Estimated GFR (eGFR) loss with glucagon-like peptide-1 (GLP-1) analogue treatment: data from SUSTAIN 6 and LEADER

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- on behalf of the LEADER and SUSTAIN 6 investigators

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Introduction and aims

- Type 2 diabetes (T2D) is associated with long-term complications, including chronic kidney disease (CKD) and cardiovascular disease (CVD).[1]
- CKD occurs in approximately 40% of adults with T2D,[2] and represents a significant burden for patients and healthcare providers.[2] Currently, blockade of the renin-angiotensin-aldosterone system is the only approved therapy to reduce CKD progression,[3] and a great unmet need for more effective treatment remains.
- A decline in estimated glomerular filtration rate (eGFR) has been shown to predict the risk of kidney failure, cardiovascular (CV) events and mortality.[4,5]
- Treatment with glucagon-like peptide-1 (GLP-1) analogues has proven to be an effective approach to improving glycaemic levels in patients with T2D. Additionally, data have suggested that GLP-1 analogues may delay CKD progression.[6-10]
- In the SUSTAIN 6[7] and LEADER[8] trials, renal events were evaluated as part of a pre-specified secondary renal outcome in patients with T2D and high CV risk who received the GLP-1 analogues semaglutide or liraglutide versus placebo, both in addition to standard of care.
- This *post hoc* analysis of SUSTAIN 6 and LEADER trial data investigated the effects of semaglutide and liraglutide on the rate of loss of kidney function, evaluated as total eGFR slope.

Methods

Study design

- SUSTAIN 6 and LEADER were global, double-blind, randomised, placebo-controlled cardiovascular outcomes trials that assessed CV, renal and safety outcomes with semaglutide (0.5 mg or 1.0 mg) and liraglutide (up to 1.8 mg) versus placebo when added to standard of care in 3297 and 9340 patients, respectively. Median follow-up was 2.1 and 3.8 years in SUSTAIN 6 and LEADER, respectively.
- Major inclusion criteria were:
  - » T2D with glycated haemoglobin (HbA_{1c}) ≥7.0%;
  - » Age ≥50 years with at least one coexisting CV condition, one of which being eGFR <60 mL/min/1.73 m^2;
  - » Alternatively, age ≥60 years with at least one CV risk factor.
- Major exclusion criteria were:
  - » Type 1 diabetes;
  - » Use of GLP-1 analogues, dipeptidyl peptidase-4 inhibitors, pramlintide or rapid-acting insulin;
  - » A familial or personal history of multiple endocrine neoplasia type 2 or medullary thyroid cancer;
  - » The occurrence of an acute coronary or cerebrovascular event within 14 days before screening.
- The primary composite outcome in both trials was the occurrence of first major adverse CV events. Secondary outcomes included a composite renal outcome of new-onset persistent macroalbuminuria, persistent doubling of serum creatinine level and the need for continuous renal-replacement therapy or death from renal disease.
- In the current analysis, the annual eGFR change was evaluated by overall population and baseline eGFR subgroup (<60 vs ≥60 mL/min/1.73 m^2) for semaglutide (0.5 mg and 1.0 mg) and liraglutide, compared with placebo.

Statistical analysis

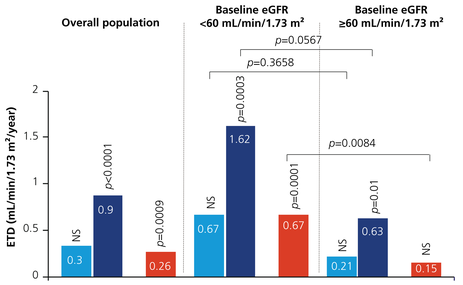
- Annual change in eGFR and estimated treatment differences in the rate of eGFR change over time (total eGFR slope) were analysed using in-trial data from baseline to end-of-treatment for SUSTAIN 6 and LEADER, respectively, by overall population and by baseline eGFR subgroup (<60 vs ≥60 mL/min/1.73 m^2) using a linear random regression model with random intercept and time slope.
- A *p*-value of <0.05 was considered significant.
- To further illustrate the eGFR decline over time, the eGFR by visit was estimated using a mixed model for repeated measures (MMRM) analysis for the overall population and by subgroup.

Table 1: Patients' baseline characteristics

	SUSTAIN 6 (N = 3297*)			LEADER (N = 9340*)	
	Semaglutide 0.5 mg (n=825)	Semaglutide 1.0 mg (n=821)	Placebo (n=1648)	Liraglutide 1.8 mg (n=4512)	Placebo (n=4498)
Age, years	64.6 ± 7.3	64.6 ± 7.1	64.6 ± 7.5	64.1 ± 7.2	64.4 ± 7.2
Sex, male, N (%)	494 (59.9)	517 (63.0)	988 (60.0)	2915 (64.6)	2884 (64.1)
Body weight, kg	91.8 ± 20.3	92.9 ± 21.1	91.9 ± 20.6	91.9 ± 21.2	91.5 ± 20.5
Diabetes duration, years	14.3 ± 8.2	14.1 ± 8.2	13.6 ± 8.0	12.7 ± 7.9	12.8 ± 8.0
Glycated haemoglobin (HbA_{1c}), %	8.7 ± 1.4	8.7 ± 1.5	8.7 ± 1.5	8.7 ± 1.6	8.6 ± 1.5
Systolic blood pressure, mmHg	136.1 ± 17.9	135.9 ± 16.9	135.3 ± 16.8	135.9 ± 17.7	136.0 ± 17.7
Diastolic blood pressure, mmHg	77.1 ± 9.8	76.9 ± 10.2	77.1 ± 10.0	77.3 ± 10.3	77.0 ± 10.1
RAAS inhibitor use, N (%)	673 (81.6)	665 (81.0)	1327 (80.5)	3633 (80.5)	3598 (80.0)
Renal function, N (%)					
eGFR† ≥60	613 (74.3)	617 (75.2)	1221 (74.1)	3544 (78.5)	3593 (79.9)
eGFR† <60	212 (25.7)	204 (24.8)	427 (25.9)	968 (21.5)	905 (20.1)
Albuminuria status					
Normoalbuminuria	472 (58.3)	476 (59.0)	986 (60.8)	2820 (63.6)	2737 (62.3)
Microalbuminuria	235 (29.0)	237 (29.4)	412 (30.9)	1168 (26.4)	1185 (27.0)
Macroalbuminuria	102 (12.6)	94 (11.6)	224 (16.8)	443 (10.0)	474 (10.8)

*These values represent the total number of patients recruited into SUSTAIN 6 and LEADER, respectively; only patients with eGFR at baseline and at least one post-baseline eGFR measurement have been included in this analysis. Normoalbuminuria defined as UACR <30 mg/g; microalbuminuria defined as UACR ≥30 to 300 mg/g; macroalbuminuria defined as UACR >300 mg/g. Full analysis set. Data are means ± standard deviation unless otherwise indicated. Renal function is calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula. †mL/min/1.73 m^2. eGFR, estimated glomerular filtration rate; N, number of patients; RAAS, renin-angiotensin-aldosterone system; UACR, urinary albumin-to-creatinine ratio

Figure 1: Annual change in eGFR and ETD in SUSTAIN 6 and LEADER



Key results

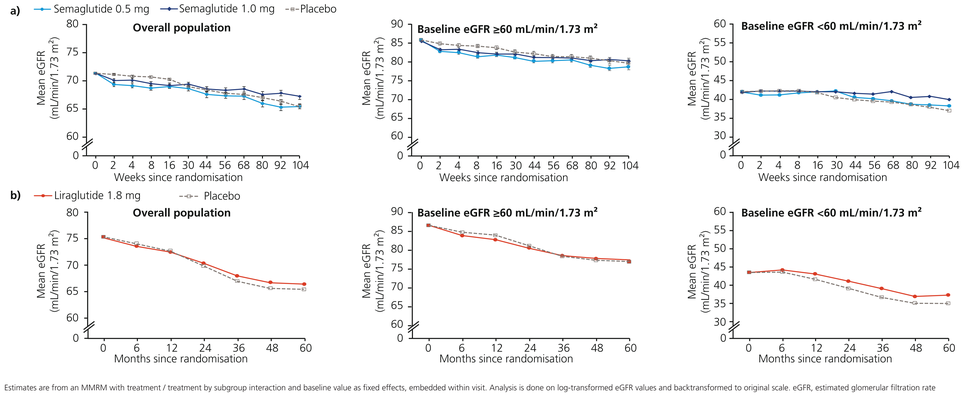
Annual eGFR change (mL/min/1.73 m²)/year	Estimate [95% CI]; *p*-value				
	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo	Liraglutide 1.8 mg	Placebo
Overall population	N=825 −1.59 [−1.95; −1.23]	N=821 −1.05 [−1.41; −0.69]	N=1648 −1.92 [−2.18; −1.67]	N=4512 −1.72 [−1.84; −1.61]	N=4498 −1.98 [−2.10; −1.87]
<60 mL/min/1.73 m²	N=212 −1.20 [−1.90; −0.49]	N=204 −0.25 [−0.97; 0.48]	N=427 −1.87 [−2.37; −1.36]	N=968 −1.44 [−1.68; −1.19]	N=905 −2.11 [−2.37; −1.85]
≥60 mL/min/1.73 m²	N=613 −1.73 [−2.15; −1.32]	N=617 −1.31 [−1.72; −0.90]	N=1221 −1.94 [−2.24; −1.64]	N=3544 −1.80 [−1.92; −1.67]	N=3593 −1.95 [−2.08; −1.83]

SUSTAIN 6
- Semaglutide 0.5 mg vs placebo
- Semaglutide 1.0 mg vs placebo

LEADER
- Liraglutide 1.8 mg vs placebo

p-values above bracketed lines are *p*-values for treatment by subgroup interaction; *p*-values directly above bars in graph are *p*-values for the ETD. A positive ETD value indicates less reduction in eGFR with semaglutide or liraglutide versus placebo. eGFR, estimated glomerular filtration rate; ETD, estimated treatment difference; N, number of patients; NS, non-significant

Figure 2: eGFR by visit by treatment group in the overall population, and subgroups by eGFR at baseline, in a) SUSTAIN 6 and b) LEADER



Estimates are from an MMRM with treatment / treatment by subgroup interaction and baseline value as fixed effects, embedded within visit. Analysis is done on log-transformed eGFR values and backtransformed to original scale. eGFR, estimated glomerular filtration rate

Results

- Patient demographic and clinical characteristics at baseline were comparable across treatment groups (Table 1).
- Of the 3297 patients in SUSTAIN 6, 3294 with baseline and post-baseline eGFR measurements are included in this analysis:
  - » 2451 (74.4%) patients had a preserved eGFR of ≥60 mL/min/1.73 m^2 and 1934 (59.7%) had normoalbuminuria (UACR <30 mg/g).
- Of the 9340 patients in LEADER, 9010 with baseline and post-baseline eGFR measurements are included in this analysis:
  - » 7137 (79.2%) patients had a preserved eGFR of ≥60 mL/min/1.73 m^2 and 5557 (63.0%) had normoalbuminuria (UACR <30 mg/g).
- Mean duration of T2D was 13.9 years and 12.8 years in SUSTAIN 6 and LEADER, respectively. The mean HbA_{1c} was 8.7% in both trials.
- In the SUSTAIN 6 overall population, a significantly slower rate of annual eGFR decline was observed with semaglutide 1.0 mg versus placebo (p<0.0001); a lower rate was also observed with 0.5 mg versus placebo, but this was not significant (p=0.1382) (Figure 1).
- In the SUSTAIN 6 subgroup analysis by baseline eGFR <60 or ≥60 mL/min/1.73 m^2 (Figure 1):
  - » Semaglutide 1.0 mg significantly slowed the rate of annual eGFR decline compared with placebo, with a trend towards a larger treatment difference in those with eGFR <60 mL/min/1.73 m^2 (*p*-value for interaction=0.0567);
  - » A similar effect was not seen with semaglutide 0.5 mg and there was no effect of subgroup on the treatment difference (*p*-value for interaction=0.3658).
- In the overall LEADER population, the annual rate of decline in eGFR was significantly slower for liraglutide than for placebo (p=0.0009) (Figure 1).
  - » In the subgroup analysis, the effect was more marked in patients with baseline eGFR <60 mL/min/1.73 m^2 than for the ≥60 mL/min/1.73 m^2 subgroup (*p*-value for interaction=0.0084).
- eGFR by treatment group in the overall population and subgroups by eGFR at baseline are shown in Figure 2.

Conclusions

- The annual rate of decline in renal function among patients with T2D (and at high CV risk) was slower over the trial duration in patients treated with semaglutide 1.0 mg or liraglutide when compared with placebo.
- The benefit of semaglutide and liraglutide treatment appears to be more pronounced in patients with reduced kidney function (eGFR <60 mL/min/1.73 m^2).
- Total eGFR slope has been shown to correlate with hard renal outcomes, and the effects observed in the current analysis are potentially clinically important, suggesting a renal benefit with semaglutide and liraglutide.

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