard to demographic and disease-related characteristics and had similar incidences of SAEs during the trial.

Whilst the overall incidence of severe hypoglycemia was approximately two-fold higher in the CKD compared with the non-CKD cohort, no difference was seen between the two treatment groups despite the somewhat lower within-trial HbA1c levels observed in the sitagliptin group. Investigator-reported diabetic complications also occurred with a generally similar incidence in the two treatment groups.

In the overall TECOS population, a modest decline in eGFR was noted in both treatment groups over the course of the study, with a small but statistically significant difference of -1.34 mL/min per 1.73 m^2 in the sitagliptin group compared with the placebo group.[13] Thus, the profile of renal safety in the TECOS CKD cohort, which might be especially sensitive to any detrimental renal effect, is of particular interest. Within the CKD cohort, the incidences of the investigator-reported outcomes of renal failure did not differ. Interestingly, although the within-trial mean eGFR levels in the sitagliptin group were marginally lower than the placebo group, they did not decline over time in the CKD population. This small between-group difference of ~1.7 ml/min/1.73 m^2 is not meaningfully different from the difference observed in the overall population and, as with the change in the overall population, the difference was observed early and did not progress over time, making it unlikely that this represents a drug-related toxicity. The stability of mean eGFR levels in the CKD cohort over time is somewhat surprising given the natural history of diabetic nephropathy, and given the decline seen in the overall cohort, but may reflect an increased focus on renoprotective treatment strategies (e.g., blood pressure management) in this subgroup during the course of the study, or could simply be a reflection of regression to the mean.

There are limitations to these additional TECOS analyses. First, the study did not include the entire spectrum of patients with CKD, as participants with end-stage renal disease or with eGFR <30 mL/min per 1.73 m^2 were excluded. Second, the eligibility criteria required an entry HbA1c of 6.5 to 8.0% (48 to 64 mmol/mol), meaning these findings may not be applicable to patients with more severe degrees of hyperglycemia. Additionally, the study reflects findings over the median 2.8 years of follow-up in the CKD cohort, and may not reflect a longer-term impact. Finally, the study was not designed to collect information on non-serious adverse events, and did not include potential cardiovascular endpoints or events on the clinical events list in the analysis of serious adverse events.

In conclusion, CKD participants in TECOS had higher incidences of SAEs and diabetic complications than non-CKD participants. Treatment with sitagliptin was well tolerated in CKD participants, with no evidence of adverse impact on the safety endpoints in TECOS.

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Author contributions: S.S.E. contributed to the study design, data analysis and interpretation, and drafted and edited the manuscript. S.S., R.G.J., J.H.C., N.J., A.R., T.T., J.W., and E.D.P. edited the manuscript. S.R.S. performed the statistical analysis and edited the manuscript. R.R.H. contributed to the study design, data analysis and interpretation, and edited the manuscript. S.S.E. and R.R.H. are the guarantors of this work and, as such, had full access to all of the data in the study and take full responsibility for the work as a whole, including the study design and integrity of the data.

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References

1. Parving H-H, Lewis JB, Ravid M, et al. Prevalence and risk factors for microalbuminuria in a referred cohort of type II diabetic patients: A global perspective. Kidney Int. 2006;69(11):2057–2063.
2. Iglay K, Hannachi H, Howie PJ, et al. Prevalence and co-prevalence of comorbidities among patients with type 2 diabetes mellitus. Curr Med Res Opin. 2016;32(7):1243-1252.
3. Thomas MC, Cooper ME, Zimmet P. Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. Nat Rev Nephrol. 2016;12(2):73-81.
4. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015 Jan;38(1):140-149.
5. Inzucchi SE, Lipska KJ, Mayo H, et al. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. JAMA. 2014;312(24):2668-2675.
6. European Medicines Agency. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Metformin_and_metformin-containing_medicines/human_referral_000397.jsp&mid=WC0b01ac05805c516f. Accessed October 25, 2016.
7. US Food and Drug Administration. http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm. Accessed October 25, 2016.
8. Arjona Ferreira JC, Marre M, Barzilai N, et al. Efficacy and safety of sitagliptin versus glipizide in patients with type 2 diabetes and moderate-to-severe chronic renal insufficiency. Diabetes Care. 2013;36(5):1067-1073.
9. Arjona Ferreira JC, Corry D, Mogensen CE, et al. Efficacy and safety of sitagliptin in patients with type 2 diabetes and ESRD receiving dialysis: a 54-week randomized trial. Am J Kidney Dis. 2013;61(4):579-587.

10. Nowicki M, Rychlik I, Haller H, et al. Saxagliptin improves glycaemic control and is well tolerated in patients with type 2 diabetes mellitus and renal impairment. Diabetes Obes Metab. 2011;13(6):523-532.

11. Cornel JH, Bakris GL, Stevens SR, et al. Effect of sitagliptin on kidney function and respective cardiovascular outcomes in type 2 diabetes: outcomes from TECOS. Diabetes Care. 2016;39(12):2304-2310.

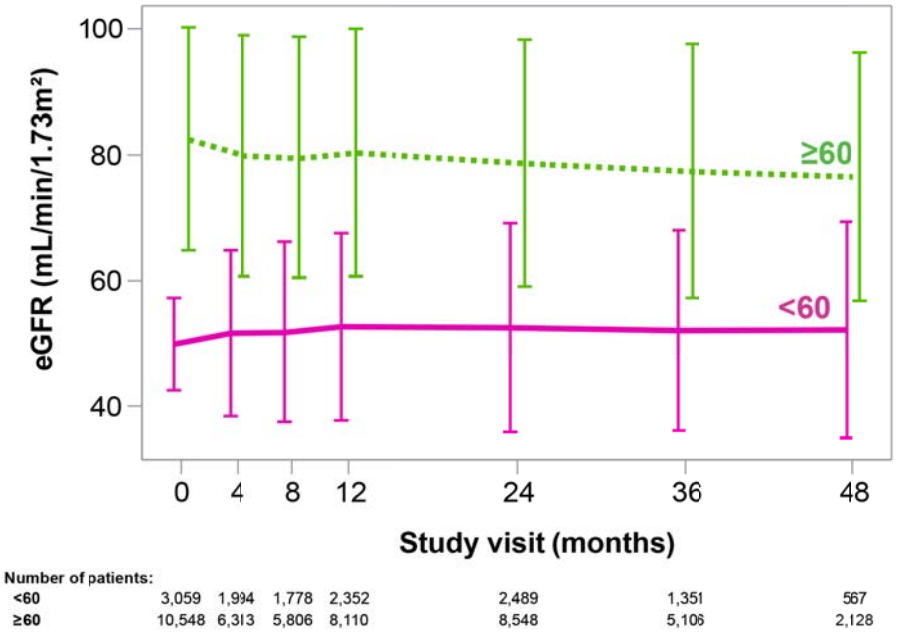
12. Green JB, Bethel MA, Paul SK, et al. Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease. Am Heart J. 2013;166(6):983-989.

13. Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015;373(3):232-242.

Figure Legends

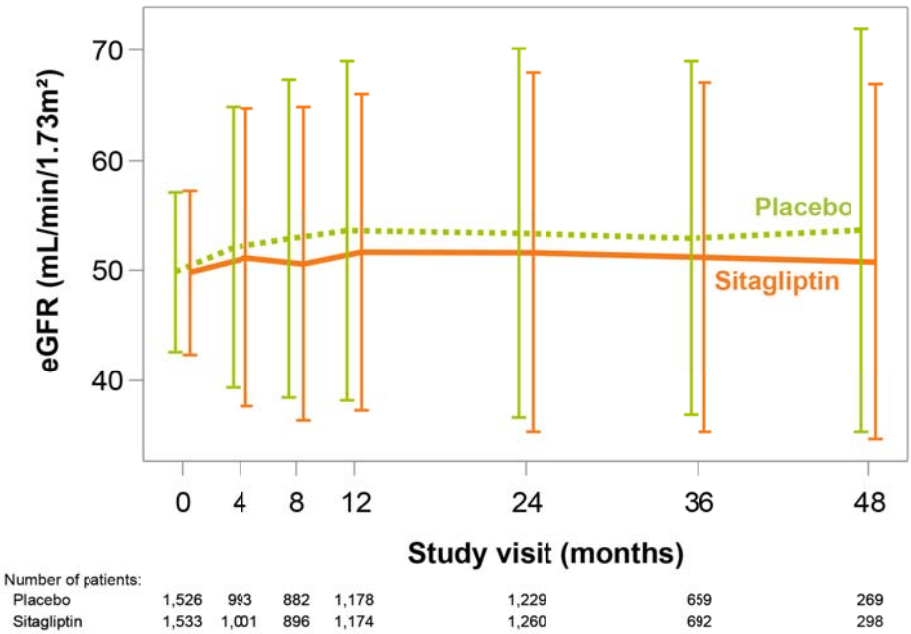
Figure 1. eGFR levels over 4 years comparing: A) CKD (N=3324) and non-CKD (N=11,204) cohorts; B) Within the CKD cohort, those allocated to sitagliptin (N=1667) and to placebo (N=1657). Data are plotted at each visit mean ±1 SD. Participants without baseline and at least one post-baseline measure are not shown at any visit.

A.



Number of patients:							
<60	3,059	1,994	1,778	2,352	2,489	1,351	567
≥60	10,548	6,313	5,806	8,110	8,548	5,106	2,128

B.



Number of patients:							
Placebo	1,526	993	882	1,178	1,229	659	269
Sitagliptin	1,533	1,001	896	1,174	1,260	692	298

Table 1: Baseline demographic and anthropometric characteristics for the CKD cohort, and for the non-CKD cohort overall and by treatment allocation.

	Non-CKD cohort eGFR ≥60 mL/min/1.73m^2	CKD Cohort eGFR <60 mL/min/1.73m^2				
Parameter	**All N = 11,204**	**All N = 3324**	**Sitagliptin N = 1667**	**Placebo N = 1657**	**P-value comparing treatments**	**P-value comparing CKD cohorts**
Age, years	64.5 ± 7.7	68.8 ± 7.9	68.4 ± 7.9	69.1 ± 7.8	0.02	<0.01
Sex, female	3000 (26.8%)	1255 (37.8%)	619 (37.1%)	636 (38.4%)	0.46	<0.01
Duration of type 2 diabetes, years	11.0 ± 7.7	13.7 ± 9.0	13.7 ± 9.0	13.7 ± 9.1	0.90	<0.01
BMI, kg/m^2	30.1 ± 5.5	30.7 ± 6.0	30.5 ± 6.0	30.8 ± 5.9	0.13	<0.01
SBP, mmHg	134.8 ± 16.7	135.7 ± 18.2	135.7 ± 18.0	135.7 ± 18.5	0.97	0.03
DBP, mmHg	77.6 ± 10.3	75.9 ± 10.8	76.0 ± 10.5	75.9 ± 11.1	0.73	<0.01
LDL-C, mg/dL[1]	90.5 ± 36.9	90.0 ± 37.1	90.3 ± 36.7	89.6 ± 37.6	0.52	0.33
Qualifying HbA1c, %	7.2 ± 0.5	7.2 ± 0.5	7.2 ± 0.5	7.2 ± 0.5	0.66	0.88
Qualifying HbA1c, mmol/mol	55.6 ± 5.2	55.5 ± 5.2	55.6 ± 5.3	55.5 ± 5.1	0.68	0.75
eGFR, mL/min/1.73m^2	82.3 ± 17.9	49.8 ± 7.4	49.7 ± 7.5	49.8 ± 7.3	0.97	<0.01
Urine albumin/creatinine ratio, mg/g	41.7 ± 104.6[2]	68.1 ± 135.5[3]	73.2 ± 146.3[4]	62.6 ± 122.3[5]	0.14	<0.01
Insulin use	2321 (20.7%)	1040 (31.3%)	522 (31.3%)	518 (31.3%)	0.97	<0.01
Metformin use	9560 (85.3%)	2301 (69.2%)	1149 (68.9%)	1152 (69.5%)	0.71	<0.01
Sulfonylurea use	5096 (45.5%)	1496 (45.0%)	765 (45.9%)	731 (44.1%)	0.30	0.63
Thiazolidinedione use	284 (2.5%)	111 (3.3%)	58 (3.5%)	53 (3.2%)	0.65	0.01

Data are expressed as frequency (n [%]) or mean ± standard deviation and represent all available measurements.
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.
[1]One patient in each treatment group had implausible LDL cholesterol values (2741 mg/dL and 3954 mg/dL). These data are not included in the summaries.
[2]Obtained in subset of cohort (n=3948).
[3]Obtained in subset of cohort (n=1111).
[4]Obtained in subset of cohort (n=582).
[5]Obtained in subset of cohort (n=529).

Table 2: Serious adverse events categorized by System Organ Class and occurring at a frequency of ≥1% in ≥1 cohort.

	Non-CKD cohort eGFR ≥60 mL/min/1.73m^2	CKD Cohort eGFR <60 mL/min/1.73m^2			Risk difference for CKD vs. non CKD (95% CI, M-N method)	P-value comparing CKD groups	Risk difference for sitagliptin vs. placebo (95% CI, M-N method)	P-value comparing treatment groups
System Organ Class	All N=11,106*	All N=3296*	Sitagliptin N= 1654	Placebo N=1642				
All events	12.2 (11.6, 12.8)	14.3 (13.1, 15.5)	13.8 (12.3, 15.6)	14.7 (13.0, 16.5)	2.04 (0.73, 3.41)	0.0020	-0.83 (-3.23, 1.56)	0.4946
Neoplasms	4.8 (4.4, 5.2)	5.4 (4.7, 6.2)	4.8 (3.8, 5.9)	6.0 (5.0, 7.3)	0.65 (-0.19, 1.55)	0.1313	-1.25 (-2.82, 0.29)	0.1116
Injury, poisoning and procedural complications	1.7 (1.5, 1.9)	2.8 (2.3, 3.4)	3.0 (2.3, 4.0)	2.6 (1.9, 3.5)	1.15 (0.57, 1.81)	<0.0001	0.40 (-0.74, 1.56)	0.4835
Gastrointestinal disorders	1.5 (1.3, 1.7)	2.0 (1.6, 2.5)	2.2 (1.6, 3.0)	1.8 (1.3, 2.6)	0.51 (0.02, 1.08)	0.0420	0.35 (-0.62, 1.34)	0.4739
Musculoskeletal and connective tissue disorders	1.4 (1.2, 1.7)	1.5 (1.1, 2.0)	1.5 (1.0, 2.2)	1.5 (1.0, 2.2)	0.05 (-0.39, 0.56)	0.8463	0.05 (-0.81, 0.91)	0.9059
Respiratory, thoracic and mediastinal disorders	0.9 (0.7, 1.1)	1.4 (1.0, 1.9)	1.0 (0.6, 1.6)	1.8 (1.2, 2.5)	0.53 (0.13, 1.02)	0.0067	-0.74 (-1.60, 0.07)	0.0708

Values are percentage (95% CI).

* All-patients-as-treated population.

Table 3: Incidence of investigator-reported diabetic complications.*

	Non-CKD cohort eGFR ≥60 mL/min/1.73m^2	CKD Cohort eGFR <60 mL/min/1.73m^2			Risk difference for CKD vs. non-CKD (95% CI, M-N method)	P-value comparing CKD groups	Risk difference for sitagliptin vs. placebo (95% CI, M-N method)	P-value comparing treatment groups
Diabetic Complication	**All N=11,204**	**All N=3324**	**Sitagliptin N=1667**	**Placebo N=1657**				
All events	34.0 (33.1, 34.9)	41.1 (39.4, 42.8)	40.1 (37.7, 42.6)	42.1 (39.7, 44.6)	7.12 (5.18, 9.07)	<0.0001	-1.97 (-5.42, 1.48)	0.2623
Peripheral arterial disease	2.6 (2.3, 2.9)	3.4 (2.9, 4.1)	3.9 (3.0, 4.9)	3.0 (2.3, 4.0)	0.86 (0.21, 1.59)	0.0083	0.82 (-0.43, 2.09)	0.1953
Amputation	0.7 (0.6, 0.9)	1.3 (1.0, 1.7)	1.4 (1.0, 2.1)	1.2 (0.7, 1.8)	0.57 (0.20, 1.04)	0.0016	0.29 (-0.50, 1.11)	0.4571
Gangrene	0.5 (0.4, 0.6)	1.2 (0.9, 1.6)	1.1 (0.7, 1.8)	1.3 (0.8, 1.9)	0.73 (0.37, 1.17)	<0.0001	-0.13 (-0.91, 0.64)	0.7329
Diabetic eye disease	2.7 (2.4, 3.0)	3.1 (2.5, 3.7)	3.1 (2.3, 4.0)	3.1 (2.4, 4.0)	0.39 (-0.24, 1.09)	0.2316	-0.02 (-1.22, 1.17)	0.9703
Diabetic neuropathy	4.1 (3.8, 4.5)	3.7 (3.2, 4.4)	3.9 (3.0, 4.9)	3.6 (2.8, 4.7)	-0.37 (-1.08, 0.42)	0.3440	0.21 (-1.09, 1.53)	0.7452
Microalbuminuria	7.7 (7.2, 8.2)	8.4 (7.5, 9.4)	7.7 (6.5, 9.1)	9.1 (7.8, 10.7)	0.68 (-0.38, 1.81)	0.2111	-1.43 (-3.39, 0.51)	0.1484
Renal failure	0.9 (0.7, 1.1)	3.4 (2.8, 4.1)	3.3 (2.5, 4.2)	3.6 (2.8, 4.6)	2.55 (1.95, 3.24)	<0.0001	-0.33 (-1.59, 0.93)	0.6068
Any hospitalization due to complications of diabetes	3.0 (2.7, 3.3)	5.1 (4.4, 5.9)	5.0 (4.0, 6.1)	5.2 (4.2, 6.4)	2.12 (1.35, 2.97)	<0.0001	-0.21 (-1.72, 1.29)	0.7818
Hyperglycemia requiring hospitalization	1.1 (0.9, 1.3)	1.4 (1.1, 1.9)	1.0 (0.6, 1.6)	1.8 (1.3, 2.6)	0.30 (-0.11, 0.80)	0.1588	-0.80 (-1.66, 0.01)	0.0530
Infections	16.9 (16.2, 17.6)	22.3 (20.9, 23.7)	22.5 (20.6, 24.6)	22.1 (20.1, 24.1)	5.43 (3.87, 7.03)	<0.0001	0.44 (-2.40, 3.28)	0.7597

Values are percentage (95% CI).

*37 have missing data for all complications, and a few participants have missing data for particular complications with on average 11,180 and 3310 in the non-CKD and CKD cohorts, respectively.

Table 4: Adverse events of interest.

	Non-CKD cohort eGFR ≥60 mL/min/1.73m^2	CKD Cohort eGFR <60 mL/min/1.73m^2			Risk difference for CKD vs. non-CKD (95% CI, M-N method)	Risk difference for sitagliptin vs. placebo (95% CI, M-N method)
Adverse event	**All N = 11,204**	**All N = 3324**	**Sitagliptin N=1667**	**Placebo N=1657**		
Severe hypoglycemia	1.7 (1.5, 1.9)	3.3 (2.8, 4.0)	3.4 (2.6, 4.4)	3.3 (2.5, 4.2)	1.65 (1.04, 2.36)	0.16 (-1.08, 1.40)
Any bone fracture	2.3 (2.0, 2.6)	3.5 (2.9, 4.2)	3.7 (2.9, 4.7)	3.3 (2.5, 4.2)	1.20 (0.55, 1.92)	0.46 (-0.80, 1.73)
Acute pancreatitis	0.3 (0.2, 0.4)	0.1 (0.0, 0.3)	0.1 (0.0, 0.4)	0.1 (0.0, 0.4)	-0.15 (-0.29, 0.05)	0.00 (-0.33, 0.33)
Overall malignancy	3.6 (3.3, 3.9)	4.7 (4.0, 5.5)	4.3 (3.4, 5.4)	5.1 (4.1, 6.2)	1.11 (0.35, 1.95)	-0.75 (-2.21, 0.69)
Pancreatic malignancy	0.2 (0.1, 0.3)	0.2 (0.1, 0.4)	0.1 (0.0, 0.4)	0.2 (0.1, 0.5)	-0.01 (-0.14, 0.20)	-0.06 (-0.42, 0.27)

Values are percentage (95% CI).