Post hoc analysis of SUSTAIN 6 and PIONEER 6 trials suggests that people with type 2 diabetes at high cardiovascular risk treated with semaglutide experience more stable kidney function compared with placebo

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Glucagon-like peptide-1 receptor agonists reduce albuminuria and may stabilize the estimated glomerular filtration rate (eGFR) in people with type 2 diabetes (T2D). In this *post hoc* analysis of the SUSTAIN 6/PIONEER 6 trials encompassing 6480 participants at high cardiovascular risk (semaglutide, 3239 participants; placebo, 3241 participants), we investigated the effects of semaglutide versus placebo on eGFR decline. Pooled data by treatment were evaluated for annual eGFR change (total annual eGFR slope in ml/min per 1.73 m^2) from baseline to end of treatment and time to persistent eGFR reductions of 30%, 40%, 50% and 57% or more, including subgroup analyses by baseline eGFR (30 to under 60 or 60 and over ml/min per 1.73 m^2). In the overall population, the estimated treatment difference (ETD; semaglutide versus placebo) in annual eGFR slope was significant at 0.59 ml/min per 1.73 m^2 (95% confidence interval 0.29; 0.89). The ETD was numerically largest in the 30 to under 60 ml/min per 1.73 m^2 eGFR subgroup, 1.06 ml/min per 1.73 m^2 (0.45; 1.67), but no significant interaction was observed for treatment effect by subgroup. Hazard ratios (semaglutide versus placebo) for time to persistent eGFR decline were under 1.0 for all eGFR thresholds in the overall population; and were numerically lower in the baseline eGFR 30 to under 60 ml/min per 1.73 m^2 subgroup versus the overall population, although no significant interaction was observed for treatment effect by subgroup. Thus, pooled analyses of clinical trial data in patients with T2D suggest that semaglutide may reduce the rate of eGFR decline.

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Lay Summary

Patients with type 2 diabetes (T2D) often develop chronic kidney disease. Semaglutide is a medicine used to treat T2D; previous studies have shown these medicines may also reduce the decline of kidney function. However, more studies are needed to confirm the kidney benefits with semaglutide. In 2 clinical trials, 6480 patients with T2D and at high risk of a cardiovascular event were treated with semaglutide or placebo. We used the results of kidney function tests from these studies to assess how fast kidney function declined in those treated with semaglutide or placebo. Our analysis showed that semaglutide significantly slowed the rate of kidney function decline and non-significantly extended the time taken to reach specified estimated glomerular filtration rate thresholds. We also saw that kidney function at the start of the trial did not impact these findings.

Type 2 diabetes (T2D) markedly increases the risk of both cardiovascular (CV) disease and chronic kidney disease (CKD).[1,2] Approximately 40% of patients with T2D will develop CKD, and T2D is now the most common cause of progression to kidney failure worldwide.[3,4] Moreover, most of the diabetes-associated excess CV disease risk in individuals with T2D, compared with the general population, occurs in those with T2D who also have CKD.[5,6]

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are an effective treatment for people with T2D and have been shown to have a beneficial effect on glycemic control and weight loss.[7] Furthermore, findings from CV outcomes trials with GLP-1RAs have demonstrated the CV safety of these medications, with some agents within the class demonstrating CV benefits in individuals with T2D.[8–11] As a result, clinical guidelines recommend that in individuals with T2D at high risk of, or with established, atherosclerotic CV disease or CKD, GLP-1RAs or sodium–glucose cotransporter-2 inhibitors with proven CV benefit should be prescribed,[12] the latter only if estimated glomerular filtration rate (eGFR) is ≥20 ml/min per 1.73 m^2.[13]

Many of the CV outcomes trials of GLP-1RAs included kidney disease outcomes as secondary endpoints, and the accumulating evidence suggests that GLP-1RAs have beneficial effects on such outcomes.[14,15] In particular, a reduction in the onset and progression of macroalbuminuria and slowing in the rate of decline in eGFR has been reported.[14,15] However, more information is needed to confirm these effects.

Semaglutide is a GLP-1RA that reduces the risk of adverse atherosclerotic CV events and development of macroalbuminuria in patients with T2D at high CV risk.[8,9] Semaglutide is available as either a once-weekly subcutaneous (s.c.) formulation or a once-daily oral formulation. The half-life (∼7 days), pharmacokinetics, and clinical effects of semaglutide have been shown to be similar, irrespective of mode of administration.[16–18] The 2 formulations were studied in separate CV outcomes trials: the Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN 6; s.c. once-weekly semaglutide) and the Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes (PIONEER 6; once-daily oral semaglutide). The trials had similar designs, trial populations, and prespecified outcomes, but different lengths of follow-up.[8,9] A pooled analysis of SUSTAIN 6 and PIONEER 6 showed beneficial effects on major adverse cardiovascular events,[19] and these CV outcomes trials also showed reductions in glycated hemoglobin (HbA_{1c})[8,9]; a mediation analysis of SUSTAIN 6 and Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) data showed that reductions in HbA_{1c} might only partially mediate the kidney effects of semaglutide and liraglutide.[20] The aim of this *post hoc* pooled analysis of SUSTAIN 6 and PIONEER 6 data was to investigate the effects of semaglutide versus placebo on eGFR over time by a more robust and novel assessment of the potential kidney benefits of semaglutide, using eGFR slope as a measure of kidney-disease progression.[21]

METHODS

Trial design

The trial designs for SUSTAIN 6 (NCT01720446) and PIONEER 6 (NCT02692716) have been reported previously.[8,9] In brief, adults with T2D at high risk of a CV event were randomized to semaglutide or placebo in addition to standard-of-care treatment. Having a high CV risk was defined as being aged ≥50 years and having established CV disease or CKD, or being aged ≥60 years with CV risk factors. Exclusion criteria for both trials included kidney failure treated by chronic hemodialysis or peritoneal dialysis; PIONEER 6 additionally excluded those with an eGFR <30 ml/min per 1.73 m^2.[8,9] In SUSTAIN 6, participants received s.c. once-weekly semaglutide 0.5 or 1.0 mg (median follow-up of 104 weeks), whereas participants in PIONEER 6 received once-daily oral semaglutide 14 mg (median observation period of 15.9 months).[8,9] Participants were instructed to take oral semaglutide with up to 120 ml of water, in a fasting state in the morning, and to fast (no eating, drinking, or taking any other oral medication) for at least 30 minutes post-dose. In both trials, a dose-escalation schedule was used for semaglutide, and the comparator was placebo.

Both trials were approved by independent ethics committees and institutional review boards at each participating center and were conducted in compliance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. All participants provided written informed consent before any trial-related activities.

Subgroups

In this *post hoc* analysis, data from the SUSTAIN 6 and PIONEER 6 trials were pooled by treatment (semaglutide [once-weekly 0.5 and 1.0 mg s.c., once-daily 14 mg oral] or placebo) and analyzed overall or in subgroups based on eGFR at baseline (30–<60 ml/min per 1.73 m^2 or ≥60 ml/min per 1.73 m^2 for efficacy, and <60 ml/min per 1.73 m^2 or ≥60 ml/min per 1.73 m^2 for safety). Data were also stratified by renin–angiotensin system (RAS) inhibitor use (an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker [yes/no]) at baseline.

Data from participants with a baseline eGFR <30 ml/min per 1.73 m^2 were included in the analyses. However, as baseline eGFR <30 ml/min per 1.73 m^2 was an exclusion criterion in PIONEER 6, only estimates (including results from interaction analyses) pertaining to eGFR ≥30 ml/min per 1.73 m^2 are presented.

Outcomes

Change in eGFR was evaluated over time, in the overall population and in the 2 eGFR subgroups, both in a pooled analysis and in separate SUSTAIN 6 and PIONEER 6 analyses. All available data points from the 2 trials were used until week 104 for SUSTAIN 6 and week 83 for PIONEER 6.

The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 equation. eGFR, evaluated as a treatment effect on annual eGFR slope, has been shown to be predictive of kidney failure endpoints, based on a meta-analysis of 47 clinical trials evaluating CKD treatments in 60,620 participants.[21] In SUSTAIN 6, visits occurred at weeks 0, 2, 4, 8, 16, 30, 44, 56, 68, 80, 92, and 104. In PIONEER 6, visits occurred at weeks 0, 4, 8, 14, 26, 38, 50, 62, 76, and 83.

Annual eGFR slope was assessed *post hoc* in the overall population and in the 2 eGFR subgroups, both in a pooled analysis and in separate SUSTAIN 6 and PIONEER 6 analyses. As differences in the treatment effect of other glucose-lowering medication classes (e.g., sodium–glucose cotransporter-2 inhibitors) have been observed according to whether patients were also receiving RAS inhibitors,[22] the mean annual eGFR slope analyses (overall population and eGFR subgroups) were also evaluated in 2 subgroups according to use (yes/no) of RAS blockade at baseline.

The change over time in estimated urinary albumin-to-creatinine ratio (UACR) was also assessed *post hoc* in the overall population of the SUSTAIN 6 trial, and in the 2 eGFR subgroups. These data were not collected in the PIONEER 6 trial. Safety was assessed by incidence of adverse events (AEs), serious AEs, severe AEs, gastrointestinal (GI) AEs, severe hypoglycemic AEs, AEs leading to premature treatment discontinuation, and acute renal failure (acute kidney injury).

Analysis sets

Descriptive baseline characteristics were based on the full analysis set (all randomized participants). All available eGFR measurements from the full analysis set were included (in-trial data), regardless of whether participants discontinued treatment, developed kidney failure, or experienced a fatal event. All safety analyses were performed using in-trial data from the full analysis set and summarized overall and per subgroup.

Analyses of eGFR and UACR across visits

eGFR and UACR changes over time (per visit) were assessed using mixed models for repeated measurements with treatment group, subgroup, trial, and the interaction between treatment group and subgroup as fixed factors, and baseline value as a covariate, all nested within visit. The change from baseline in eGFR and the change from baseline in log-transformed UACR were evaluated at week 80 and 83 in the semaglutide and placebo groups, respectively.

Slope analyses of eGFR

Annual eGFR slope was assessed as a continuous time variable using a linear random slope regression model with an interaction between slope and treatment group and with individual intercepts and time slope adjusted for baseline eGFR and trial as a fixed effect. The individual intercepts and time slopes were assumed to follow a bivariate normal distribution. The subgroup analyses included an interaction term between slope and treatment by subgroup.

The annual eGFR slope was expressed as estimated treatment difference (ETD) between slopes with 95% confidence intervals (CIs). The *P* value for interaction evaluated the potential treatment heterogeneity across the 2 presented eGFR subgroups (30–<60 ml/min per 1.72 m^2 and ≥60 ml/min per 1.72 m^2).

Time to persistent reduction in eGFR

Time to persistent reductions in eGFR was based on the Modification of Diet in Renal Disease equation (used for the inclusion criteria and the adjudicated eGFR reduction component in the nephropathy endpoint in SUSTAIN 6) corresponding to the eGFR decline thresholds ≥30%, ≥40%, ≥50%, and ≥57%, and it was assessed in the overall population and the 2 eGFR subgroups using both pooled data and data separated by trial (SUSTAIN 6 and PIONEER 6). A persistent eGFR decline was defined as the time from randomization to the first visit at which the eGFR change threshold was attained, with this value confirmed at the subsequent visit. If no subsequent visit occurred, confirmation of the eGFR value was not required.

Hazard ratios (HRs; semaglutide:placebo) and 95% CIs for time to persistent reductions in eGFR were estimated using a Cox proportional hazards model, with treatment and eGFR subgroups and the interaction between treatment group and eGFR subgroups as fixed factors, stratified by trial. The *P* value for interaction evaluated potential treatment heterogeneity across the 2 presented eGFR subgroups (30–<60 ml/min per 1.72 m^2 and ≥60 ml/min per 1.72 m^2).

Supplementary analyses in relation to annual eGFR slope

To explore whether the treatment effect on eGFR may be explained by changes in other parameters, 2 supplementary analyses were conducted using the random slope model—one adjusted for change from baseline in HbA_{1c} across trial visits, and one adjusted for changes from baseline in HbA_{1c}, body weight (BW), and systolic blood pressure (SBP), and baseline diuretic use (yes/no) across trial visits.

A supplementary analysis excluding eGFR data before week 14 (PIONEER 6) or week 16 (SUSTAIN 6) was also conducted to assess the chronic effect of semaglutide on annual eGFR slope, as an early decline in eGFR was observed with GLP-1RAs in participants with eGFR >60 ml/min per 1.73 m^2 in prior reports.[23] Hence, in the chronic slope analyses, change from week 14 or 16, respectively, was evaluated, with eGFR at week 14 or 16 considered the baseline.

General considerations

Statistical significance was achieved with a P value < 0.05. No adjustment was made for multiplicity.

RESULTS

Baseline characteristics

SUSTAIN 6 and PIONEER 6 included 6480 participants, of whom 3239 received semaglutide and 3241 received placebo; baseline characteristics were similar in the 2 groups (Table 1). The numbers of participants (semaglutide/placebo) in the 30–<60 ml/min per 1.73 m^2 and ≥60 ml/min per 1.73 m^2 eGFR subgroups were, respectively, 779/781 and 2382/2380. Baseline characteristics for the eGFR subgroups are detailed in Table 1. In SUSTAIN 6 and PIONEER 6, a total of 2668 of 3297 (81%) and 2569 of 3183 (81%) participants, respectively, were on RAS blockade at baseline.

Change in eGFR over time

Overall changes in eGFR and change in eGFR by subgroup, in the pooled population and by trial, are shown in Figure 1 and Supplementary Figures S1–S3. Overall, mean eGFR decreased from baseline to week 80/83 by 2.47 ml/min per 1.73 m^2 (2.54%) with semaglutide, and by 2.27 ml/min per 1.73 m^2 (2.66%) with placebo, respectively, in the pooled population from the SUSTAIN 6 and PIONEER 6 trials (ETD –0.20 [95% CI –0.72; 0.32]; Figure 1). By week 104, mean eGFR decreased from baseline by 3.77 ml/min per 1.73 m^2 with semaglutide, and by 4.33 ml/min per 1.73 m^2 with placebo (ETD 0.56 [95% CI –0.12; 1.24]; $P = 0.1046$). eGFR also generally decreased over time when each trial was analyzed separately, although the change was greater in SUSTAIN 6 than in PIONEER 6 (Supplementary Figures S2 and S3).

Annual eGFR slope

To reflect that eGFR <30 ml/min per 1.73 m^2 was an exclusion criterion in PIONEER 6, trial effect (SUSTAIN 6 – PIONEER 6) was estimated as –0.98 ([95% CI –1.31; –0.66], $P < 0.0001$), and this trial effect was used to adjust the annual eGFR slope analyses.

In the overall population and in both eGFR subgroups, semaglutide was associated with a significantly reduced annual rate of eGFR decline, compared with placebo

Table 1 | Baseline characteristics

Characteristic	Overall population		Baseline eGFR, ml/min per 1.73 m^2			
			30–<60		≥60	
	Semaglutide pooled (N = 3239)	Placebo pooled (N = 3241)	Semaglutide pooled (n = 779)	Placebo pooled (n = 781)	Semaglutide pooled (n = 2382)	Placebo pooled (n = 2380)
Age, yr	65.3 (7.2)	65.5 (7.4)	68.3 (7.2)	68.8 (7.3)	64.2 (6.9)	64.3 (7.0)
Sex, male, n (%)	2097 (65)	2081 (64)	472 (61)	486 (62)	1579 (66)	1554 (65)
Body weight, kg	91.7 (21.1)	91.3 (20.8)	94.0 (22.6)	93.0 (21.4)	91.1 (20.6)	91.0 (20.6)
Diabetes duration, yr	14.4 (8.4)	14.3 (8.3)	16.6 (8.7)	16.4 (8.8)	13.6 (8.1)	13.5 (8.0)
HbA_{1c}, %	8.4 (1.5)	8.4 (1.6)	8.3 (1.5)	8.2 (1.5)	8.5 (1.6)	8.5 (1.6)
Systolic blood pressure, mm Hg	135.7 (17.5)	135.5 (17.2)	136.0 (18.3)	135.4 (17.7)	135.4 (17.1)	135.3 (16.9)
Diastolic blood pressure, mm Hg	76.6 (10.1)	76.5 (10.0)	75.1 (10.4)	75.4 (10.2)	77.0 (9.8)	77.0 (9.8)
eGFR (CKD-EPI), ml/min per 1.73 m^2	75.0 (21.8)	75.1 (22.1)	47.4 (8.0)	46.9 (7.9)	85.5 (13.7)	85.9 (13.7)
Kidney function, eGFR, ml/min per 1.73 m^2, n (%)						
≥90	1032 (32)	1021 (32)	0	0	1032 (43)	1021 (43)
60–>90	1350 (42)	1359 (42)	0	0	1350 (57)	1359 (57)
30–<60	779 (24)	781 (24)	779 (100)	781 (100)	0	0
<30[a]	71 (2)	68 (2)	0	0	0	0
UACR, mg/g, geometric mean (%CV)[b]	24.7 (710.2)	23.7 (779.4)	48.9 (869.3)	48.0 (1186)	17.8 (480.0)	17.1 (496.4)
Albuminuria status, UACR, mg/g, n (%)[b]						
Normoalbuminuria (<30)	948 (59)	986 (61)	155 (44)	161 (44)	785 (65)	811 (68)
Microalbuminuria (30–≤300)	472 (29)	412 (25)	133 (38)	114 (31)	327 (27)	290 (24)
Macroalbuminuria (>300)	196 (12)	224 (14)	66 (19)	91 (25)	95 (8)	100 (8)

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; N/n, number of participants; PIONEER 6, A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes; SUSTAIN 6, a Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes; UACR, urinary albumin-to-creatinine ratio.
[a]Data from participants with a baseline eGFR <30 ml/min per 1.73 m^2 were included in the analyses, and they are presented for the overall analyses but not for the subgroup analyses.
[b]Albuminuria percentage is calculated based on number of participants from SUSTAIN 6 with a UACR measurement at baseline (semaglutide, n = 1616; placebo, n = 1622), as these data were not collected in PIONEER 6.
Data from the full analysis set are mean (SD), unless stated otherwise. Kidney function is based on eGFR ml/min per 1.73 m^2 calculated using the CKD-EPI 2009 equation.

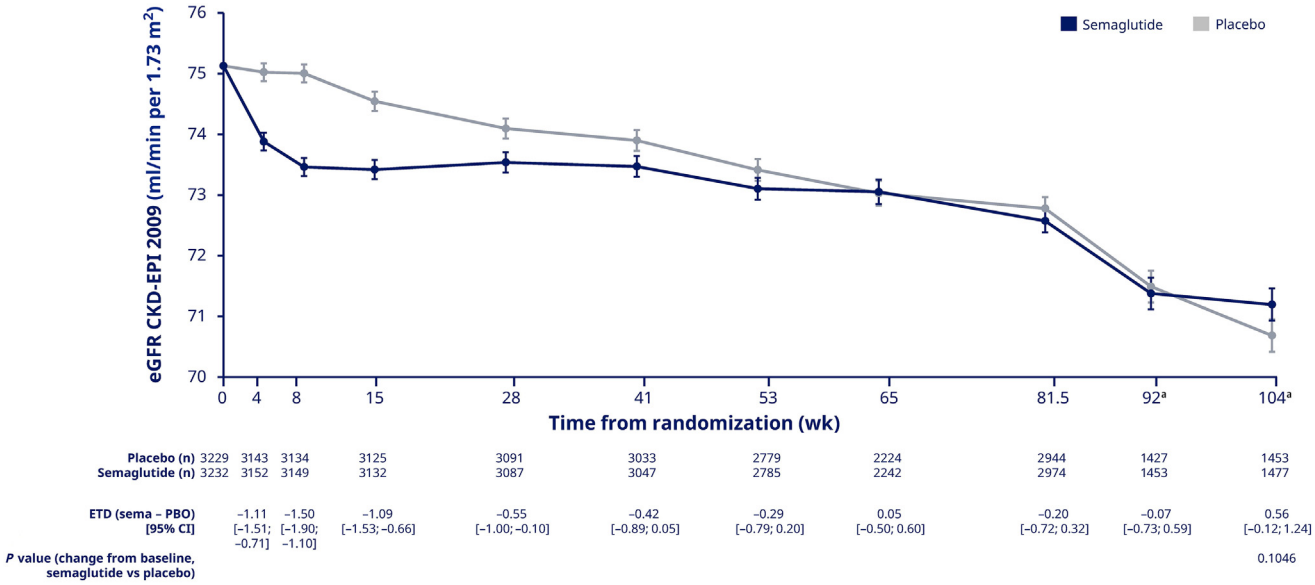


Figure 1 | Change from baseline in estimated glomerular filtration rate (eGFR) over time (mixed model for repeated measurements [MMRM]) for the overall population. eGFR over time was analyzed using an MMRM with treatment group, subgroup, trial and the interaction between treatment group and subgroup as fixed factors, and baseline value as a covariant, all nested within visit. Error bars represent 95% confidence intervals (CIs). CKD-EPI, chronic kidney disease epidemiology collaboration; ETD, estimated treatment difference; PBO, placebo; PIONEER 6, A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes; sema, semaglutide; SUSTAIN 6, a Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes. [a]SUSTAIN 6 only; last visit in the PIONEER 6 trial was at week 83.

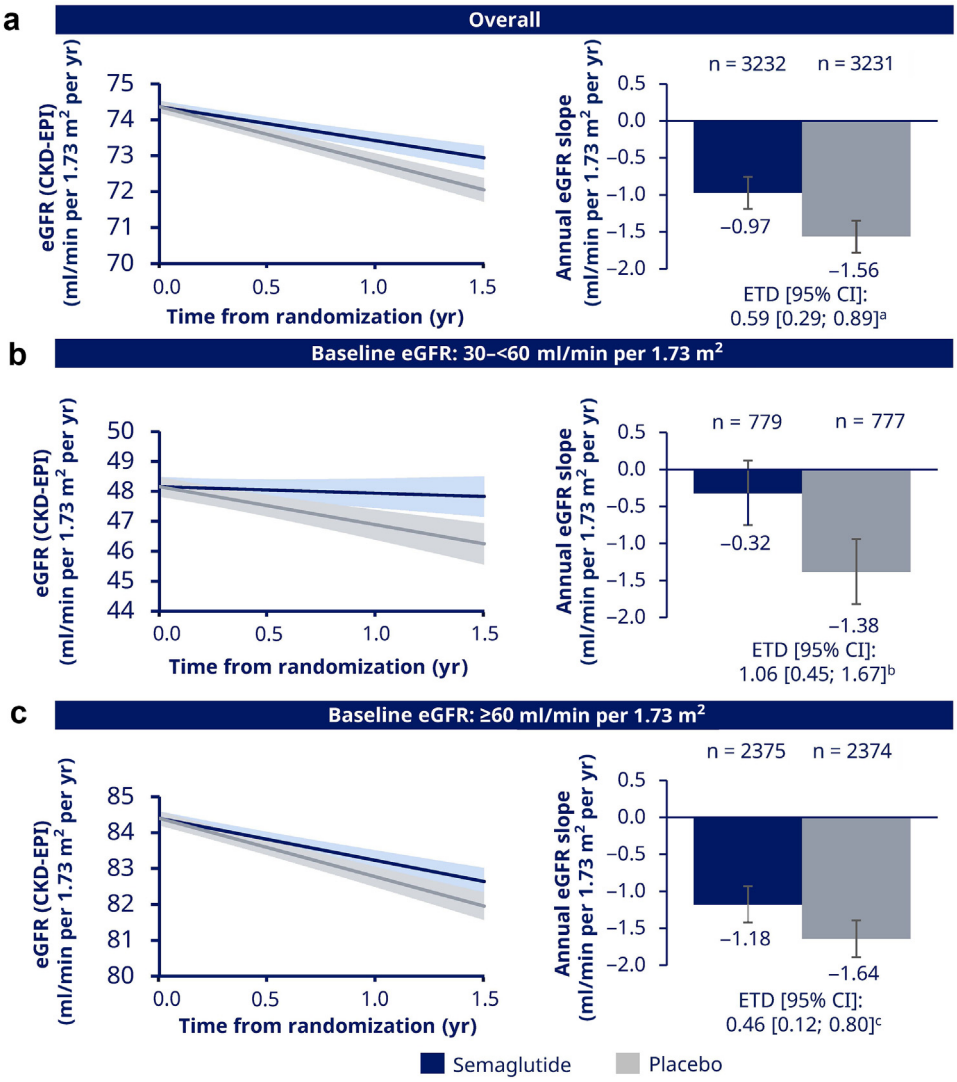
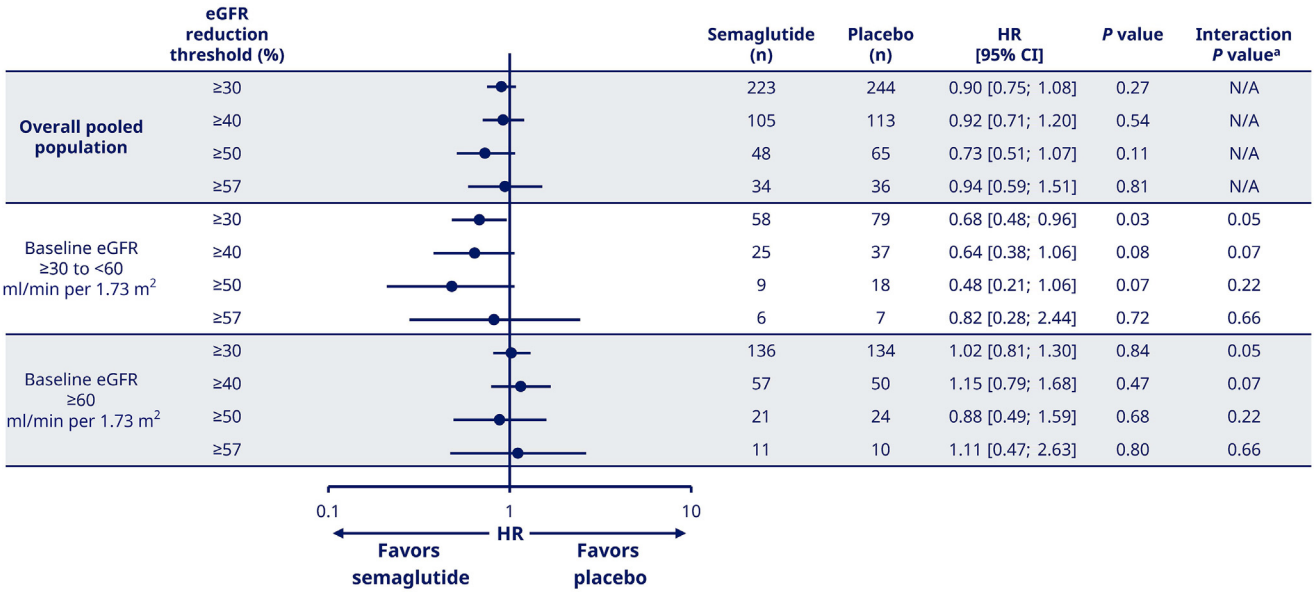


Figure 2 | Annual change in estimated glomerular filtration rate (eGFR; model-based total annual eGFR slope) over time and from baseline to end of treatment in (a) the overall population, and by baseline eGFR subgroups: (b) 30–<60 ml/min per 1.73 m^2 and (c) ≥60 ml/min per 1.73 m^2. Data from the full analysis set. One-year annual change in eGFR is depicted as a random slope model (line graphs) and as total 1-year annual eGFR change from randomization to end of treatment (bar graphs). The interaction between treatment effect and eGFR subgroups was not significant ($P = 0.10$). Data from participants with a baseline eGFR <30 ml/min per 1.73 m^2 were included in the analyses, and they are presented for the overall analyses but not for the subgroup analyses. Random slope model with change from baseline as a dependent variable and with baseline and time (in years) interacting with treatment (and subgroup for [**b**] and [**c**]), adjusted for trial. Intercept and slopes of effect of time were assumed to vary randomly among patients based on a bivariate normal distribution. The area within the 95% confidence interval (CI) is shown in blue and gray shading (line graphs) and as error bars (bar graphs). Kidney function is based on eGFR in ml/min per 1.73 m^2 per the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) 2009 formula. The timing of visits varied between the Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN 6) and the Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes (PIONEER 6). In SUSTAIN 6, visits occurred at weeks 0, 2, 4, 8, 16, 30, 44, 56, 68, 80, 92, and 104; SUSTAIN 6 data up to week 80 were included in the pooled analysis. In PIONEER 6, visits occurred at weeks 0, 4, 8, 14, 26, 38, 50, 62, 76, and 83; PIONEER 6 data up to week 83 were included in the pooled analysis. CI, confidence interval; ETD, estimated treatment difference; n, number of participants contributing to analysis ([**b,c**] subjects with missing eGFR at baseline excluded). [a]$P < 0.0001$; [b]$P = 0.0007$; [c]$P = 0.0083$.

(Figure 2). In the overall population, annual eGFR slopes with semaglutide and placebo were, respectively, –0.97 [95% CI –1.19; –0.76] and –1.56 [95% CI –1.78; –1.35] ml/min per 1.73 m^2 (ETD 0.59 [95% CI 0.29; 0.89], $P < 0.0001$). Annual eGFR slopes (ml/min per 1.73 m^2) in the subgroup with baseline eGFR 30–<60 ml/min per 1.73 m^2 were –0.32 [95% CI –0.75; 0.12] with semaglutide and –1.38 [95% CI –1.82; –0.94] with placebo (ETD 1.06 [95% CI 0.45; 1.67], $P = 0.0007$) and in the subgroup with baseline eGFR ≥60 ml/min per 1.73 m^2 were –1.18 [95% CI –1.42; –0.93] with semaglutide and –1.64 [95% CI –1.89; –1.39] with placebo (ETD 0.46 [95% CI 0.12; 0.80], $P = 0.0083$). Similar results were observed when the analyses were adjusted for change from baseline in HbA_{1c} (Supplementary Figure S4) and for changes



	eGFR reduction threshold (%)	Semaglutide (n)	Placebo (n)	HR [95% CI]	*P* value	Interaction *P* value[a]
Overall pooled population	≥30	223	244	0.90 [0.75; 1.08]	0.27	N/A
	≥40	105	113	0.92 [0.71; 1.20]	0.54	N/A
	≥50	48	65	0.73 [0.51; 1.07]	0.11	N/A
	≥57	34	36	0.94 [0.59; 1.51]	0.81	N/A
Baseline eGFR ≥30 to <60 ml/min per 1.73 m^2	≥30	58	79	0.68 [0.48; 0.96]	0.03	0.05
	≥40	25	37	0.64 [0.38; 1.06]	0.08	0.07
	≥50	9	18	0.48 [0.21; 1.06]	0.07	0.22
	≥57	6	7	0.82 [0.28; 2.44]	0.72	0.66
Baseline eGFR ≥60 ml/min per 1.73 m^2	≥30	136	134	1.02 [0.81; 1.30]	0.84	0.05
	≥40	57	50	1.15 [0.79; 1.68]	0.47	0.07
	≥50	21	24	0.88 [0.49; 1.59]	0.68	0.22
	≥57	11	10	1.11 [0.47; 2.63]	0.80	0.66

Figure 3 | Time to onset of persistent reductions in estimated glomerular filtration rate (eGFR) in the overall population and by baseline eGFR subgroups. Time to persistent reductions in eGFR (based on the eGFR- Modification of Diet in Renal Disease equation) was defined as the time from randomization to the first visit in which the value from the subsequent visit was confirmed by fulfilling the same relative reduction from baseline as the value from the previous visit. If no subsequent visit was performed, the confirmation was not required. Data from participants with a baseline eGFR <30 ml/min per 1.73 m^2 were included in the analyses, and they are presented for the overall analyses but not for the subgroup analyses. CI, confidence interval; HR, hazard ratio; n, number of participants achieving eGFR reduction threshold; N/A, not applicable. [a]Test for heterogeneity between treatment effects across eGFR subgroups.

from baseline in HbA_{1c}, BW, and SBP, and baseline diuretic use (yes/no; Supplementary Figure S5). In the analysis excluding data before week 14/16, similar results were observed, with ETDs favoring semaglutide versus placebo (Supplementary Figure S6), although in both treatment groups, reduced absolute annual eGFR slopes were observed from week 14/16 to end of treatment than from baseline to end of treatment in the 30–≤60 ml/min per 1.73 m^2 subgroup.

The interaction between treatment effect and eGFR subgroups in the main eGFR slope analysis was not significant ($P = 0.10$); results were also homogeneous when the analyses were adjusted by change from baseline in HbA_{1c} ($P = 0.12$), changes from baseline in HbA_{1c}, BW, SBP, and baseline diuretic use (yes/no; $P = 0.26$), and in the analysis excluding data before week 14/16 ($P = 0.12$). The interaction between treatment effect and RAS blockade subgroups was also not significant ($P = 0.18$; Supplementary Table S1).

Broadly similar results were also observed when the data were analyzed by trial, although reduced absolute annual eGFR slopes were observed in SUSTAIN 6 (Supplementary Figure S7) than in PIONEER 6 (Supplementary Figure S8). No interactions occurred between treatment effect and eGFR subgroups in either trial.

Persistent reductions (≥30%; ≥40%; ≥50%; ≥57%) in eGFR

For the ≥30%, ≥40%, ≥50%, and ≥57% eGFR reduction thresholds, HRs (semaglutide:placebo) were <1 in the baseline ≥30–<60 ml/min per 1.73 m^2 subgroup and the overall population, and were generally close to 1 in the >60 ml/min per 1.73 m^2 subgroup; the only statistically significant treatment difference was for risk of developing a persistent ≥30% eGFR reduction in the ≥30–<60 ml/min per 1.73 m^2 subgroup (HR: 0.68 [0.48; 0.96], $P = 0.03$; Figure 3). No significant interactions occurred between treatment effect and eGFR subgroups for any eGFR reduction threshold ($P \geq 0.05$ for all).

Persistent reductions in eGFR in each trial showed broadly similar results (Supplementary Figures S9 and S10), although a significant interaction occurred between treatment effect and eGFR subgroup for the ≥30% eGFR reduction threshold in SUSTAIN 6 only ($P = 0.01$; Supplementary Figure S9).

Changes in UACR

In the overall SUSTAIN 6 trial population, semaglutide significantly reduced estimated UACR from baseline to end of treatement, compared with placebo (treatment ratio 0.74 [95% CI 0.67–0.81] $P < 0.001$; Supplementary Figure S11). Statistically significant reductions in UACR were also reported in both eGFR subgroups ($P < 0.05$ in both subgroups), without a significant interaction ($P = 0.81$).

Safety

Within each eGFR subgroup, the proportions of participants experiencing AEs, serious AEs, severe AEs, severe hypoglycemic AEs, or acute kidney injury with semaglutide and placebo were comparable (Table 2). Within each eGFR subgroup, the proportions of participants experiencing GI AEs or discontinuing treatment prematurely due to AEs were higher among those

Table 2 | Safety data by estimated glomerular filtration rate (eGFR) subgroup

	Overall		Baseline eGFR, ml/min per 1.73 m^2			
			<60		≥60	
Measure	Semaglutide (N = 3239)	Placebo (N = 3241)	Semaglutide (n = 850)	Placebo (n = 849)	Semaglutide (n = 2382)	Placebo (n = 2380)
AEs	2129 (66)	2015 (62)	582 (68)	552 (65)	1545 (65)	1460 (61)
Serious AEs	889 (27)	998 (31)	299 (35)	314 (37)	590 (25)	682 (29)
Severe AEs	635 (20)	626 (19)	219 (26)	234 (28)	416 (17)	392 (16)
GI AEs	1118 (35)	657 (20)	310 (36)	186 (22)	806 (34)	471 (20)
Severe hypoglycemic AEs	51 (2)	45 (1)	24 (3)	21 (2)	27 (1)	24 (1)
AEs leading to premature treatment discontinuation	641 (20)	378 (12)	210 (25)	126 (15)	429 (18)	251 (11)
Acute kidney injury	88 (3)	91 (3)	52 (6)	51 (6)	36 (2)	40 (2)

AE, adverse event; GI, gastrointestinal; n, number of participants with event; N, overall number of participants per subgroup; %, proportion of participants with event.
Data from participants with a baseline eGFR <30 ml/min per 1.73 m^2 were included in the analyses and are presented for the overall analyses but not for the subgroup analyses.
Data are presented as n (%) and are from the full analysis set.

who received semaglutide than those who received placebo (Table 2). However, the proportion of semaglutide-treated participants experiencing GI AEs was similar in the 2 eGFR subgroups (Table 2). Regardless of the treatment assigned, serious and severe AEs, AEs leading to premature treatment discontinuation, severe hypoglycemic AEs, and acute kidney injury were detected more often in the subgroup with baseline eGFR <60 ml/min per 1.73 m^2 than in the subgroup with baseline eGFR ≥60 ml/min per 1.73 m^2 (Table 2).

DISCUSSION

The present analyses of SUSTAIN 6 and PIONEER 6 data found a reduced annual rate of eGFR decline with semaglutide compared with placebo, despite relatively short durations of follow-up within these CV outcomes trials. Our results suggest that semaglutide has kidney benefits, in comparison with placebo, in the overall population. However, the main kidney benefit appeared to be for those with lower baseline eGFR, although no significant interactions occurred between the 2 eGFR subgroups in any of the analyses. These results were consistent when analyzed by trial and when adjusted for change from baseline in HbA_{1c}, and for changes from baseline in HbA_{1c}, BW, and SBP, and baseline diuretic use, in the overall population and among eGFR subgroups.

An initial drop in eGFR appeared to occur in the semaglutide group, followed by stabilization. Although the eGFR slope model alleviates the effect of the initial drop in eGFR by assuming that each individual has their own intercept and slope, to assess any potential impact on the longer-term results, an analysis of eGFR slope data from week 14/16 to end of treatement was conducted. This analysis excluded data from the initial treatment period, when a decline in eGFR might occur with GLP-1RAs.[23] This analysis showed results similar to those of the main analysis, indicating a potential long-term reduction in the rate of eGFR decline with semaglutide versus placebo.

Although the findings seen with the eGFR slope and the change in eGFR analyses appear to differ slightly, this difference is due to use of different methods of analysis and statistical approaches and reflects observations from similar studies.[24,25]

In addition to a reduced rate of eGFR decline, HRs for all eGFR reduction thresholds were <1 in the overall population and ≥30–<60 ml/min per 1.73 m^2 subgroup and were generally close to 1 in the ≥60 ml/min per 1.73 m^2 subgroup. These findings again emphasize that the main kidney benefit with semaglutide appeared to be for those with lower baseline eGFR. Improvements in albuminuria were also seen with semaglutide versus placebo in SUSTAIN 6. This finding occurred in the overall population and in the 2 eGFR subgroups.

Analyses from other studies with GLP-1RAs also suggest that this glucose-lowering class of medications may have benefits relating to kidney function and albuminuria in patients with T2D and CKD.[20,23–30] A *post hoc* analysis of change in kidney function over time in the LEADER trial, which included an analysis according to eGFR subgroups (>90, 60–90, 30–59, or <30 ml/min per 1.73 m^2) indicated that eGFR declined significantly slower over 36 months with liraglutide than it did with placebo in participants with baseline eGFR of 30–59 ml/min per 1.73 m^2 (estimated trial-group ratio 1.07 [95% CI 1.04; 1.10]; $P < 0.001$), but not in the other eGFR groups.[28] The relatively small number of patients and events in some groups precludes the drawing of any firm conclusion from this analysis. Similarly, in the A Study Comparing Dulaglutide With Insulin Glargine in Participants With Type 2 Diabetes and Moderate or Severe Chronic Kidney Disease (AWARD 7) trial, participants with T2D and moderate-to-severe CKD had significantly smaller declines in eGFR with dulaglutide (with either the higher or lower dose used) versus insulin glargine at 52 weeks.[27] This result occurred despite the similar level of glycemic control that was achieved either with once-weekly dulaglutide or with insulin glargine. In the Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) CV outcomes trial that evaluated once-weekly dulaglutide 1.5 mg versus placebo in adults aged ≥50 years with T2D, during a median follow-up of 5.4 years, *post hoc* analyses showed that there was a lower

incidence of sustained eGFR decline >40% (HR 0.70, 95% CI 0.57; 0.85) and ≥50% (HR 0.56, 95% CI 0.41; 0.76) with dulaglutide, compared with placebo, whereas a prespecified analysis (based on persistent reductions in eGFR ≥30%) did not provide evidence of a difference between treatment groups.[30] In a meta-analysis of 8 CV outcomes trials involving 60,080 participants, treatment with a GLP-1RA versus placebo was associated with a 21% reduction in a composite kidney outcome that included macroalbuminuria.[31]

Our analyses adjusted for change from baseline in HbA_{1c} alone, and for changes from baseline in HbA_{1c}, BW, and SBP, and baseline diuretic use indicated that annual eGFR slope was only slightly affected by these parameters. Findings from a mediation analysis of SUSTAIN 6 and LEADER data, which pertained to adjudicated kidney disease endpoints, indicated that SBP and HbA_{1c} might partially mediate the kidney effects of semaglutide and liraglutide.[20] Other parameters, such as BW, diastolic blood pressure, heart rate, low-density lipoprotein and total cholesterol levels, and white blood cell count, were shown to have either a small impact or no impact.[20] However, *post hoc* analyses of data from SUSTAIN 6 and LEADER indicated that the kidney effects of semaglutide and liraglutide occur irrespectively of baseline diabetes duration, body mass index, and blood pressure.[32–34]

The SUSTAIN 6 and PIONEER 6 trials were not designed to evaluate the mechanisms underlying changes in kidney function. However, possible mechanisms might include kidney tubular effects, hemodynamic effects, reduction in oxidative stress, and/or anti-inflammatory effects.[15] Hyperglycemia and CKD are associated with inflammation, and in previous animal models of atherosclerosis, semaglutide has been reported to regulate multiple inflammatory genes.[35] Additionally, in animal models of CKD, nondiabetic kidney injury, and diabetes, GLP-1RAs have been shown to reduce macrophage infiltration and inflammatory mediators,[36,37] suggesting that the nephroprotection reported in SUSTAIN 6 and PIONEER 6 might be a result of anti-inflammatory properties of semaglutide.

With the exception of GI AEs (a known side effect of the GLP-1RA class of glucose-lowering agents) and AEs leading to premature treatment discontinuation, safety outcomes were similar with semaglutide and placebo. In addition, semaglutide has not been associated with higher risk of kidney AEs, versus a range of comparators in previous analyses.[23] Furthermore, no notable difference occurred between the eGFR subgroups in the incidence of GI AEs, indicating that the GI tolerability of semaglutide is unaffected by kidney function.

Previous analyses have shown that the risk of hypoglycemia is increased in people with eGFR <60 ml/min per 1.73 m^2.[38] This finding was also evident from our analysis, in which, for participants in either the semaglutide or placebo group, the proportion reporting hypoglycemia was greater in the subgroup with lower baseline eGFR. As it was seen with both semaglutide and placebo, this increased risk of hypoglycemia may be the effect of other glucose-lowering agents used in the setting of impaired kidney function.

Although this present analysis of results from SUSTAIN 6 and PIONEER 6 adds to the accumulating evidence of a possible benefit of GLP-1RAs on kidney function in patients with T2D, it has a number of limitations. First, the data analyses were conducted *post hoc* from trials that were not designed nor sufficiently powered to evaluate eGFR outcomes. Second, the relatively short duration of follow-up limits the capability of these analyses to fully elucidate the effect of treatment on kidney outcomes. Third, the relatively low numbers in the subgroups might have resulted in insufficient power to detect differences in treatment effect on loss of eGFR. Finally, differences seen in eGFR change over time in the 30–<60 and ≥60 ml/min per 1.73 m^2 subgroups could represent a regression to the mean effect. However, this possibility is unlikely, as similar changes were not seen in the placebo groups.

In conclusion, the results provide supporting evidence that, in patients with T2D and high CV risk, semaglutide reduced the rate of eGFR decline. These findings were achieved together with no increase in the risk of AEs or new safety concerns identified. Whether the difference in annual eGFR slopes translates into reduced kidney disease events with semaglutide remains to be determined, along with the mechanisms behind any potential benefits on kidney outcomes. More evidence is therefore needed from randomized controlled trials with kidney disease endpoints as the primary outcome. The ongoing A Research Study to See How Semaglutide Works Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease (FLOW; NCT03819153) and A Research Study to Find Out How Semaglutide Works in the Kidneys Compared to Placebo, in People with Type 2 Diabetes and Chronic Kidney Disease (REMODEL; NCT04865770) trials of once-weekly s.c. semaglutide will address these evidence gaps on the use of and mechanisms behind GLP-1RA treatment for CKD in T2D.[39,40] In addition, the A Heart Disease Study of Semaglutide in Patients With Type 2 Diabetes (SOUL) CV outcomes trial (NCT03914326) with once-daily oral semaglutide includes secondary kidney disease outcomes and will provide further evidence regarding semaglutide and kidney protection.[41]

DISCLOSURE

KRT reports receiving grants/contracts from Novo Nordisk; consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly & Co, Gilead, Goldfinch Bio, Janssen, Novo Nordisk and Travere; honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Gilead, Goldfinch Bio, and Novo Nordisk; and support for attending meetings or travel from Eli Lilly; and is on the Board of Directors for the Kidney Health Initiative and Chair of the Diabetic Kidney Disease Collaborative Task Force, both of which are for the American Society of Nephrology. HB-T, JL and SR are employees of Novo Nordisk A/S. HB-T and SR hold stock in Novo Nordisk A/S. DZIC reports receiving honoraria from Abbvie, AstraZeneca, Bayer, BMS, Boehringer Ingelheim-CSL-Behring, Eli Lilly, Janssen, Maze, Merck, Mitsubishi Tanabe, Otsuka, Novartis, Novo Nordisk, Prometic, Sanofi, and Yeungene; and operational funding for clinical trials from AstraZeneca, Boehringer Ingelheim-Eli Lilly, Janssen, Merck, Novo Nordisk, and Sanofi. SH reports receiving grants from AstraZeneca and Pierre

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DATA STATEMENT

The datasets generated during and/or analyzed during this *post hoc* analysis are available from the corresponding author upon reasonable request.

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SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Table S1. Annual estimated glomerular filtration rate (eGFR) slope according to use of renin-angiotensin system (RAS) blockade at baseline.

Supplementary Figure S1. Change from baseline in estimated glomerular filtration rate (eGFR) over time (mixed model for repeated measurements [MMRM]) by baseline eGFR subgroups: (**A**) 30–<60 ml/min per 1.73 m^2 and (**B**) ≥60 ml/min per 1.73 m^2.

Supplementary Figure S2. Estimated glomerular filtration rate (eGFR) over time (mixed model for repeated measurements [MMRM]) in the SUSTAIN 6 trial, for (**A**) the overall population and by baseline eGFR subgroups: (**B**) 30–<60 ml/min per 1.73 m^2 and (**C**) ≥60 ml/min per 1.73 m^2.

Supplementary Figure S3. Estimated glomerular filtration rate (eGFR) over time (mixed model for repeated measurements [MMRM]) in the PIONEER 6 trial, for (**A**) the overall population and by baseline eGFR subgroups: (**B**) 30–<60 ml/min per 1.73 m^2 and (**C**) ≥60 ml/min per 1.73 m^2.

Supplementary Figure S4. Annual change in estimated glomerular filtration rate (eGFR; model-based total annual eGFR slope) from baseline to end of treatment (EOT) adjusted for change in glycated hemoglobin (HbA_{1c}) in the SUSTAIN 6 and PIONEER 6 trials (pooled analysis), (**A**) in the overall population, and by baseline eGFR subgroups: (**B**) 30–<60 ml/min per 1.73 m^2 and (**C**) ≥60 ml/min per 1.73 m^2.

Supplementary Figure S5. Annual change in estimated glomerular filtration rate (eGFR; model-based total annual eGFR slope) from baseline to end of treatment (EOT) adjusted for change in glycated hemoglobin (HbA_{1c}), change in body weight (BW), change in systolic blood pressure (SBP) and baseline diuretic use in the SUSTAIN 6 and PIONEER 6 trials (pooled analysis), (**A**) in the overall population, and by baseline eGFR subgroups: (**B**) 30–<60 ml/min per 1.73 m^2 and (**C**) ≥60 ml/min per 1.73 m^2.

Supplementary Figure S6. Annual change in estimated glomerular filtration rate (eGFR; model-based total annual eGFR slope) excluding data before week 14/16 to end of treatment (EOT; pooled analysis), (**A**) in the overall population, and by baseline eGFR subgroups: (**B**) 30–<60 ml/min per 1.73 m^2 and (**C**) ≥60 ml/min per 1.73 m^2.

Supplementary Figure S7. Annual change in estimated glomerular filtration rate (eGFR; model-based total annual eGFR slope) over time and from baseline to end of treatment (EOT) in the SUSTAIN 6 trial, (**A**) in the overall population, and by baseline eGFR subgroups: (**B**) 30–<60 ml/min per 1.73 m^2 and (**C**) ≥60 ml/min per 1.73 m^2.

Supplementary Figure S8. Annual change in estimated glomerular filtration rate (eGFR; model-based total annual eGFR slope) over time and from baseline to end of treatment (EOT) in the PIONEER 6 trial, (**A**) in the overall population, and by baseline eGFR subgroups: (**B**) 30–<60 ml/min per 1.73 m^2 and (**C**) ≥60 ml/min per 1.73 m^2.

Supplementary Figure S9. Time to onset of persistent reductions in estimated glomerular filtration rate (eGFR) in the overall population and by baseline eGFR subgroups in the SUSTAIN 6 trial.

Supplementary Figure S10. Time to onset of persistent reductions in estimated glomerular filtration rate (eGFR) in the overall population and by baseline eGFR subgroups in the PIONEER 6 trial.

Supplementary Figure S11. Estimated urinary albumin-to-creatinine ratio (UACR) over time and from baseline to end of treatment (EOT; week 104) in the SUSTAIN 6 trial, (**A**) in the overall population, and by baseline estimated glomerular filtration rate (eGFR) subgroups: (**B**) 30–<60 ml/min per 1.73 m^2 and (**C**) ≥60 ml/min per 1.73 m^2.

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