103-OR

Association of Tirzepatide With Kidney Parameters in People With Obesity and Prediabetes From SURMOUNT-1 Over 176 Weeks

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Presenter Disclosures

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Background and Aims

- Obesity and type 2 diabetes (T2D) lead to kidney damage and decline in eGFR over time[1,2]
- Tirzepatide is a once-weekly dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist approved for the treatment of T2D,[3] obesity, and obstructive sleep apnea[a,4]
- Tirzepatide has been associated with kidney protective effects
  - In a post hoc analysis of the SURPASS-4 trial, in people with T2D with obesity or overweight, tirzepatide was associated with improved eGFR and UACR compared to insulin glargine after 72 weeks treatment[1]
  - In a post hoc analysis of the SURMOUNT-1 trial, in participants with obesity or overweight, tirzepatide was associated with improved cystatin-C-based eGFR and UACR compared to placebo after 72 weeks treatment[5]
- Effects of tirzepatide on kidney parameters over longer follow-up periods are unknown

[a]For US indication of ZEPBOUND only.
eGFR=estimated glomerular filtration rate; UACR=urine albumin-creatinine ratio.
1. Heerspink HJL, et al. *Lancet Diabetes Endocrinol*. 2022;10:774-785. 2. Maric-Bilkan C. *Med Clin North Am*. 2013;97:59-74. 3. MOUNJARO (tirzepatide) [US Highlights of Prescribing Information]. Indianapolis, IN: Eli Lilly and Company, 2024.
4. ZEPBOUND (tirzepatide) [US Highlights of Prescribing Information]. Indianapolis, IN: Eli Lilly and Company, 2025. 5. Heerspink HJL, et al. *Diabetes*. 2024;73(Suppl 1):264-OR.
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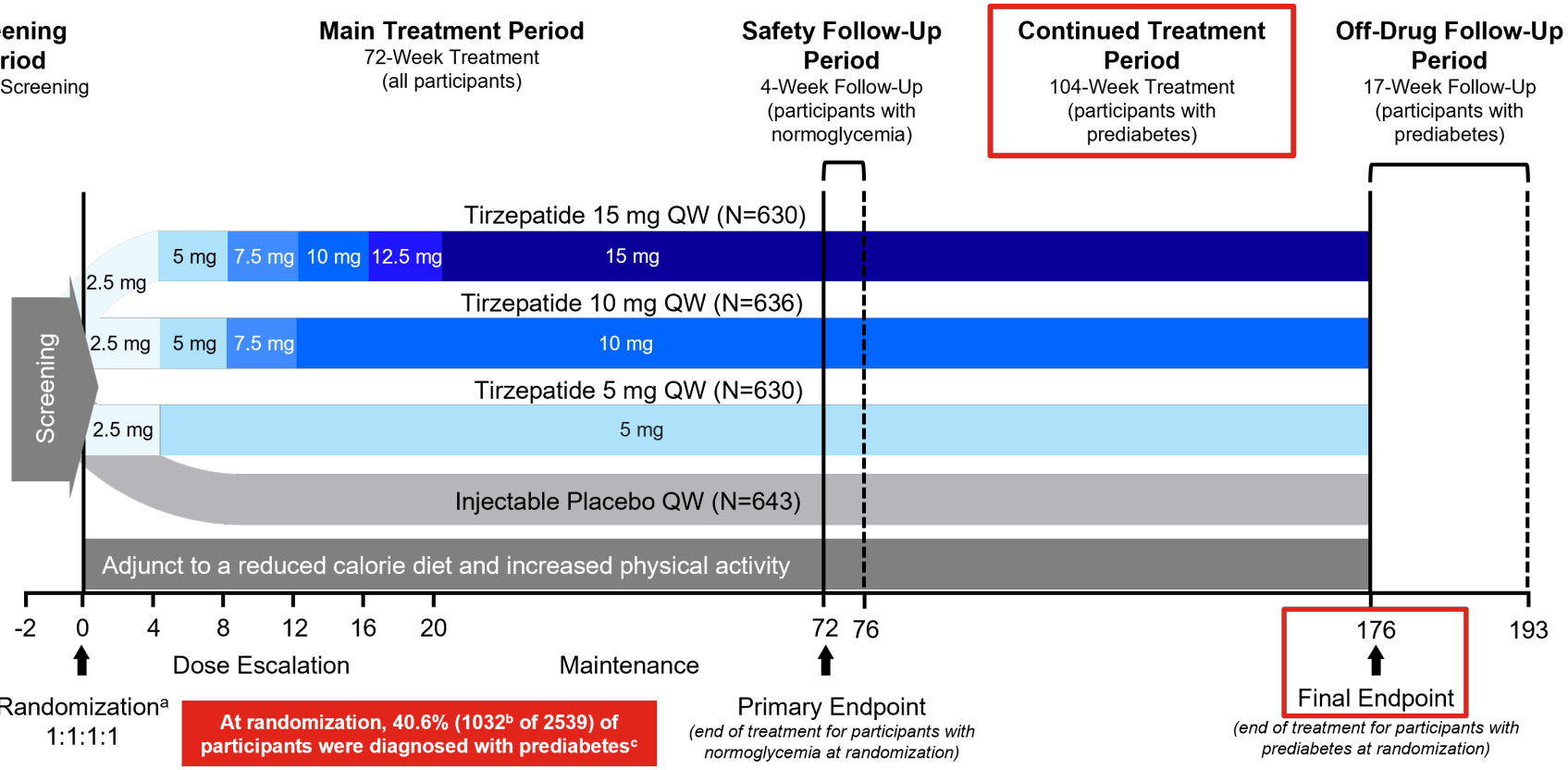
Objective and Study Design

Objective

To analyze kidney parameters over 176 weeks in people with obesity and prediabetes treated with tirzepatide as compared with placebo in a post hoc analysis of SURMOUNT-1



Key Eligibility Criteria

Inclusion criteria

- Adults with obesity (body mass index [BMI] ≥30 kg/m^2), or overweight (BMI ≥27 kg/m^2) with ≥1 weight-related comorbidities[d]
  - Prediabetes at randomization was an eligibility requirement for the 3-year portion of the study[e]

Exclusion criteria

- Type 1 or 2 diabetes
- >5-kg body weight change within 90 days before screening
- Prior or planned surgical treatment for obesity
- Treatment that promotes weight loss within 90 days before screening
- eGFR <30 mL/min/1.73 m^2

[a]At randomization, glycemic status was assessed using fasting glucose, HbA1c, and 2-hour OGTT; participants with normoglycemia completed the study after 72 weeks of treatment, whereas those with prediabetes completed the study after 176 weeks of treatment; [b]762 participants treated with tirzepatide (5 mg: n=247; 10 mg: n=262; 15 mg: n=253) and 270 participants treated with placebo had prediabetes at randomization; [c]As defined by the 2019 American Diabetes Association guidelines[1]; see Jastreboff AM, et al. *N Engl J Med*. 2022;387:205-216; [d]Hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease; [e]Prediabetes defined as FBG of 100-125 mg/dL (5.6-6.9 mmol/L), 2-hour glucose following OGTT of 140-199 mg/dL (7.8-11.0 mmol/L), and HbA1c of 5.7-6.4% (39-47 mmol/mol).
BMI=body mass index; eGFR=estimated glomerular filtration rate; FBG=fasting blood glucose; HbA1c=glycated hemoglobin; OGTT=oral glucose tolerance test; QW=once weekly.

1. American Diabetes Association. *Diabetes Care*. 2019;42(Suppl1):S13-S28.

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Post Hoc Analysis Methods

- UACR and eGFR (CKD-EPI Creatinine-Cystatin Equation 2021) were assessed in the pooled tirzepatide (5 mg, 10 mg, and 15 mg) group and placebo group
- Change from baseline to Week 176 was analyzed using mixed models for repeated measures with on-treatment data for participants with prediabetes at randomization for:
  - Creatinine-cystatin-C-based eGFR (Cr-Cys-C-eGFR) subgroups:
    - Baseline <90 mL/min/1.73 m^2
    - Baseline ≥90 mL/min/1.73 m^2
  - Creatinine-based eGFR (Cr-eGFR)
  - Cystatin-C-based eGFR (Cys-C-eGFR)
  - UACR subgroups:
    - Baseline UACR <30 mg/g
    - Baseline UACR ≥30 mg/g

CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; eGFR=estimated glomerular filtration rate; UACR=urine albumin-creatinine ratio.

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Baseline Demographics and Clinical Characteristics From the SURMOUNT-1 Trial[1]

Characteristic	All Participants With Prediabetes at Baseline (N=1032)
Age, years	48.2 (11.8)
Female, n (%)	659 (63.9)
Race, n (%)	
White	758 (73.4)
Asian	105 (10.2)
Black	77 (7.5)
Other[a]	79 (7.7)
Multiple	13 (1.3)
Weight, kg	107.3 (23.4)
BMI, kg/m^2	38.8 (7.1)
HbA1c, %	5.8 (0.3)
FPG, mg/dL	101.3 (9.6)
SBP, mm Hg	125.6 (12.7)

[a]Includes American Indian or Alaska Native and Native Hawaiian or other Pacific Islander.
Note: Data are mean (SD) unless stated otherwise. 1. Jastreboff AM, et al. *N Engl J Med*. 2025;392:958-971.
BMI=body mass index; FPG=fasting plasma glucose; HbA1c=glycated hemoglobin; SBP=systolic blood pressure; SD=standard deviation.

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Baseline Kidney Function

Parameter	Placebo (N=270)	Pooled TZP 5 mg, 10 mg, and 15 mg (N=762)	Total (N=1032)
Cr-Cys-C-eGFR, mL/min/1.73 m^2, mean (SD)	97.3 (17.8)	97.0 (17.5)	97.1 (17.6)
Cr-Cys-C-eGFR category, n (%)			
<90 mL/min/1.73 m^2	158 (58.5)	492 (64.6)	650 (63.0)
≥90 mL/min/1.73 m^2	85 (31.5)	216 (28.3)	301 (29.2)
Cr-eGFR, mL/min/1.73 m^2, mean (SD)	97.2 (17.6)	97.2 (17.1)	97.2 (17.3)
Cys-C-eGFR, mL/min/1.73 m^2, mean (SD)	92.3 (19.8)	91.7 (19.2)	91.9 (19.3)
UACR, mg/g, median (IQR)	7.0 (4.0-13.0)	7.0 (4.3-12.0)	7.0 (4.0-12.0)
UACR category			
Normal albuminuria (UACR <30 mg/g)	240 (88.9)	684 (90.0)	924 (89.7)
Microalbuminuria (UACR ≥30-≤300 mg/g)	27 (10.0)	67 (8.8)	94 (9.1)
Macroalbuminuria (UACR >300 mg/g)	3 (1.1)	9 (1.2)	12 (1.2)

Note: The denominator may vary based on the total N in each category.

Cr-Cys-C-eGFR=creatinine-cystatin-C-based estimated glomerular filtration rate; Cr-eGFR=creatinine-based estimated glomerular filtration rate; Cys-C-eGFR=cystatin-C-based estimated glomerular filtration rate; IQR=interquartile range; SD=standard deviation; TZP=tirzepatide; UACR=urine albumin-creatinine ratio.

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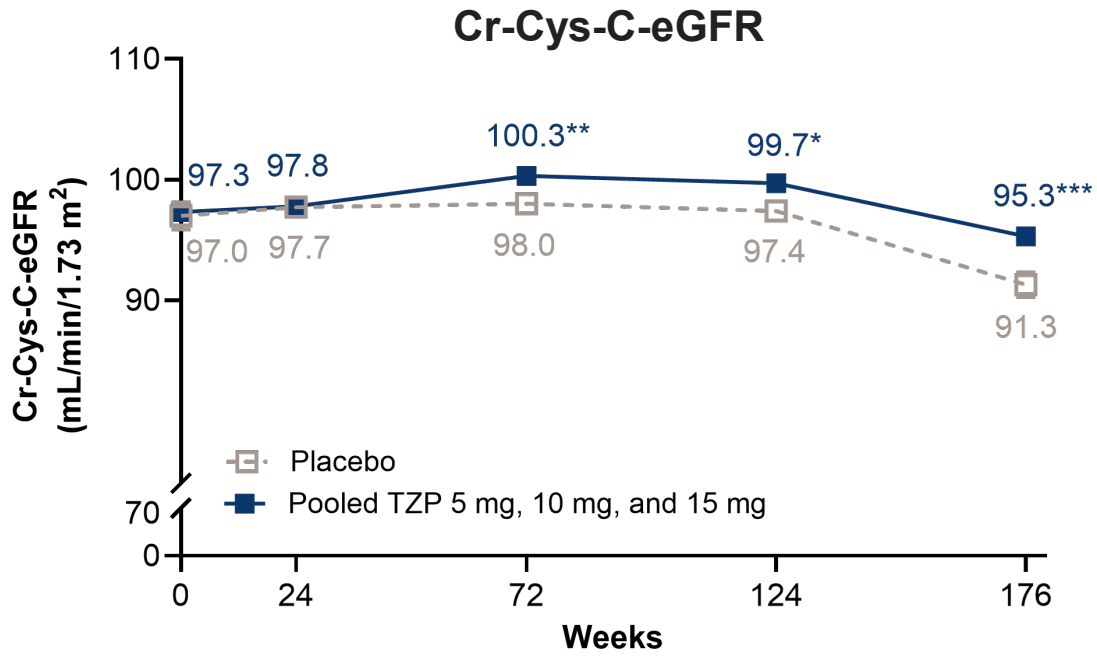
Tirzepatide Treatment Was Associated With a Significantly Smaller Decline in Cr-Cys-C-eGFR vs. Placebo Over 176 Weeks

N	Slope (Per Year) Cr-Cys-C-eGFR Decline, mL/min per 1.73 m^2 Per Year		
	Pooled TZP 5 mg, 10 mg, and 15 mg	Placebo	Difference (95% CI)
1032	-0.56 (0.16)	-1.56 (0.31)	1.01 (0.33-1.69)

Notes: Data are mean decline (SE). Mixed effect regression model including random effects for intercept and time within participant. Change in eGFR included baseline, country, sex, treatment, time, treatment*time as variables.



ETD (95% CI)	0.2 (-2.3 to 2.8)	0.1 (-1.2 to 1.4)	2.3 (0.8 to 3.8)	2.3 (0.6 to 4.0)	3.9 (1.7 to 6.2)
n	243	239	186	140	113
n	708	691	624	559	440

*p<0.05, **p<0.01, ***p<0.001 vs. placebo.
Notes: Data are LSM (SE) unless stated otherwise. The MMRM model for post-baseline measures included baseline value, country, sex, treatment, time, treatment*time (type III sum of squares) as variables. The ANOVA model for baseline measures include treatment (type III sum of squares) as a variable.

ANOVA=analysis of variance; CI=confidence interval; Cr-Cys-C-eGFR=creatinine-cystatin-C-based estimated glomerular filtration rate; ETD=estimated treatment difference; LSM=least squares mean; MMRM=mixed model for repeated measures; N=number of participants in specific subgroup; SE=standard error; TZP=tirzepatide.

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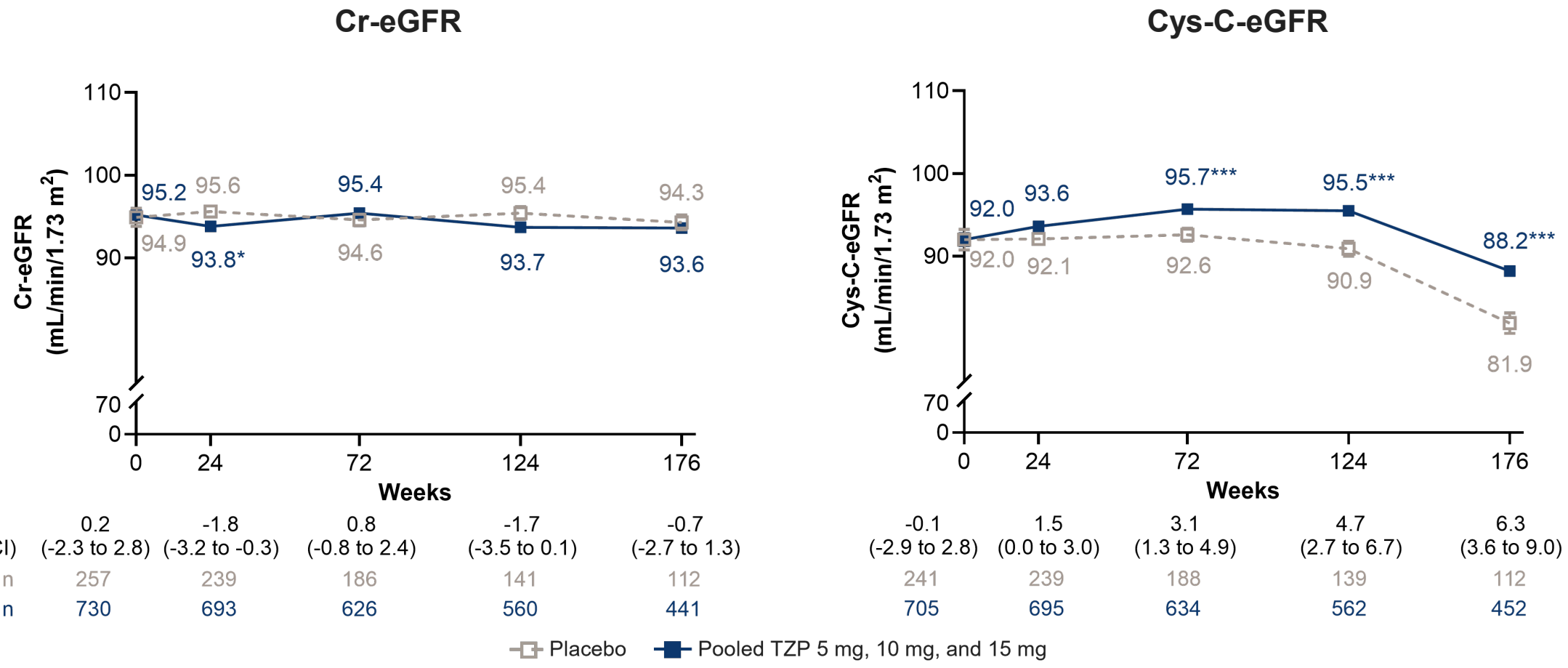
Tirzepatide Treatment Was Associated With a Smaller Decline in Cys-C-eGFR vs. Placebo Over 176 Weeks



*p<0.05, ***p<0.001 vs. placebo.

Notes: Data are LSM (SE) unless stated otherwise. The MMRM model for post-baseline measures included baseline value, country, sex, treatment, time, treatment*time (type III sum of squares) as variables. The ANOVA model for baseline measures include treatment (type III sum of squares) as a variable.

ANOVA=analysis of variance; CI=confidence interval; Cr-eGFR=creatinine-based estimated glomerular filtration rate; Cys-C-eGFR=cystatin-C-based estimated glomerular filtration rate; ETD=estimated treatment difference; LSM=least squares mean; MMRM=mixed model for repeated measures; SE=standard error; TZP=tirzepatide.

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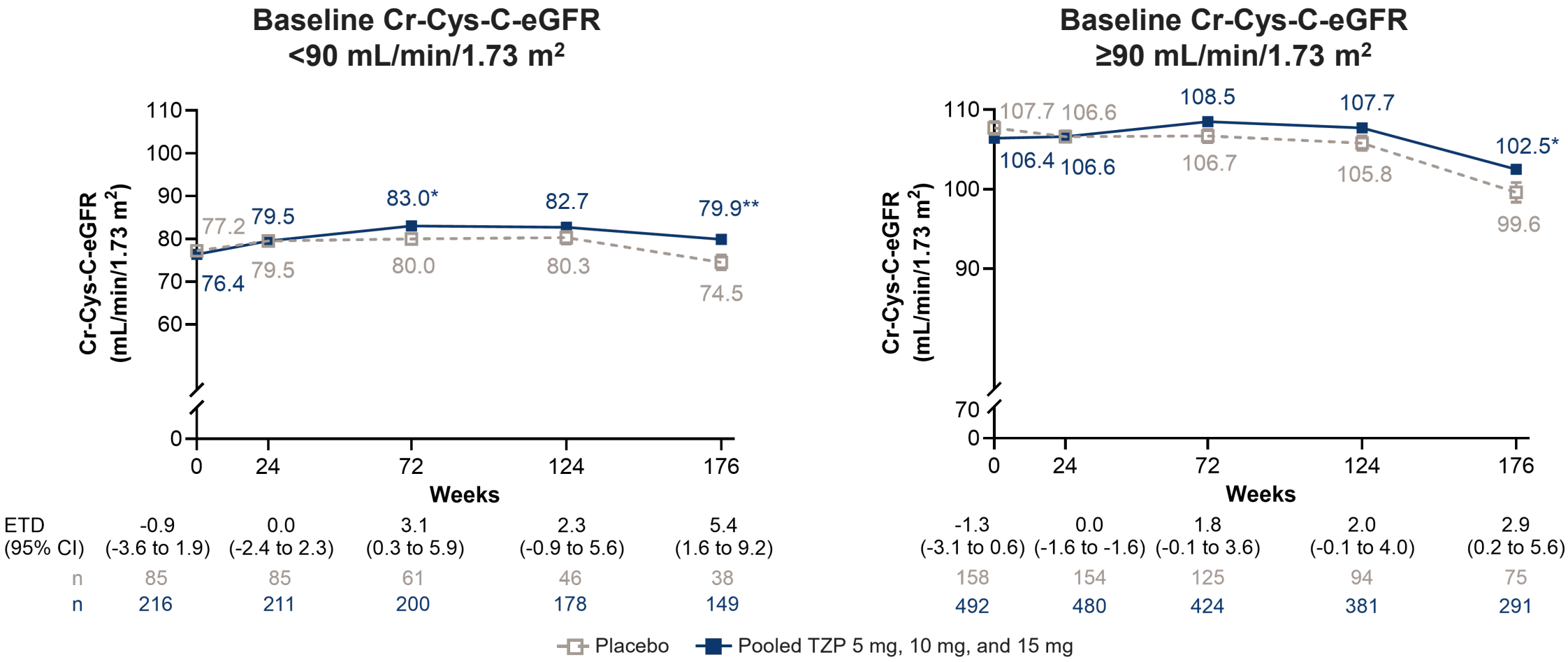
Tirzepatide Treatment Was Associated With a Smaller Decline in eGFR vs. Placebo After 176 Weeks, Regardless of Baseline eGFR



*p<0.05, **p<0.01 vs. placebo.

Notes: Data are LSM (SE) unless stated otherwise. The MMRM model for post-baseline measures included baseline value, country, sex, treatment, time, treatment*time (type III sum of squares) as variables. The ANOVA model for baseline measures include treatment (type III sum of squares) as a variable.

ANOVA=analysis of variance; CI=confidence interval; Cr-Cys-C-eGFR=creatinine-cystatin-C-based estimated glomerular filtration rate; eGFR=estimated glomerular filtration rate; ETD=estimated treatment difference; LSM=least squares mean; MMRM=mixed model for repeated measures; SE=standard error; TZP=tirzepatide.

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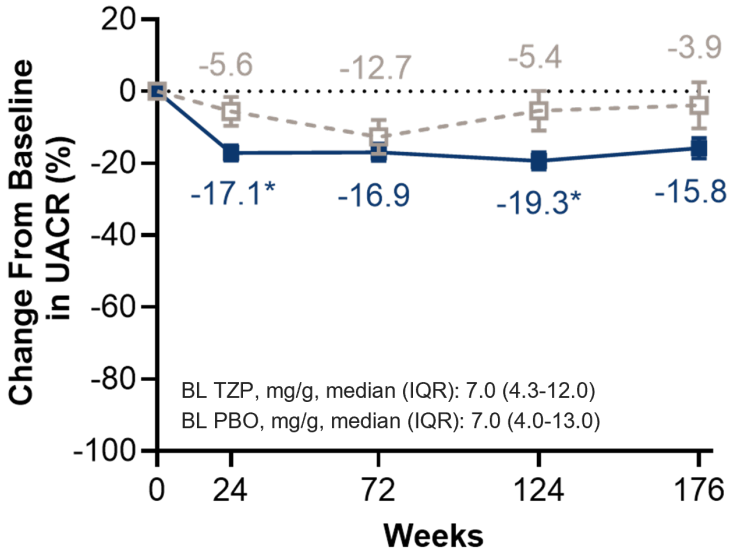
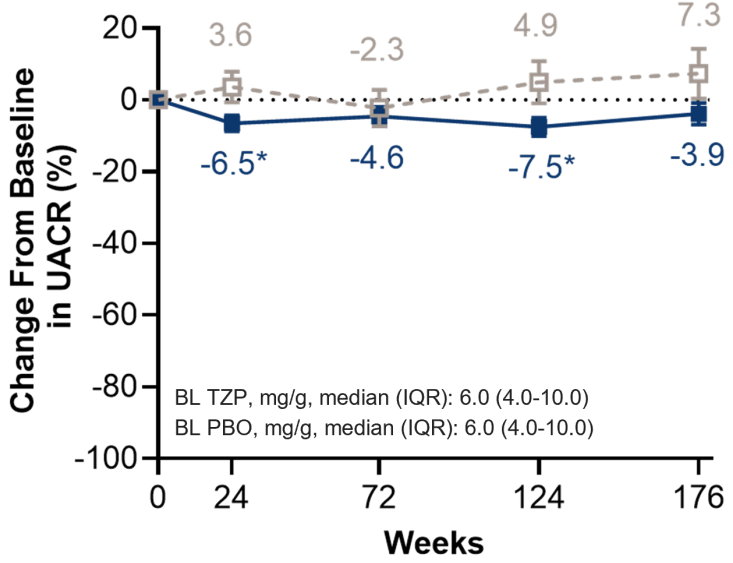
Tirzepatide Was Associated With a Numerically Greater Percentage Reduction in UACR vs. Placebo After 176 Weeks

All Participants



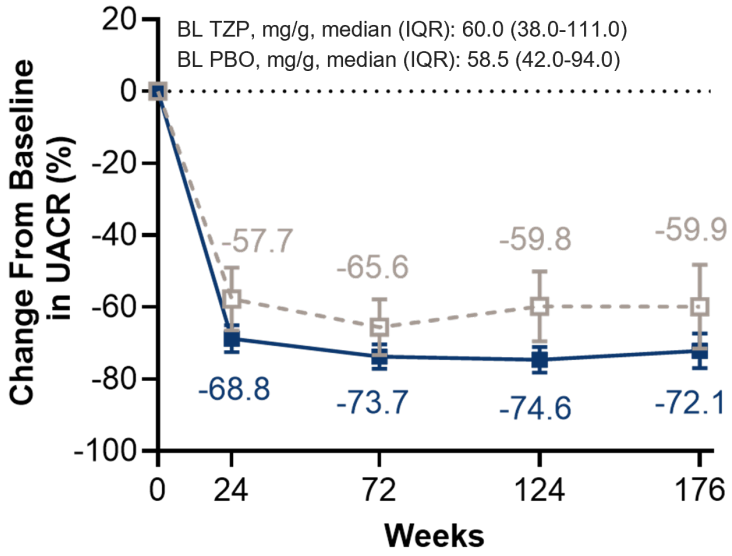
ETD (95% CI)	-12.1 (-20.3 to -3.1)	-4.8 (-15.6 to 7.5)	-14.7 (-25.1 to -2.9)	-12.4 (-24.4 to 1.5)
n	241	189	142	113
n	694	635	557	448

Baseline UACR <30 mg/g



ETD (95% CI)	-9.8 (-17.8 to -1.0)	-2.4 (-13.1 to 9.8)	-11.8 (-22.1 to -0.2)	-10.4 (-22.3 to 3.2)
n	215	167	122	96
n	624	570	499	405

Baseline UACR ≥30 mg/g



ETD (95% CI)	-26.1 (-54.5 to 20.0)	-23.6 (-54.8 to 29.1)	-36.9 (-64.2 to 11.0)	-30.4 (-64.7 to 37.3)
n	26	22	20	17
n	70	65	58	43

Placebo Pooled TZP 5 mg, 10 mg, and 15 mg

*p<0.05 vs. placebo.

Notes: Data are estimate (SE) unless stated otherwise. The MMRM model for post-baseline measures was calculated as the log(actual measurement/baseline) with log(baseline value), country, sex, treatment, time, treatment*time (type III sum of squares) as variables. The ANOVA model for baseline measures was calculated as the log(actual measurement) and included treatment (type III sum of squares) as a variable.

BL=baseline; ANOVA=analysis of variance; CI=confidence interval; ETD=estimated treatment difference; IQR=interquartile range; MMRM=mixed model for repeated measures; PBO=placebo; SE=standard error; TZP=tirzepatide; UACR=urine albumin-creatinine ratio.

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Conclusion

- From this post hoc analysis of the SURMOUNT-1 trial in participants with obesity or overweight, with prediabetes and normal kidney function at baseline, treatment with tirzepatide was associated with:
  - A smaller decline of Cr-Cys-C-eGFR over 176 weeks to that of the placebo group
  - A numerically greater percentage reduction in UACR between tirzepatide and placebo
- The association between tirzepatide treatment and Cr-Cys-C-eGFR did not appear to be different in participants with baseline eGFR <90 or ≥90 mL/min/1.73 m^2
- These findings support further in-depth analysis of the effect of tirzepatide in participants with obesity and chronic kidney disease, with or without T2D, in the ongoing Phase 2b TREASURE-CKD trial and Phase 3 trials, SURPASS-CVOT and SURMOUNT-MMO

eGFR=estimated glomerular filtration rate; Cr-Cys-C-eGFR=creatinine-cystatin-C-based estimated glomerular filtration rate; T2D=type 2 diabetes; UACR=urine albumin-creatinine ratio.

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Disclosures

- **H. J. L. Heerspink** has served as consultant for: AstraZeneca, Alexion, Alnylam, Bayer Pharmaceuticals, Boehringer Ingelheim, Dimerix, Eli Lilly and Company, Novartis, Novo Nordisk, Roche, and Travere Therapeutics; and has received grant support from: AstraZeneca, Boehringer Ingelheim, Janssen, and Novo Nordisk. All payments and honoraria are to his employer; **D. H. van Raalte** has received grants from: AstraZeneca, Boehringer Ingelheim, and Merck; and has received consulting fees from: AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, and Merck; **K. Tuttle** has received consulting fees from: Bayer Pharmaceuticals, Boehringer Ingelheim, Eli Lilly and Company, Novo Nordisk; has received payment or honoraria for speaking from: Bayer Pharmaceuticals and Novo Nordisk; has participated on data safety monitoring or advisory boards for: AstraZeneca, the George Clinical Institute for Global Health, National Institutes of Health, and the US National Institute of Diabetes and Digestive and Kidney Diseases; and reports a leadership or fiduciary role as: Chair of the Diabetic Kidney Disease Collaborative Task Force, American Society of Nephrology; **D. Z. I. Cherney** has received grants or contracts from: AstraZeneca, Boehringer Ingelheim, CSL Behring, Eli Lilly and Company, Janssen, Merck, Novo Nordisk, and Sanofi; and consulting fees and speaking honoraria from: AbbVie, AstraZeneca, Bayer Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, CSL Behring, Eli Lilly and Company, Gilead Sciences, Janssen, Maze Therapeutics, Merck, Mitsubishi Tanabe Pharma, Novartis, Novo Nordisk, Otsuka, Prometic, Sanofi, and Yeungene; **P. Bjornstad** has received advisory panel, consultancy, or research support from: AstraZeneca, Bayer Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly and Company, Horizon Pharma/Amgen, LG Chem, Merck, and Novo Nordisk; serves on steering committees for: Eli Lilly and Company and Novo Nordisk; and chairs data monitoring committees for: Bayer Pharmaceuticals; **G. K. Dimitriadis**, **D. Cao**, **B. Linetzky**, **I. Jouravskaya**, and **R. Griffin** are employees and shareholders of: Eli Lilly and Company; **C. Piras De Oliveira** was an employee of: Eli Lilly and Company at the time of the study
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