

Effects of Semaglutide on Albuminuria and Kidney Function in People With Overweight or Obesity With or Without Type 2 Diabetes: Exploratory Analysis From the STEP 1, 2, and 3 Trials

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Semaglutide improves albuminuria in people with overweight or obesity and type 2 diabetes

Context and Objective(s)





STEP 1–3 post hoc analyses explored the effects of semaglutide 1.0 mg and 2.4 mg versus placebo on kidney function




Design and Methods



Participants:

-  STEP 1 and 3: adults with overweight or obesity
-  STEP 2: adults with overweight or obesity and type 2 diabetes

Treatment arms:

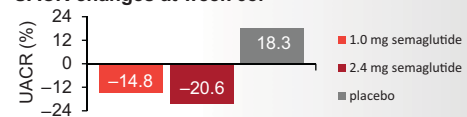
-  1.0 mg semaglutide (STEP 2)
- 2.4 mg semaglutide
- Placebo


End points assessed:


-  Changes in urine albumin-to-creatinine ratio (UACR) and UACR status (STEP 2)
-  Changes in estimated glomerular filtration rate (eGFR) (STEP 1–3 pooled)

Results


UACR changes at week 68:



 58.6% of the UACR-lowering effect was statistically independent of changes in glycated hemoglobin (HbA_{1c}) or body weight

 The effect of semaglutide versus placebo was consistent across subgroups by baseline BMI, HbA_{1c}, eGFR, or use of renin–angiotensin system or sodium–glucose cotransporter-2 inhibitors

eGFR changes at week 68:

 No difference between semaglutide 1.0 mg and 2.4 mg semaglutide and placebo

Diabetes Care

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ARTICLE HIGHLIGHTS

- The objective of the study was to explore the effects of semaglutide on kidney parameters in people with overweight or obesity.
- The study sought to answer the question of whether semaglutide effectively reduces albuminuria and improves estimated glomerular filtration rate.
- In people living with overweight/obesity and type 2 diabetes, semaglutide reduced albuminuria by 30% and improved urine albumin-to-creatinine ratio status but did not affect estimated glomerular filtration rate in people with overweight/obesity with or without type 2 diabetes.
- The reduction in albuminuria and improvement in urine albumin-to-creatinine ratio status support ongoing trials assessing the effects of semaglutide on long-term clinical kidney outcomes.



Effects of Semaglutide on Albuminuria and Kidney Function in People With Overweight or Obesity With or Without Type 2 Diabetes: Exploratory Analysis From the STEP 1, 2, and 3 Trials

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OBJECTIVE

These post hoc analyses of the Semaglutide Treatment Effect in People with obesity (STEP) 1–3 trials (NCT03548935, NCT03552757, and NCT03611582) explored the effects of semaglutide (up to 2.4 mg) on kidney function.

RESEARCH DESIGN AND METHODS

STEP 1–3 included adults with overweight/obesity; STEP 2 patients also had type 2 diabetes. Participants received once-weekly subcutaneous semaglutide 1.0 mg (STEP 2 only), 2.4 mg, or placebo for 68 weeks, plus lifestyle intervention (STEP 1 and 2) or intensive behavioral therapy (STEP 3). Changes in urine albumin-to-creatinine ratio (UACR) and UACR status from baseline to week 68 were assessed for STEP 2. Changes in estimated glomerular filtration rate (eGFR) were assessed from pooled STEP 1–3 data.

RESULTS

In STEP 2, 1,205 (99.6% total cohort) patients had UACR data; geometric mean baseline UACR was 13.7, 12.5, and 13.2 mg/g with semaglutide 1.0 mg, 2.4 mg, and placebo, respectively. At week 68, UACR changes were –14.8% and –20.6% with semaglutide 1.0 mg and 2.4 mg, respectively, and +18.3% with placebo (between-group differences [95% CI] vs. placebo: –28.0% [–37.3, –17.3], $P < 0.0001$ for semaglutide 1.0 mg; –32.9% [–41.6, –23.0], $P = 0.003$ for semaglutide 2.4 mg). UACR status improved in greater proportions of patients with semaglutide 1.0 mg and 2.4 mg versus placebo ($P = 0.0004$ and $P = 0.0014$, respectively). In the pooled STEP 1–3 analyses, 3,379 participants had eGFR data; there was no difference between semaglutide 2.4 mg and placebo in eGFR trajectories at week 68.

CONCLUSIONS

Semaglutide improved UACR in adults with overweight/obesity and type 2 diabetes. In participants with normal kidney function, semaglutide did not have an effect on eGFR decline.

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Clinical practice guidelines for patients with type 2 diabetes recommend lifestyle interventions, including increased physical activity and weight loss, glucose-lowering agents to optimize glycemic control, and pharmacological treatment with renin-angiotensin system (RAS) inhibitors and sodium-glucose cotransporter 2 (SGLT2) inhibitors to slow progression of kidney function loss and reduce the incidence of cardiovascular disease (CVD) events (1,2). Despite the fact that clinical trials have demonstrated the efficacy of these lifestyle and pharmacological interventions (3–10), residual cardiovascular (CV) and kidney risk remains present even with guideline-recommended treatment (8,10). Part of this high residual risk of kidney function decline is associated with the biomarker of persistently elevated levels of albuminuria (11). New treatment strategies that further reduce body weight, improve glycemic control, and directly or indirectly reduce albuminuria are therefore needed.

Glucagon-like peptide 1 receptor agonists (GLP-1RAs) are recommended by clinical practice guidelines for the treatment of type 2 diabetes and obesity to reduce CV risk (1,12). CV outcomes trials with GLP-1RAs, including semaglutide, have demonstrated that these agents reduce CV risk and slow kidney function decline. These benefits may be partially due to improvements in glycemic control but are likely also mediated by other effects, such as reductions in blood pressure, body weight, and albuminuria, beneficial effects on endothelial function, and inhibition of proinflammatory mediators (13).

The body weight-lowering effects of GLP-1RAs are clinically important as the prevalence of obesity continues to rise. In people with type 2 diabetes, once-weekly subcutaneous semaglutide doses of 1.0 and 2.0 mg reduce body weight (14). A higher dose (2.4 mg once weekly) has been approved for the treatment of overweight and obesity (15,16). The Semaglutide Treatment Effect in People with obesity (STEP) clinical trial program examined the effect of semaglutide 2.4 mg (administered subcutaneously once weekly) on body weight compared with placebo in people with overweight or obesity (17). The STEP 1, 2, 3, and 4 trials demonstrated that semaglutide 2.4 mg compared with placebo, as adjunct to lifestyle management or intensive behavioral

therapy, led to mean weight losses of 6–15% in participants with and without type 2 diabetes (14,18–20). The effects of semaglutide 2.4 mg on albuminuria and estimated glomerular filtration rate (eGFR) are unknown, as are the potential benefits of semaglutide in patients using and not using SGLT2 inhibitors. It is also unknown whether the effects on albuminuria can be explained by concomitant changes in glycated hemoglobin (HbA_{1c}), body weight, and blood pressure.

The aims of these post hoc analyses were to first explore the effect of semaglutide compared with placebo on albuminuria in patients with type 2 diabetes, as albuminuria was only measured in the STEP 2 trial, and second, to assess the effects of semaglutide on eGFR in a pooled analysis of the STEP 1–3 trials.

RESEARCH DESIGN AND METHODS

Trial Designs

The current study is a post hoc analysis of the STEP 1–3 trials. The full methods, trial profile and patient flow, and primary results for the STEP 1–3 trials have previously been described (14,18,19). In brief, STEP 1–3 (NCT03548935, NCT03552757, and NCT03611582) were all phase 3a, double-blind, placebo-controlled, multicenter trials. In STEP 1 and 3, participants were randomized 2:1 to escalating doses of semaglutide up to 2.4 mg/week or placebo for 68 weeks as an adjunct to either lifestyle intervention (counseling on diet and physical activity; STEP 1) or an initial meal-replacement diet plus intensive behavioral therapy (low-calorie diet and intensive counseling on diet and physical activity followed by randomization to semaglutide or placebo to assess maintenance and/or further weight loss; STEP 3) (18,19). In STEP 2, participants were randomized 1:1:1 to 68 weeks of semaglutide 2.4 mg, 1.0 mg, or placebo, all plus lifestyle intervention (similar to that in STEP 1) (14). In all trials, semaglutide was initiated at 0.25 mg once weekly and escalated every 4 weeks until the target dose was achieved (2.4 mg over 16 weeks, or 1.0 mg over 8 weeks for participants assigned that dose in STEP 2). At the end of the 68-week double-blind treatment period, participants proceeded to a 7-week off-drug follow-up period in each trial. All three trials were conducted according to the International Conference on Harmonisation Good Clinical Practice

Guideline and the Declaration of Helsinki; all participants provided written informed consent (14,18,19). STEP 4 was not included in this analysis because key differences in trial design, including its 20-week run-in period in which all participants received semaglutide, made it unsuitable to pool the results with the STEP 1–3 trials.

Participants

Male or female adults (≥ 18 years of age) with a stable body weight (≤ 5 kg weight change within 90 days before screening) and a history of at least one self-reported unsuccessful dietary effort to lose body weight were eligible for the STEP 1–3 trials (14,18,19). In addition, participants in STEP 1 and 3 were required to have either a BMI of ≥ 30 kg/m² or ≥ 27 kg/m² plus at least one weight-related comorbidity (excluding type 2 diabetes) (18,19). In STEP 2, participants were required to have a BMI of ≥ 27 kg/m², a diagnosis of type 2 diabetes that was managed by diet and physical activity or ≤ 3 oral glucose-lowering therapies, and an HbA_{1c} of 7–10% (53–86 mmol/mol) (14). Participants were excluded from the trials if they had an eGFR of < 15 mL/min/1.73 m² in STEP 1 and 3 (18,19) and of < 30 mL/min/1.73 m² (< 60 mL/min/1.73 m² in those receiving SGLT2 inhibitors) in STEP 2 (14).

Outcomes

The coprimary outcome in STEP 1–3 was the percent change from baseline in body weight (alongside the achievement of $\geq 5\%$ weight loss) as reported previously (14,18,19). Changes in albuminuria and eGFR were assessed as exploratory post hoc outcomes (14,18,19). Albuminuria was expressed as urine albumin-to-creatinine ratio (UACR). Urinary albumin and creatinine were measured in a central laboratory at weeks 0, 20, and 68 in STEP 2 only; UACR was not measured in STEP 1 or 3. The albuminuria-related outcomes assessed from baseline to week 68 were: mean percent change in urinary albumin concentration, mean percent change in UACR in the overall population and in patient subgroups; proportions of patients with normoalbuminuria (UACR < 30 mg/g), microalbuminuria (UACR ≥ 30 to ≤ 300 mg/g), and macroalbuminuria (UACR > 300 mg/g); and proportions of patients whose UACR status improved or worsened. For the subgroup analyses of the change in UACR, patients were

grouped according to the following variables: baseline UACR (<30 or ≥ 30 mg/g), baseline systolic blood pressure (<130 or ≥ 130 mmHg), baseline eGFR (<90 or ≥ 90 mL/min/1.73 m²), baseline HbA_{1c} (<8.0 or ≥ 8.0 %), baseline BMI (<35 or ≥ 35 kg/m²), SGLT2 inhibitor use (yes/no), and RAS inhibitor use (yes/no). For the analysis of change in UACR status, an improvement was defined as regression from microalbuminuria at baseline to normoalbuminuria, or macroalbuminuria at baseline to micro-/normoalbuminuria by week 68, while a worsening was defined as either progression from normoalbuminuria at baseline to micro-/macroalbuminuria, or microalbuminuria at baseline to macroalbuminuria by week 68. A mediation analysis was performed to investigate whether the effect of semaglutide in reducing UACR was mediated by concomitant changes in HbA_{1c}, body weight, and blood pressure from baseline to week 68.

Serum creatinine was measured at screening and at weeks 20, 52, and 68 in STEP 1–3. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration 2009 creatinine equation (21). A sensitivity analysis was performed using the race-free Chronic Kidney Disease Epidemiology Collaboration 2021 creatinine equation (22). The change from baseline to week 68 in eGFR was assessed in STEP 1–3.

Statistical Analysis

Statistical analyses were based on the trial product estimand (the secondary estimand in the STEP trials), which assessed the treatment effect in all randomized participants when each drug was taken as intended. The analyses only included data from all randomized assigned participants until first treatment discontinuation or use of a rescue intervention (initiation of other antiobesity medications or bariatric surgery). Observed data from the on-treatment observation period (during treatment with trial product; any dose of trial medication administered within the previous 2 weeks [i.e., any period of temporary treatment interruption with trial product was excluded]) are reported for the following outcomes (STEP 2 only unless otherwise stated): urinary albumin by week, UACR by week, proportions of patients by UACR status, proportions of patients with an improvement or worsening in UACR status, and eGFR by week (STEP 1–3). In a sensitivity analysis, the

effects of semaglutide versus placebo were analyzed according to the treatment policy estimand, which assessed the effect in all randomized participants irrespective of discontinuation of randomized treatment or use of rescue medication. The proportions of patients whose UACR status improved were compared by treatment using a Chi-square test.

The changes from baseline to week 68 in urinary albumin concentration (STEP 2), UACR (STEP 2), and eGFR (STEP 1–3) were assessed using a mixed model for repeated measurements with randomized treatment, randomization stratification groups (background type 2 diabetes medication and HbA_{1c}; STEP 2 only), and the interaction between stratification groups (STEP 2 only) as factors and baseline value of the outcome measure of interest as a covariate, all nested within visit. For the subgroup analysis of the change in UACR, subgroup and the interaction between treatment and subgroup were also included in the model as factors. None of the analyses were adjusted for multiplicity.

The mediation analysis was performed using the medflex package in R (23). A natural effects model was fitted using an imputation-based procedure (24), allowing for decomposition of the treatment effect estimates into natural direct and indirect effect estimates. The percent mediated was then calculated as the natural indirect effect divided by the total treatment effect and the CI obtained using Fieller's method (25).

Urinary albumin and UACR were analyzed on a log scale as estimated ratios to baseline (within treatment groups) and estimated treatment ratios (between treatment groups). For interpretation, data are expressed as relative percent changes and estimated relative percent differences between groups, respectively, calculated using the formula (estimated ratio – 1) × 100. *P* values <0.05 were considered to indicate statistical significance. Analyses were performed with R version 4.20/SAS version 9.4. No adjustment for multiple comparisons was made, and as such, all results should be considered exploratory.

Data and Resource Availability

Data will be shared with bona fide researchers who submit a research proposal approved by the independent review board. Individual patient data will be shared in

data sets in a de-identified and anonymized format. Data will be made available after research completion and approval of the product and product use in the European Union and U.S. Information about data access request proposals can be found at <https://www.novonordisk-trials.com>.

RESULTS

Participants

In STEP 2, the baseline characteristics were well balanced among the three treatment groups (Table 1). The geometric mean (coefficient of variation) for UACR at baseline was 13.2 (199.8) mg/g in the placebo group and 13.7 (249.6) mg/g and 12.5 (225.1) mg/g in the semaglutide 1.0 mg and 2.4 mg treatment groups, respectively. A total of 248 participants had UACR of ≥ 30 mg/g at baseline. In STEP 2, the mean \pm SD for eGFR at baseline was 95.4 ± 18.1 and 96.3 ± 18.5 mL/min/1.73 m² in the semaglutide 1.0 mg and 2.4 mg groups and 94.6 ± 19.3 mL/min/1.73 m² in the placebo group.

Baseline characteristics for STEP 1 and STEP 3 are presented in Supplementary Tables 1 and 2. The mean \pm SD for eGFR at baseline in STEP 1 was 97.9 ± 16.9 mL/min/1.73 m² for semaglutide 2.4 mg and 97.4 ± 16.7 mL/min/1.73 m² for placebo. In STEP 3, the mean \pm SD for eGFR at baseline was 98.6 ± 19.3 mL/min/1.73 m² for semaglutide 2.4 mg and 98.5 ± 19.3 mL/min/1.73 m² for placebo.

Effect of Semaglutide Versus Placebo on UACR (STEP 2)

Figure 1A shows the albuminuria change from baseline to week 68, and Supplementary Fig. 1 shows the change over time in UACR by week. In the placebo group, UACR increased by 18.3%. In the semaglutide 1.0 mg and 2.4 mg dose groups, UACR changed from baseline by -14.8% and -20.6% , respectively, at week 68. Accordingly, mean percentage UACR difference compared with placebo at week 68 was -28.0% (95% CI $-37.3, -17.3$) ($P < 0.0001$) and -32.9% (95% CI $-41.6, -23.0$) ($P = 0.003$) in the semaglutide 1.0 mg and 2.4 mg groups, respectively. Changes in urinary albumin concentration from baseline to week 68 were -8.6% in the semaglutide 1.0 mg treatment group (estimated treatment difference, -22.6 [95% CI $-34.1, -9.1$]) and -12.6% in

Table 1—Baseline demographics and clinical characteristics (STEP 2)

	Semaglutide 1.0 mg (n = 403)	Semaglutide 2.4 mg (n = 404)	Placebo (n = 403)
Age, years, mean (SD)	56 (10)	55 (11)	55 (11)
Sex			
Male	200 (49.6)	181 (44.8)	213 (52.9)
Female	203 (50.4)	223 (55.2)	190 (47.1)
Race			
American Indian or Alaska Native	0	4 (1.0)	2 (0.5)
Asian	97 (24.1)	112 (27.7)	108 (26.8)
Black or African American	28 (6.9)	35 (8.7)	37 (9.2)
White	272 (67.5)	237 (58.7)	242 (60.0)
Other	6 (1.5)	16 (4.0)	13 (3.2)
Native Hawaiian or Other Pacific Islander	0	0	1 (0.2)
Duration of diabetes, years [no.*], mean (SD)	7.7 (5.9)	8.2 (6.2)	8.2 (6.2) [402]
HbA _{1c} , mmol/mol, mean (SD)	65.4 (8.5)	65.3 (8.7)	65.3 (9.0)
HbA _{1c} , %	8.1 (0.8)	8.1 (0.8)	8.1 (0.8)
Body weight, kg, mean (SD)	99.0 (21.1)	99.9 (22.5)	100.5 (20.9)
BMI, kg/m ² , mean (SD)	35.3 (5.9)	35.9 (6.4)	35.9 (6.5)
eGFR, CKD-EPI, mL/min/1.73 m ²			
Mean (SD)	95.4 (18.1)	96.3 (18.5)	94.6 (19.3)
Distribution† [no.*]	[402]	[403]	[402]
≥90	265 (65.9)	270 (67.0)	259 (64.4)
<90	137 (34.1)	133 (33.0)	143 (35.6)
UACR, mg/g† [no.*]	[402]	[403]	[402]
Geometric mean (CV)	13.7 (249.6)	12.5 (225.1)	13.2 (199.8)
Normal albuminuria (UACR <30)	306 (77.5)	318 (80.5)	317 (79.4)
Microalbuminuria (UACR ≥30 to <300)	72 (18.2)	64 (16.2)	71 (17.8)
Macroalbuminuria (UACR ≥300)	17 (4.3)	13 (3.3)	11 (2.8)
Blood pressure, mmHg, mean (SD)			
Systolic blood pressure	130 (14)	130 (13)	130 (13)
Diastolic blood pressure	80 (9)	80 (9)	80 (9)
History of CV	90 (22.3)	58 (14.4)	69 (17.1)
SGLT2 inhibitor use	90 (22.3)	95 (23.5)	99 (24.6)
Agents acting on the RAS	244 (60.5)	216 (53.5)	241 (59.8)

Data are n (%) and are for the full analysis set unless otherwise indicated. n is number of patients. Novo Nordisk data published in Davies M, Færch L, Jeppesen OK, et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet* 2021;397:971–984. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, coefficient of variation. *[no.] is number of participants analyzed (where different from the number in the full analysis set). †Data are for the safety analysis set.

the semaglutide 2.4 mg treatment group (estimated treatment difference, -26.0 [95% CI $-37.0, -13.1$]) versus 18.1% in the placebo group. The change over time in urinary albumin by week is shown in Supplementary Fig. 2. Results were essentially similar when we repeated the analysis according to the treatment policy estimand. Mean percentage UACR difference compared with placebo at week 68 was -27.2% (95% CI $-37.6, -15.0$) ($P < 0.0001$) and -30.5% (95% CI $-40.3, -19.1$) ($P < 0.0001$) in the semaglutide 1.0 mg and 2.4 mg groups, respectively.

Estimated changes in UACR by subgroups of patients are shown in Fig. 2.

The effect of semaglutide compared with placebo was consistent in subgroups by baseline BMI, HbA_{1c}, eGFR, or use of RAS or SGLT2 inhibitors. The reduction in UACR with semaglutide 2.4 mg compared with placebo was more pronounced in patients with microalbuminuria or macroalbuminuria compared with patients with normoalbuminuria ($P = 0.0009$).

A higher proportion of patients on semaglutide 2.4 mg and semaglutide 1.0 mg had normoalbuminuria by week 68 compared with those receiving placebo (87.1% vs. 84.9% vs. 72.8%, respectively) (Fig. 1B). The percentage of patients with microalbuminuria and macroalbuminuria at week 68

was lower in the semaglutide 2.4 mg and 1.0 mg treatment groups compared with placebo (11.5% and 1.4% vs. 12.2%, and 2.9% vs. 22.4% and 4.8%, respectively).

The proportion of patients with a $>30\%$ reduction in UACR at week 68 in the semaglutide 1.0 mg and 2.4 mg groups was 37.4% ($P = 0.0014$ vs. placebo) and 38.0% ($P = 0.0008$ vs. placebo), respectively, compared with 25.9% in the placebo group. The corresponding proportions of patients who improved from macroalbuminuria or microalbuminuria categories to a lower category (microalbuminuria or normoalbuminuria) were 57.9% for semaglutide 1.0 mg ($P = 0.0004$) and 56.1% for

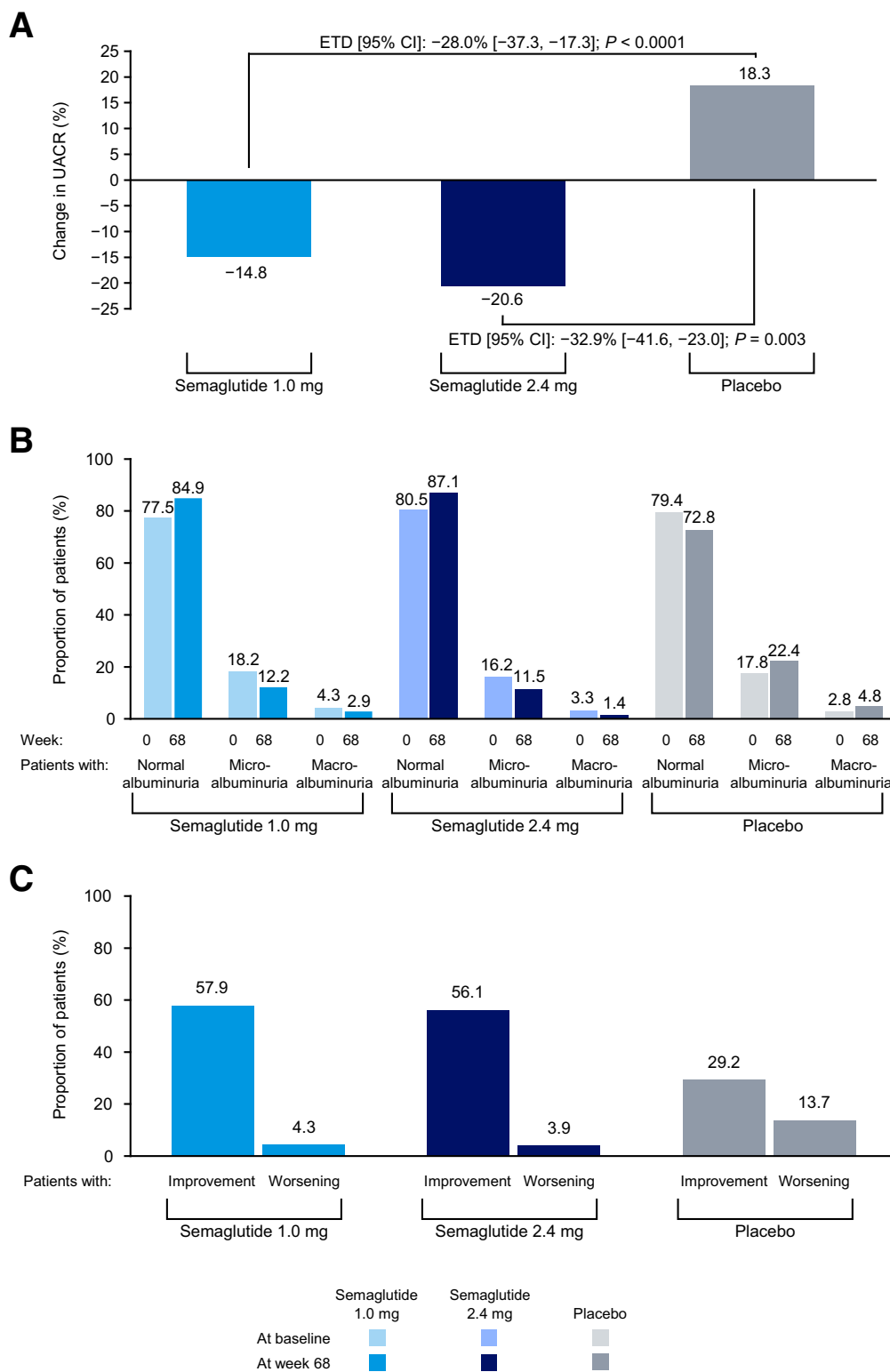


Figure 1—A: Percent change in UACR from baseline to week 68. B: Distribution of patients by UACR status at baseline and week 68. Proportions are based on the number of patients in each UACR status category at the visit over the total number of patients with a UACR observation at the visit. The left-hand bar in each pair refers to baseline and the right-hand bar to week 68. C: Patients with changes in UACR status from baseline to week 68. Proportions are based on the number of patients with an improvement in UACR status from baseline to week 68 over the total number of patients with a UACR observation at both time points; a large proportion of patients were not included in this analysis because of missing data at baseline ($n = 7$ for semaglutide 1.0 mg, $n = 8$ for semaglutide 2.4 mg, and $n = 3$ for placebo) or week 68 ($n = 57$ for semaglutide 1.0 mg, $n = 55$ for semaglutide 2.4 mg, and $n = 67$ for placebo). Improvement is regression of baseline macroalbuminuria to microalbuminuria/normal or microalbuminuria to normal at week 68. Worsening is progression of baseline normal albuminuria to microalbuminuria/macroalbuminuria or microalbuminuria to macroalbuminuria at week 68. ETD, estimated treatment difference.

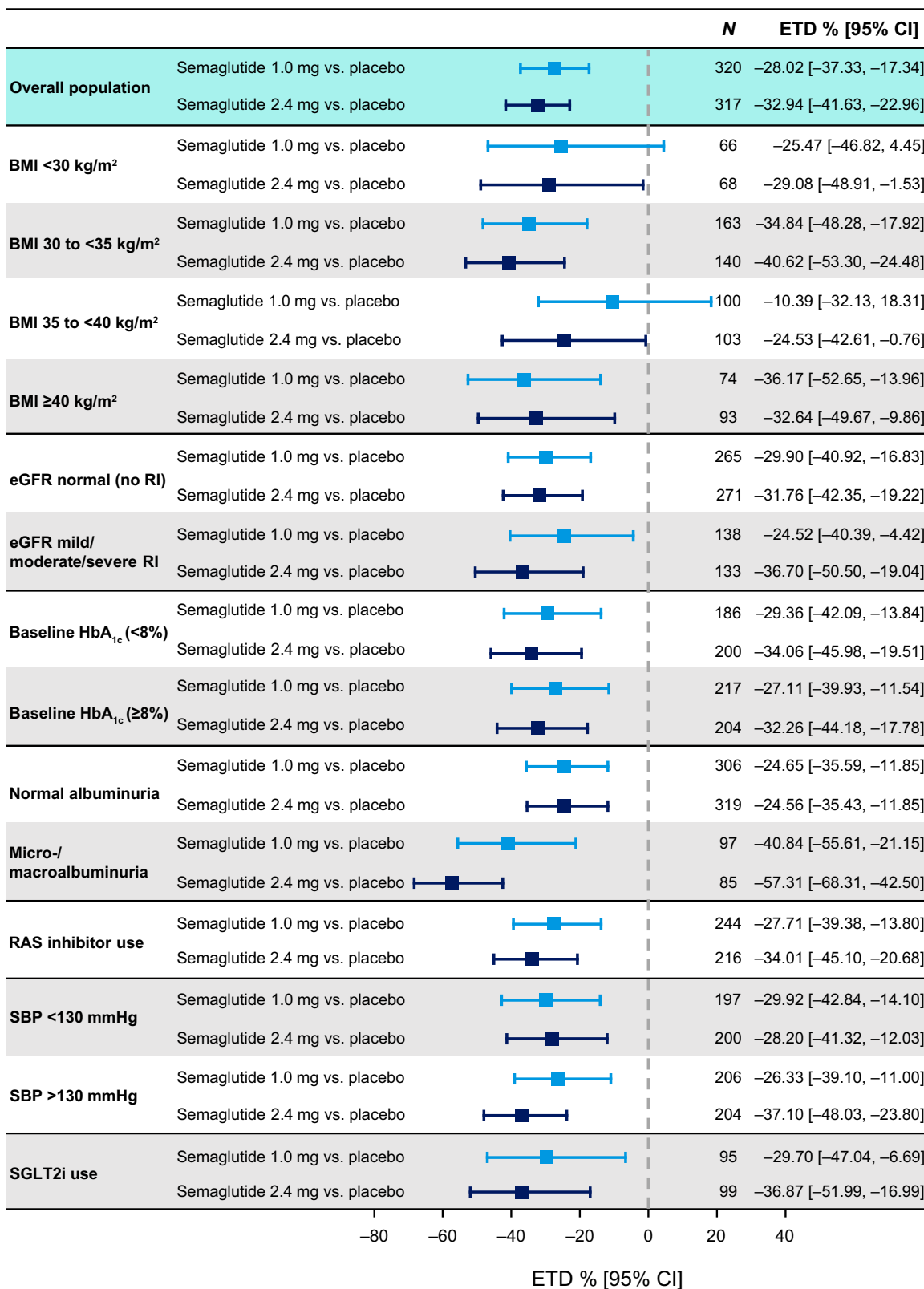


Figure 2—Change in UACR by subgroup analyses. Data are for the trial product estimand (assesses treatment effect if all patients adhered to treatment without rescue intervention) unless otherwise stated. RI, renal impairment; SBP, systolic blood pressure; SGLT2i, SGLT2 inhibitor.

semaglutide 2.4 mg ($P = 0.0014$) versus 29.2% for placebo (Fig. 1C). The proportions of patients who showed progression

from normoalbuminuria or microalbuminuria to a higher category for semaglutide 1.0 mg and 2.4 mg were 4.3% and 3.9%

($P < 0.0001$ for both doses vs. placebo), respectively, versus 13.7% with placebo (Fig. 1C).

Effect of Semaglutide on UACR Explained by Changes in HbA_{1c}, Body Weight, and Systolic Blood Pressure (STEP 2)

At week 68, patients receiving semaglutide 2.4 mg had placebo-corrected changes in HbA_{1c} of -1.5% (95% CI $-1.7, -1.4$). The corresponding changes in body weight and systolic blood pressure were -7.6% (95% CI $-8.6, -6.6$) and -4.8 mmHg (95% CI $-6.7, -2.9$), respectively, for semaglutide 2.4 mg versus placebo (14). To assess the extent to which the effect of semaglutide on albuminuria could be explained by concomitant changes in HbA_{1c}, body weight, or systolic blood pressure, the main analysis of change in UACR was repeated with adjustments for week 68 changes in these parameters (Supplementary Fig. 3). The effect of semaglutide 2.4 mg compared with placebo after adjustment for HbA_{1c}, body weight, and systolic blood pressure was 58.6% (95% CI 26.5, 97.8), suggesting that more than half of the effect of semaglutide on UACR may be related to its HbA_{1c}, body weight, and systolic blood pressure-lowering effects (Supplementary Fig. 3). Repeating the analysis for semaglutide 1.0 mg revealed similar results (Supplementary Fig. 4).

Effects on Overall eGFR Change (STEP 1–3)

To characterize the effect of semaglutide on kidney function, we pooled the data from the STEP 1–3 clinical trials, involving 3,379 participants with overweight or obesity with or without type 2 diabetes (data for the semaglutide 1.0 mg treatment arm from STEP 2 were not included in this analysis, but are included for baseline data). Of these participants, 1,262 were assigned to placebo and 2,117 to semaglutide 2.4 mg. Mean \pm SD eGFR at baseline was 99.3 ± 17.0 mL/min/1.73 m²

for the total population, and eGFR was <60 mL/min/1.73 m² in 85 (2.5%) participants. At week 68, no between-group differences in eGFR were observed. During the total 68 weeks of treatment, the rate of change in eGFR from baseline did not differ between the semaglutide (-0.70% [95% CI $-1.17, -0.22$]) and placebo group (-0.21% [95% CI $-0.85, 0.42$]; $P = 0.2351$) (Supplementary Fig. 5). Results were similar for semaglutide 1.0 mg treatment versus placebo in the STEP 2 trial (Supplementary Fig. 6). Results were also similar when the Chronic Kidney Disease Epidemiology Collaboration 2021 equation was used to estimate eGFR (Supplementary Fig. 7).

Safety

Frequency of adverse events potentially related to kidney function (i.e., renal and urinary disorders, acute kidney injury, and renal impairment) were similar across the STEP 1 and 2 trials and were relatively low. In STEP 3, there were no events of acute renal failure reported (Table 2). Overall, semaglutide was well tolerated with no increase in adverse events leading to study drug discontinuation. Nausea and vomiting occurred more frequently with semaglutide than placebo.

CONCLUSIONS

In the STEP phase 3a trials, semaglutide has been shown to markedly reduce body weight and improve glycemic control in adults with overweight or obesity with or without type 2 diabetes (14,18–20). In these post hoc exploratory analyses from the STEP program, semaglutide significantly reduced albuminuria and increased the likelihood of

improvement from a high to lower albuminuria category in the population with type 2 diabetes (14). Semaglutide did not affect the rate of change in eGFR over time in the pool of participants from the three trials, of whom the vast majority had normal kidney function.

In patients with type 2 diabetes who participated in the SUSTAIN 6 trial, semaglutide 1.0 mg reduced albuminuria and the risk of new-onset macroalbuminuria (26). This current analysis is the first from the STEP program to assess the effects of the semaglutide 2.4 mg dose on kidney outcomes. Numerically, a higher UACR reduction was observed with semaglutide 2.4 mg compared with the 1.0 mg dose, which seems to confirm the albuminuria-lowering effect of semaglutide. Moreover, both doses of semaglutide increased the probability of regression in albuminuria categories and reduced the likelihood of progression to worsening albuminuria categories. These effects are clinically relevant because therapies that reduce albuminuria by 25–30% are likely to confer significant benefits in reducing the risk of long-term clinical kidney outcomes (27,28). These analyses also report for the first time that the albuminuria-lowering effects of semaglutide were consistent in patients using or not using SGLT2 inhibitors. This is clinically relevant since SGLT2 inhibitors are now guideline-recommended therapies for kidney protection in people with type 2 diabetes, and guidelines suggest that semaglutide can be prescribed as an adjunct to RAS inhibitors and SGLT2 inhibitors to further reduce albuminuria (1,2).

The effects of semaglutide in reducing albuminuria in STEP 2 were also consistent in patients with various degrees of glycemic control and overweight or obesity, supporting the generalizability of our

Table 2—Kidney-related adverse events (STEP 1–3)

	STEP 1		STEP 2			STEP 3*	
	Semaglutide 2.4 mg (n = 1,306)	Placebo (n = 655)	Semaglutide 1.0 mg (n = 402)	Semaglutide 2.4 mg (n = 403)	Placebo (n = 402)	Semaglutide 2.4 mg (n = 407)	Placebo (n = 204)
Renal and urinary disorders	3 (0.2)	2 (0.3)	2 (0.5)	4 (1.0)	2 (0.5)	0	0
Acute kidney injury	3 (0.2)	1 (0.2)	2 (0.5)	3 (0.7)	2 (0.5)	0	0
Renal impairment	1 (<0.1)	1 (0.2)	0	1 (0.2)	0	0	0

Data are n (%) and are for the safety analysis set unless otherwise indicated. N is number of patients experiencing at least one event and % is percentage of patients experiencing at least one event. Adverse events with onset date during on-treatment period. A time point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Sorted in descending order by System Organ Class and Preferred Term based, respectively, on the percentage of patients in the semaglutide 2.4 mg arm experiencing at least one event. *There were no events of acute renal failure identified by the Medical Dictionary for Regulatory Activities terminology search in either of the treatment groups.

findings. The albuminuria-lowering effects of semaglutide are more pronounced in patients with micro- or macroalbuminuria at higher risk, which may translate into larger relative and absolute treatment effects on CV and kidney benefits, but this hypothesis requires confirmation in future studies.

The mechanism by which semaglutide reduces albuminuria may involve both direct intrarenal and indirect effects outside of the kidneys. The reductions in HbA_{1c}, body weight, and blood pressure with semaglutide may account in part for lowering albuminuria. Of these clinical parameters, the reduction in HbA_{1c} appears to explain the largest part of the albuminuria-lowering effect. However, some of the benefit in lowering albuminuria does not appear to be explained or accounted for by changes in these parameters alone. Semaglutide may also reduce albuminuria through direct means that may lead to beneficial effects on endothelial function or the endothelial glycocalyx, and increased natriuresis, either through inhibition of the sodium–hydrogen transporter or through anti-inflammatory or antifibrotic effects (13,29). Mechanistic studies are ongoing to study potential mechanisms for how semaglutide may confer kidney protection in patients with type 2 diabetes (REMODEL; NCT04865770) and in patients with overweight or obesity (SMART; NCT04889183).

Semaglutide 2.4 mg had no appreciable effect on eGFR over time compared with placebo. Since kidney function was in the normal range in the vast majority of participants at baseline, eGFR was only modestly decreased in the placebo group, and thus, it was not unexpected that there was no effect with semaglutide in slowing progressive kidney function loss, given the relatively short trial duration. The FLOW trial (NCT03819153) in patients with type 2 diabetes and established chronic kidney disease (CKD) will determine whether semaglutide 1.0 mg slows eGFR over time and reduces the risk of kidney failure (30). For the eGFR profile over time, treatment with semaglutide 2.4 mg reduced eGFR at 20 weeks. This initial reduction in eGFR may suggest a favorable hemodynamic effect on kidney function since eGFR did not further decline during the subsequent 48 weeks. However, a relatively large decrease in eGFR was also seen for placebo at week 20. An acute reduction in eGFR occurs with other classes of kidney-protective

therapies, such as RAS inhibitors and SGLT2 inhibitors, and has been associated with long-term kidney protection (6,11,31,32). Dedicated mechanistic studies, such as the REMODEL and SMART studies, are required to confirm if the observed initial reduction in eGFR with semaglutide reflects a salutary hemodynamic effect or can be explained by other factors.

The effects of semaglutide on albuminuria and eGFR observed in the present STEP analysis are consistent with post hoc analyses of other GLP-1RA clinical trials. Dulaglutide and epeglenatide reduced albuminuria and the risk of a composite kidney end point in two CV outcomes trials involving patients with type 2 diabetes at early stages of CKD (33,34). Dulaglutide, compared with insulin glargine, also reduced albuminuria and slowed the decline in kidney function in patients with type 2 diabetes and CKD (35). A post hoc analysis of the SUSTAIN 1–7 trials reported that semaglutide was associated with initial reductions in eGFR that plateaued during chronic treatment (26). Similarly, in a post hoc analysis of the SUSTAIN-6 and LEADER trials, treatment with semaglutide or liraglutide slowed eGFR decline and reduced the risk of substantial loss of kidney function in patients with type 2 diabetes, with greater effects among those with preexisting CKD (36). More pronounced effects of GLP-1RAs in slowing kidney function decline among patients with type 2 diabetes and established CKD were also observed in the EXSCEL trial (37). This pattern of effect may potentially explain why an effect was not observed with semaglutide on eGFR in the pooled STEP 1–3 analysis, since the vast majority of participants did not have CKD or were in very early stages of CKD.

These exploratory analyses have limitations. First, the study was a post hoc analysis of randomized controlled trials. Our results are therefore hypothesis generating. Second, we recognize that by design, the STEP 2 trial was not a dedicated kidney outcome trial, and relatively few participants had established CKD. Accordingly, since many participants had baseline clinical kidney parameters in the normal range, effects on albuminuria cannot be directly generalized to people with more advanced stages of CKD. Third, there is considerable uncertainty around the estimates of the proportion of the albuminuria-lowering effect of

semaglutide that is mediated by changes in HbA_{1c}, body weight, and blood pressure. Furthermore, the mediation analysis requires an assumption that no other variables confound either the effect of semaglutide on albuminuria, HbA_{1c}, or body weight, or the associations among these. As a result, the results of the mediation analysis should be interpreted with caution. Fourth, albuminuria was not measured in the STEP 1 or STEP 3 trials, and we are therefore unable to generalize the albuminuria-lowering effects of semaglutide to people with overweight or obesity but without diabetes. Finally, semaglutide reduces body weight, which may affect serum creatinine and eGFR. Additional studies measuring cystatin (38,39), an alternative filtration marker less influenced by changes in body weight, would provide more insight about the effects of semaglutide on eGFR over time and to what extent serum creatinine-based eGFR estimates are influenced by body weight changes.

In conclusion, in people with type 2 diabetes and overweight or obesity, semaglutide reduced UACR relative to placebo, including in patients using RAS inhibitors or SGLT2 inhibitors at baseline. These results support ongoing trials examining the impact of semaglutide on kidney protection in individuals at high risk of kidney disease progression.

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Duality of Interest. H.J.L.H. is a consultant for AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook Therapeutics, CSL Pharma, Gilead Sciences, Inc., Janssen, Merck, Mitsubishi Tanabe, Mundipharma, Novo Nordisk, and Traveera Therapeutics; and has received research support for conducting investigator-initiated clinical trials from AbbVie, AstraZeneca, Boehringer Ingelheim, Janssen, and Novo Nordisk. M.D. received research funding from AstraZeneca, Boehringer Ingelheim, Janssen, Novo Nordisk, and Sanofi-Aventis; served as consultant, advisory board

member, and speaker for Boehringer Ingelheim, Eli Lilly, Novo Nordisk, and Sanofi-Aventis; served as advisory board member and speaker for AstraZeneca; is an advisory board member for Gilead Sciences, Inc., Janssen, and Lexicon Pharmaceuticals; and is a speaker for Napp Pharmaceuticals and Takeda Pharmaceuticals International Inc., co-funded by the NIHR Leicester Biomedical Research Centre. D.D. received research funding from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, and Sanofi-Aventis; and served as consultant, advisory board member, and speaker for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, and Sanofi-Aventis. K.K. and J.L. are employees of Novo Nordisk A/S. J.R. received scientific advisory board fees, honoraria, consulting fees, and grants/research support from Novo Nordisk, Applied Therapeutics, Boehringer Ingelheim, Eli Lilly, Intarcia Therapeutics, Novo Nordisk, Oramed Pharmaceuticals, and Sanofi; received honoraria or consulting fees from Zealand Pharma; and received grants/research support from Genentech, Novartis, Pfizer, REMD Biotherapeutics, and vTv Therapeutics. R.S. and N.Z. are employees and shareholders of Novo Nordisk A/S. D.C. has received honoraria from AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim-Lilly, Bristol-Myers Squibb, CSL-Behring, Gilead Sciences, Inc., Janssen, Lexicon Pharmaceuticals, Maze Therapeutics, Merck, Mitsubishi Tanabe, Novartis, Novo Nordisk, Otsuka, Prometic Pharma, Sanofi, and Youngene Therapeutics and has received operational funding for clinical trials from AstraZeneca, Boehringer Ingelheim-Lilly, CSL-Behring, Janssen, Merck, Novo Nordisk, and Sanofi. No other potential conflicts of interest relevant to this article were reported.

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