

Effects of Orforglipron Versus Insulin Glargine on Kidney Outcomes in People With Type 2 Diabetes and High Cardiovascular Risk: Results From the ACHIEVE-4 Trial

Katherine Tuttle¹, Hiddo Heerspink², Klara Klein³, David Cox⁴, Jiaxun Chen⁴, Rong Liu⁴, Eric Meskimen⁴, Lisa Ludwig⁴

¹Providence Medical Research Center, University of Washington, Spokane, WA, USA; ²University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, Netherlands; ³University of North Carolina School of Medicine, Chapel Hill, NC, USA; ⁴Eli Lilly and Company, Indianapolis, IN, USA;

62nd Annual Meeting of the European Association for the Study of Diabetes (EASD); Milan, Italy; September 28 – October 2, 2026

Presenter Disclosure: Katherine Tuttle, MD

Board Member: The National Institute of Diabetes, Digestive and Kidney Disease, George Clinical Institute, AstraZeneca, Diabetic Kidney Disease Collaborative, Kidney Week 2025 Program Committee, American Heart Association/American College of Cardiology Cardiovascular-Kidney-Metabolic Guideline Committee, Kidney Disease Improving Global Outcomes Diabetes and Chronic Kidney Disease Guideline Committee

Consultant: AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Bayer, ProKidney, Otsuka, Alnylam, Roche, and GlaxoSmithKline

Research Support: United States federal grant awards (NIDDK, NHLBI, NCATS, NIMHD, the NIH Directors' Office, and CDC). Investigator-initiated grant support from Traverso, Bayer, Otsuka, Doris Duke Charitable Foundation, Benaroya Research Institute, and Breakthrough T1D (formerly the Juvenile Diabetes Research Foundation)

Speaker's fees: Novo Nordisk, Bayer, Boehringer Ingelheim, AstraZeneca, and Traverso

Background and Objective



Orforglipron (OFG) is a novel small molecule, non-peptide glucagon-like peptide-1 receptor agonist (GLP-1 RA) that has been approved for weight management in the US and has completed phase 3 development for type 2 diabetes (T2D)



OFG has shown improvements in glycemic control and body weight as a monotherapy or in addition to various background therapies in the ACHIEVE program¹⁻⁴



In ACHIEVE-4, OFG did not increase incidence of major adverse cardiovascular (CV) events (MACE-4) vs insulin glargine in adults with T2D and obesity or overweight at high CV risk over a median study duration of 104 weeks (HR 0.84, 0.59-1.20; $p < 0.001$ for non-inferiority)



Evidence of kidney protective effects with GLP-1 RAs in T2D has been shown across several CVOTs and one dedicated kidney outcome study⁵⁻⁷

OBJECTIVE

This prespecified analysis aimed to assess the effect of OFG versus insulin glargine on kidney function and outcomes through Week 104 in the overall ACHIEVE-4 population and the subpopulation with, per KDIGO, high or very high risk for chronic kidney disease (CKD) progression^{8,a}

1. Rosenstock, J., et al. *N Engl J Med*. 2025. 2. Welch, M, et al. *Lancet*. 2026. 3. Rosenstock, J., et al. *Lancet*. 2026. 4. Giorgino, F., et al. *JAMA*. 2026. 5. Perkovic, V., et al. *N Engl J Med*. 2024. 6. Gerstein, H.C., et al. *Lancet*. 2019. 2025. 7. Tuttle, K.R., et al. *Lancet Diabetes Endocrinology*. 2018. 8. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int*. 2024. ^aHigh or very high-risk CKD based on KDIGO guideline (2024). CKD=chronic kidney disease; CV=cardiovascular; CVOT=cardiovascular outcomes trial; GLP-1 RA=glucagon-like peptide-1 receptor agonist; HR=hazard ratio; KDIGO=Kidney Disease Improving Global Outcomes; MACE-4=major adverse cardiovascular event-4 point; OFG=orforglipron; T2D=type 2 diabetes.

ACHIEVE-4 Study Design

DESIGN

Phase 3 randomized, international, open-label, multicenter, active comparator study

POPULATIONS

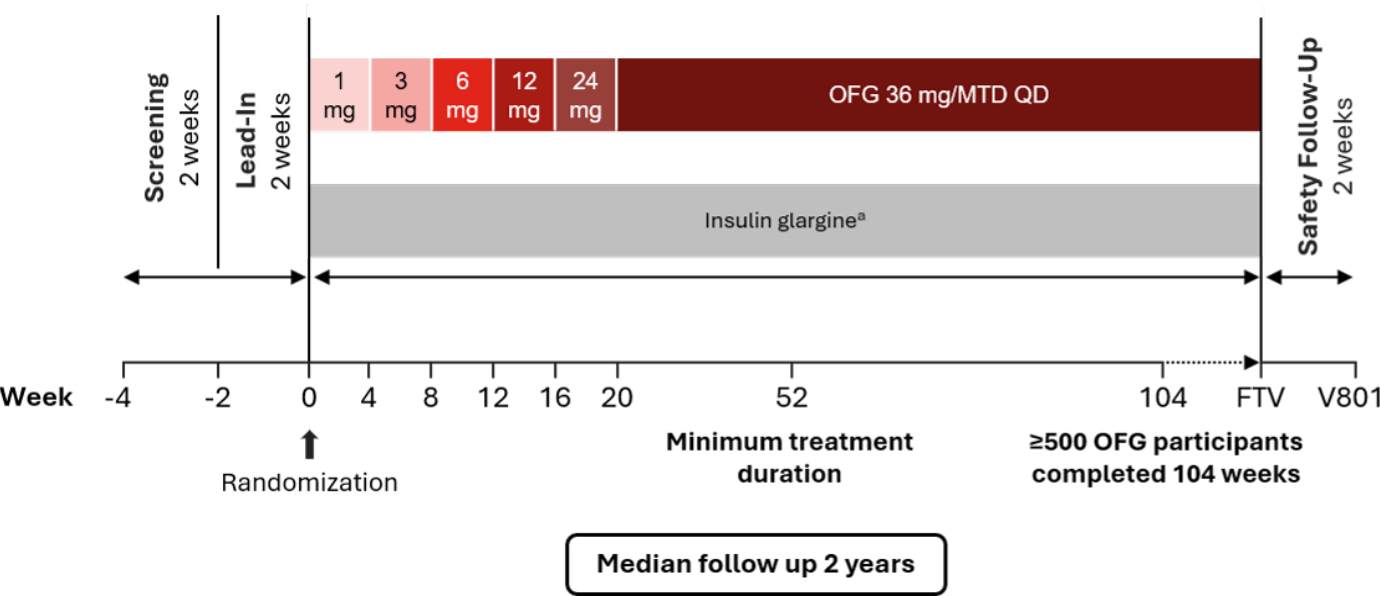
- Adults with T2D and obesity or overweight with increased risk of CV events
- Subgroup with KDIGO high/very high risk for CKD progression

TREATMENT

1:1 once-daily oral OFG (MTD up to 36 mg capsule dose, equivalent to 17.2 mg tablet dose)¹ or titrated insulin glargine

STUDY DURATION

- All participants reach Week 52
- ≥500 participants reaching 2 years of treatment
- Approx. 122 participants with ≥1 MACE-4



Orforglipron Capsule <i>Investigational use in study</i>	Orforglipron Tablet <i>Equivalent formulation*</i>
1 mg	0.8 mg
3 mg	2.5 mg
6 mg	5.5 mg
12 mg	9.0 mg
24 mg	14.5 mg
36 mg	17.2 mg

1. Ma, X., et al. *Diabetes Obes Metab.* 2026. *For matching doses (for example, 36 mg capsule and 17.2 mg tablet), the capsule and tablets were shown to deliver comparable systemic exposure to orforglipron with similar rate and extent of absorption. ^aThe starting dose of insulin glargine was 10 IU/day, titrated to a fasting blood glucose <100 mg/dL (<5.6 mmol/L) through entire trial via treat-to-target algorithm. CKD=chronic kidney disease; CV=cardiovascular; FTV=final treatment visit; KDIGO=Kidney Disease Improving Global Outcomes; MACE=4-component major adverse cardiovascular event; MTD= maximum tolerated dose; OFG=orforglipron; QD=once daily; T2D=type 2 diabetes.

ACHIEVE-4 Inclusion/Exclusion Criteria

☑ INCLUSION

- Adults with T2D and HbA1c 7.0-10.5% (53-91 mmol/mol) or 7.5-10.5% (58-91 mmol/mol) if on a background sulfonylurea
- Have increased risk of CV events:
 - Coronary heart disease
 - Peripheral arterial disease
 - Cerebrovascular disease
 - CKD^a
 - Congestive Heart Failure (NYHA class II or III)
- BMI ≥ 25 kg/m²
- On stable therapy with 1 to 3 glucose-lowering medications (metformin, sulfonylurea, and/or SGLT-2i)

⊘ EXCLUSION

- eGFR < 15 mL/min/1.73 m²
- Have a history of severe hypoglycemia or hypoglycemia unawareness within the last 6 months

^aCKD eligibility was defined as: age ≥ 35 years, history of CKD, and eGFR < 60 mL/min/1.73 m² (CKD-Epidemiology [CKD-EPI]) on consecutive measurements (Visit 1 and Visit 2). BMI=body mass index; CKD=chronic kidney disease; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; CV=cardiovascular; eGFR=estimated glomerular filtration rate; HbA1c=glycated hemoglobin; NYHA=New York Heart Association; SGLT-2i=sodium-glucose cotransporter-2 inhibitor; T2D=type 2 diabetes.

ACHIEVE-4 Kidney Endpoints

STUDY POPULATIONS & ANALYSIS

- The **kidney outcomes** were assessed in the overall population and in the subpopulation with high or very high KDIGO risk through Week 104
- **High or very high-risk stages** were defined based on the KDIGO guideline (2024)¹:
 - eGFR ≥ 60 mL/min/1.73 m² and UACR > 300 mg/g,
 - eGFR ≥ 45 to < 60 mL/min/1.73 m² with UACR ≥ 30 mg/g, or
 - eGFR < 45 mL/min/1.73 m² at baseline.
- The **eGFR total slope analysis** was conducted in participants who completed Week 104

PRESPECIFIED KIDNEY ENDPOINTS

Secondary endpoints:

1. eGFR total slope (calculated by CKD-EPI Cystatin C equation [2012]²)
2. Percent change from baseline in UACR
3. 4-component composite kidney outcome (CKO-4): New macroalbuminuria, $\geq 40\%$ eGFR decline from baseline, kidney failure, or kidney death

Exploratory endpoint:

4. Effects in subgroups by baseline SGLT-2i use were also analyzed

Note: For all kidney outcomes, family-wise Type I error was not controlled.

1. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int.* 2024. 2. Inker, L.A., et al. *N Engl J Med.* 2012. CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; CKO-4=4-component composite kidney outcome; eGFR=estimated glomerular filtration rate; KDIGO=Kidney Disease: Improving Global Outcomes; SGLT-2i=sodium-glucose cotransporter-2 inhibitor; UACR=urinary albumin-creatinine ratio.

ACHIEVE-4 Baseline Characteristics

Characteristic	Overall population			High/very high KDIGO risk subgroup		
	OFG MTD (N=1371)	Insulin glargine (N=1378)	Total (N=2749)	OFG MTD (N=362)	Insulin glargine (N=347)	Total (N=709)
Age (years)	63.2 (10.0)	63.1 (9.8)	63.1 (9.9)	67.4 (9.2)	66.9 (10.1)	67.2 (9.6)
Male, n (%)	860 (62.7)	857 (62.2)	1717 (62.5)	225 (62.2)	214 (61.7)	439 (61.9)
Duration of T2D (years)	11.9 (8.3)	12.1 (8.5)	12.0 (8.4)	14.8 (9.3)	14.8 (9.5)	14.8 (9.4)
HbA1c (%; mmol/mol)	8.2 (1.0); 66.4 (10.7)	8.2 (1.0); 66.5 (10.9)	8.2 (1.0); 66.4 (10.8)	8.3 (1.0); 67.0 (11.0)	8.3 (1.0); 67.6 (10.9)	8.3 (1.0); 67.3 (11.0)
BMI (kg/m ²)	32.6 (6.3)	32.6 (6.1)	32.6 (6.2)	33.4 (7.4)	32.7 (6.6)	33.1 (7.0)
Concomitant SGLT-2i use, n (%)	731 (53.3)	735 (53.3)	1466 (53.3)	212 (58.6)	214 (61.7)	426 (60.1)
Concomitant ACEi; ARB use, n (%)	435 (31.7); 624 (45.5)	436 (31.6); 623 (45.2)	871 (31.7); 1247 (45.4)	104 (28.7); 186 (51.4)	99 (28.5); 174 (50.1)	203 (28.6); 360 (50.8)
Kidney characteristics						
eGFR (mL/min/1.73 m ²)	69.1 (24.2)	69.1 (23.6)	69.1 (23.9)	43.3 (16.4)	42.6 (15.3)	42.9 (15.9)
eGFR <60 mL/min/1.73 m ² , n (%)	527 (38.4)	506 (36.7)	1033 (37.6)	331 (91.9)	316 (91.3)	647 (91.6)
UACR (mg/g), median (IQR)	14.0 (7.0-39.0)	15.0 (7.0-46.0)	14.0 (7.0-41.5)	50.0 (20.0-297.0)	60.0 (17.0-349.0)	55.0 (18.0-326.0)
Normoalbuminuria (<30 mg/g)	881 (69.8)	857 (68.1)	1738 (68.9)	108 (32.5)	115 (35.0)	223 (33.7)
Microalbuminuria (30-300 mg/g)	300 (23.8)	308 (24.5)	608 (24.1)	142 (42.8)	121 (36.8)	263 (39.8)
Macroalbuminuria (>300 mg/g)	82 (6.5)	93 (7.4)	175 (6.9)	82 (24.7)	93 (28.3)	175 (26.5)

Data are mean (SD) or n (%) unless otherwise stated, from all randomized participants with non-missing data. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI=body mass index; eGFR=estimated glomerular filtration rate; HbA1c=glycated hemoglobin; IQR=interquartile range; KDIGO=Kidney Disease: Improving Global Outcomes; MTD=maximum tolerated dose; OFG=orforglipron; SD=standard deviation; SGLT-2i=sodium-glucose cotransporter-2 inhibitor; T2D=type 2 diabetes; UACR=urinary albumin-creatinine ratio.

KDIGO Risk Classes by eGFR and UACR¹

The subgroup with high or very high KDIGO risk corresponds to the orange and red boxes, respectively.
eGFR was calculated with CKD-EPI Cystatin C²

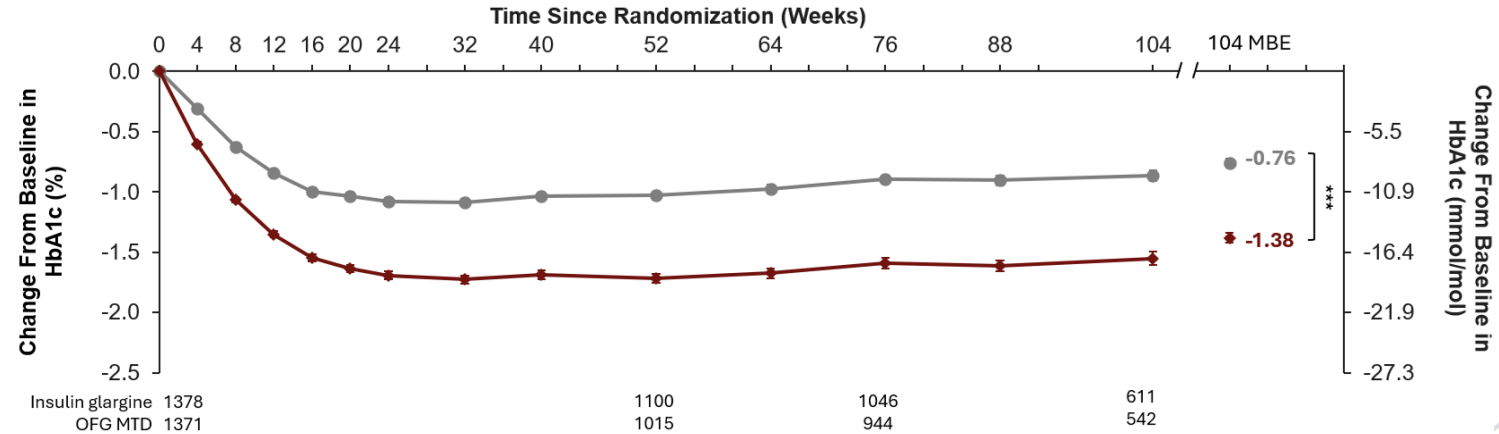
GFR category	Description	GFR (mL/min/1.73 m ²)	Persistent albuminuria categories		
			A1: Normal to mildly increased	A2: Moderately increased	A3: Severely increased
			<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
			Total N (%) ^a	Total N (%) ^a	Total N (%) ^a
G1	Normal or high	≥90	449 (17.8)	117 (4.6)	20 (0.8)
G2	Mildly decreased	60-89	734 (29.1)	228 (9.0)	39 (1.5)
G3a	Mildly to moderately decreased	45-59	332 (13.2)	129 (5.1)	33 (1.3)
G3b	Moderately to severely decreased	30-44	199 (7.9)	106 (4.2)	59 (2.3)
G4	Severely decreased	15-29	23 (0.9)	27 (1.1)	23 (0.9)
G5	Kidney failure	<15	0 (0)	1 (0)	1 (0)

1. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int.* 2024. 2. Inker, L.A., et al. *N Engl J Med.* 2012. ^aN values represent the total numbers of subjects with non-missing eGFR and UACR values in the OFG MTD and IGlar treatment groups at baseline. A total of 49 patients had missing eGFR or UACR data and were excluded from the table. CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; eGFR=estimated glomerular filtration rate; KDIGO=Kidney Disease: Improving Global Outcomes; UACR=urinary albumin-creatinine ratio.

ACHIEVE-4 Change from Baseline in HbA1c and Body Weight Through Week 104: Overall Population

HbA1c change from baseline

Mean (SD) HbA1c at baseline = 8.23 (0.99) %; 66.4 (10.83) mmol/mol



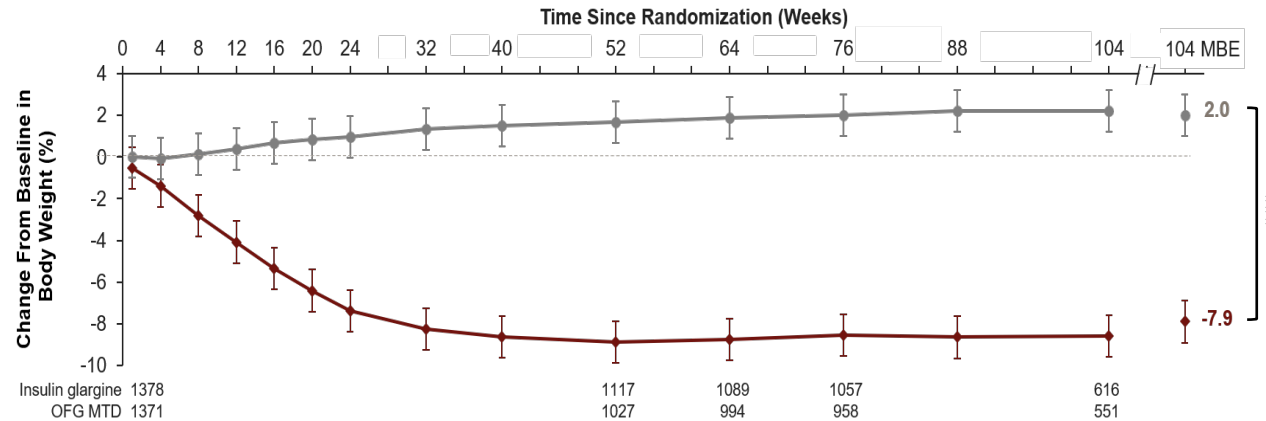
Treatment arm

Orforglipron MTD

Insulin glargine

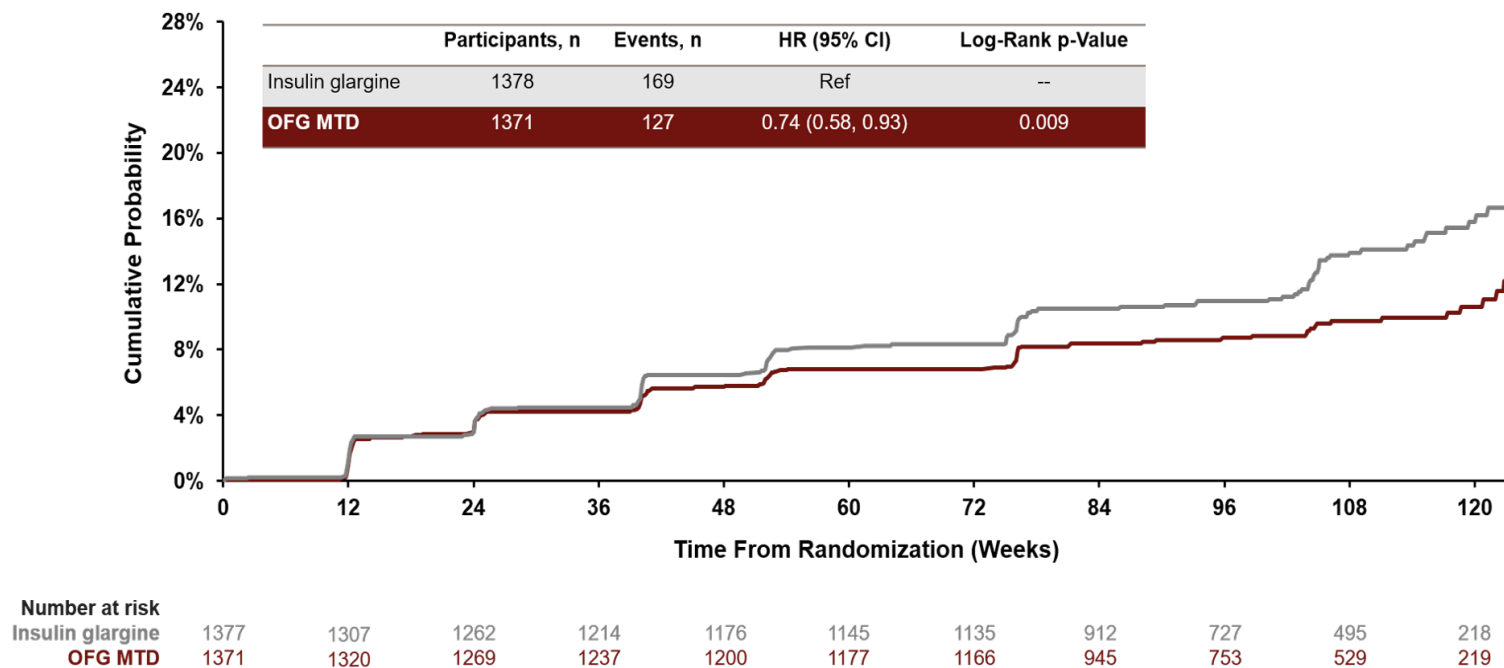
Body Weight change from baseline

Overall mean body weight at baseline = 90.91 (20.04) kg



OFG MTD vs. insulin glargine: ***p<0.001. p-values are for MBE change difference vs. insulin glargine. Data in line plot are raw mean (SE); other data are MBE (SE) unless stated otherwise. EE analysis was conducted using MMRM on randomized participants and EE data points set. Family-wise Type I error was not controlled for Week 76. EE=efficacy estimand; HbA1c=hemoglobin A1c; MBE=model-based estimate; MMRM=mixed model for repeated measures; MTD=maximum tolerated dose; N=total number of randomized participants; OFG=orforglipron; SD=standard deviation; SE=standard error.

Time to First Occurrence of 4-Component Composite Kidney Outcome (CKO-4): Overall Population



Component	OFG MTD (N=1371)	IGlar (N=1378)	HR (95% CI)	p-value
New macroalbuminuria	71 (5.2)	104 (7.5)	0.67 (0.50-0.91)	0.009
≥40% eGFR decline from baseline	58 (4.2)	72 (5.2)	0.80 (0.56-1.12)	0.193
Kidney failure	4 (0.3)	4 (0.3)	1.35 (0.30-6.03)	0.693
Kidney disease death	0 (0.0)	0 (0.0)	NE	NE

HR 0.74

95% CI 0.58-0.93; p=0.009

127 (9.3%) vs 169 (12.3%)

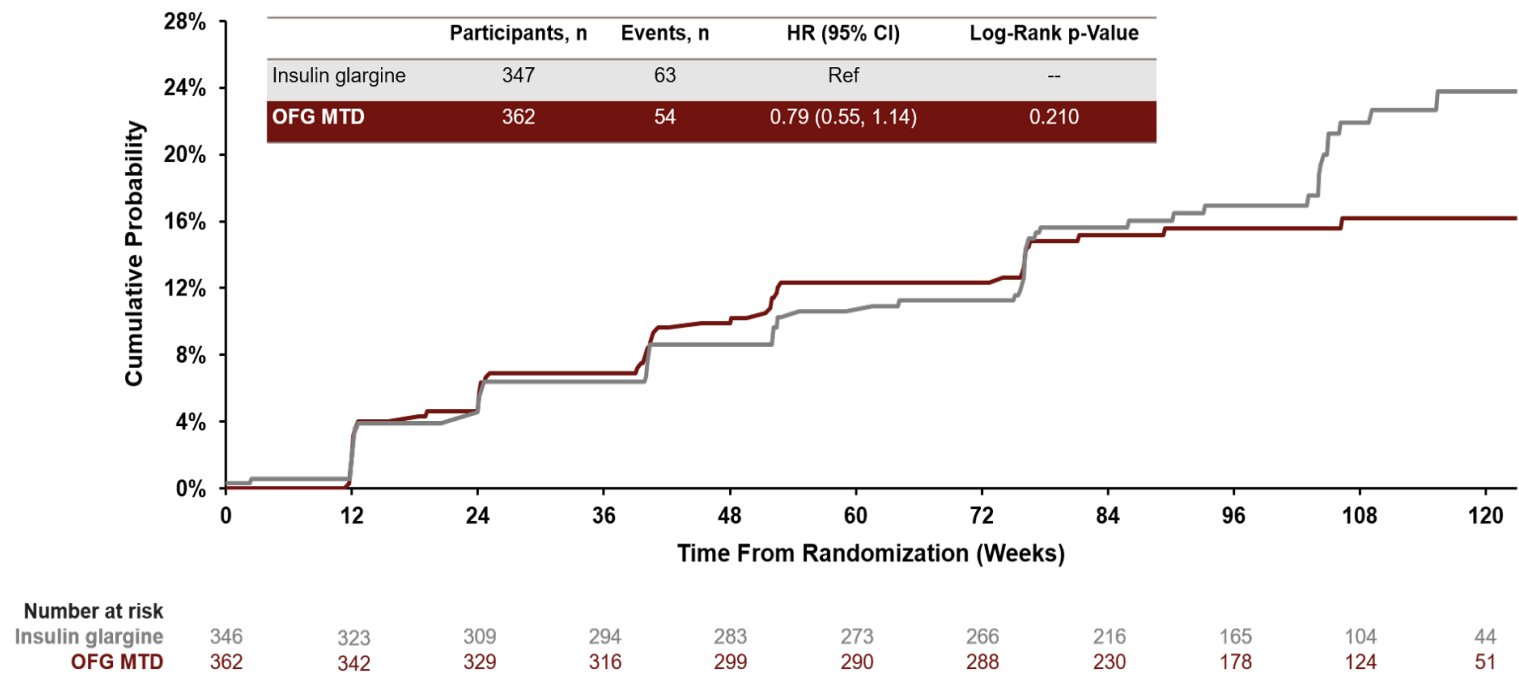
CKO-4 rate: OFG vs IGlar

103.9 weeks

Median Follow-up time

Point estimate and 95% CI of HR comparing OFG MTD and insulin glargine obtained from time-to-first-event analysis using Cox proportional hazards model. The cox model and log-rank test were stratified by Strata (joint levels of baseline HbA1c level [$\leq 8.5\%$, $> 8.5\%$], and SGLT-2i use at randomization [Y/N]). The x-axis was truncated at 123 weeks where approximately 10% of the population reached this timepoint by the end of the study. Data in table are n (%). Cases of kidney failure were reported by the investigator. CI=confidence interval; CKO-4=4-component composite kidney outcome; eGFR=estimated glomerular filtration rate; HbA1c=hemoglobin A1c; HR=hazard ratio; IGlar=insulin glargine; MTD=maximum tolerated dose; NE=not estimable; OFG=orforglipron; Ref=reference; SGLT-2i=sodium-glucose cotransporter-2 inhibitor.

Time to First Occurrence of 4-Component Composite Kidney Outcome (CKO-4): CKD Subgroup



Component	OFG MTD (N=362)	IGlar (N=347)	HR (95% CI)	p-value
New macroalbuminuria	31 (8.6)	40 (11.5)	0.75 (0.47-1.20)	0.224
≥40% eGFR decline from baseline	22 (6.1)	25 (7.2)	0.80 (0.45-1.41)	0.434
Kidney failure	4 (1.1)	4 (1.2)	NE	NE
Kidney disease death	0 (0)	0 (0)	NE	NE

HR 0.79
95% CI 0.55-1.14; p=0.210

54 (14.9%) vs 63 (18.2%)
CKO-4 rate: OFG vs IGlar

Point estimate and 95% CI of HR comparing OFG MTD and insulin glargine obtained from time-to-first-event analysis using Cox proportional hazards model. The cox model and log-rank test were stratified by Strata (joint levels of baseline HbA1c level [≤8.5%, >8.5%], and SGLT-2i use at randomization [Y/N]). The x-axis was truncated at 123 weeks where approximately 10% of the population reached this timepoint by the end of the study. Data in table are n (%). Cases of kidney failure were reported by the investigator. CI=confidence interval; CKD=chronic kidney disease; CKO-4=4-component composite kidney outcome; eGFR=estimated glomerular filtration rate; HbA1c=hemoglobin A1c; HR=hazard ratio; IGlar=insulin glargine; MTD=maximum tolerated dose; NE=not estimable; OFG=orforglipron; Ref=reference; SGLT-2i=sodium-glucose cotransporter-2 inhibitor.

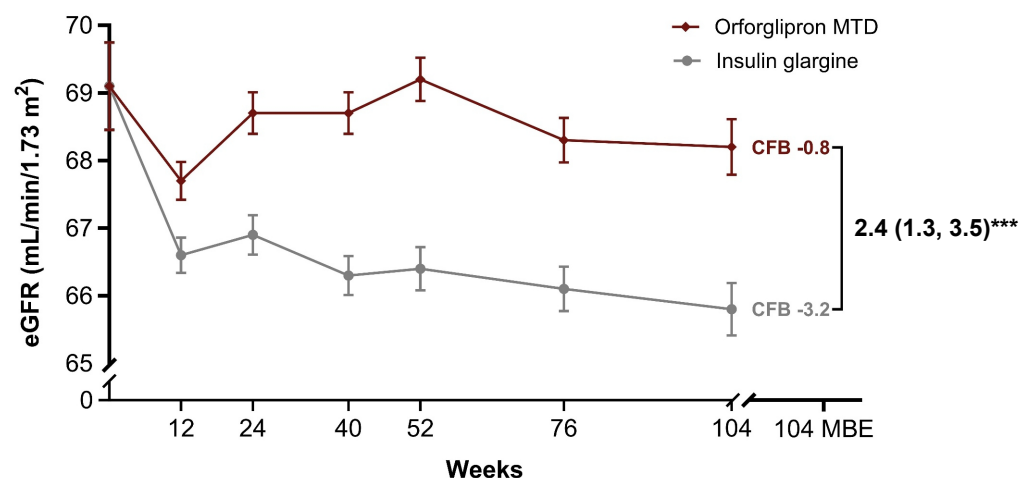
Annual Rate of Change in eGFR Over Time: Total Slope

Annual rate of eGFR change was **significantly reduced** with OFG vs insulin glargine in the overall population, and numerically increased in the high/very high KDIGO risk subgroup

Annual rate of change in eGFR (mL/min/1.73m²)

Population	OFG MTD	Insulin glargine	p-value
Overall population	-0.05	-1.08	0.001
High/very high KDIGO risk	0.72	0.37	0.544

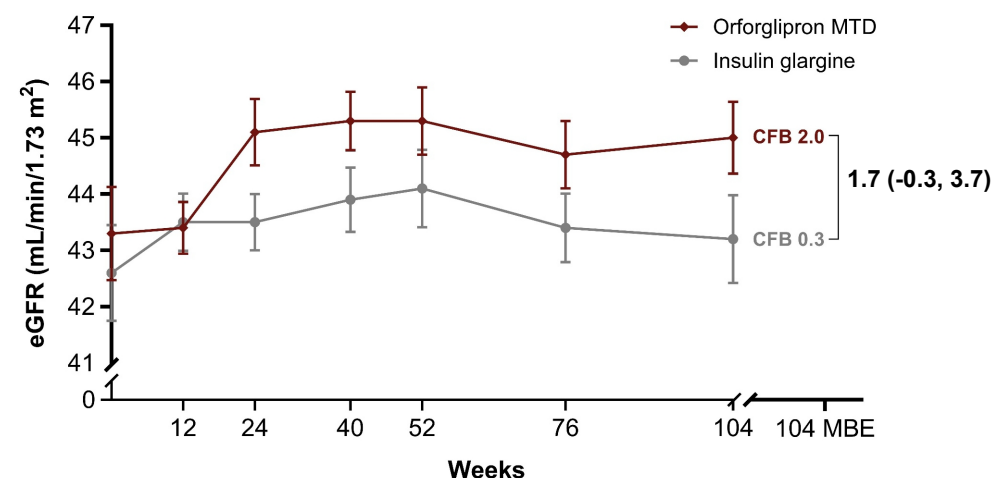
Mean eGFR over time in all participants (N=2749)



Number of participants

Orforglipron MTD	1370	1209	1148	1058	1013	944	535
Insulin glargine	1378	1241	1195	1122	1093	1045	606

Mean eGFR over time in participants with high/very high-risk CKD (N=709)



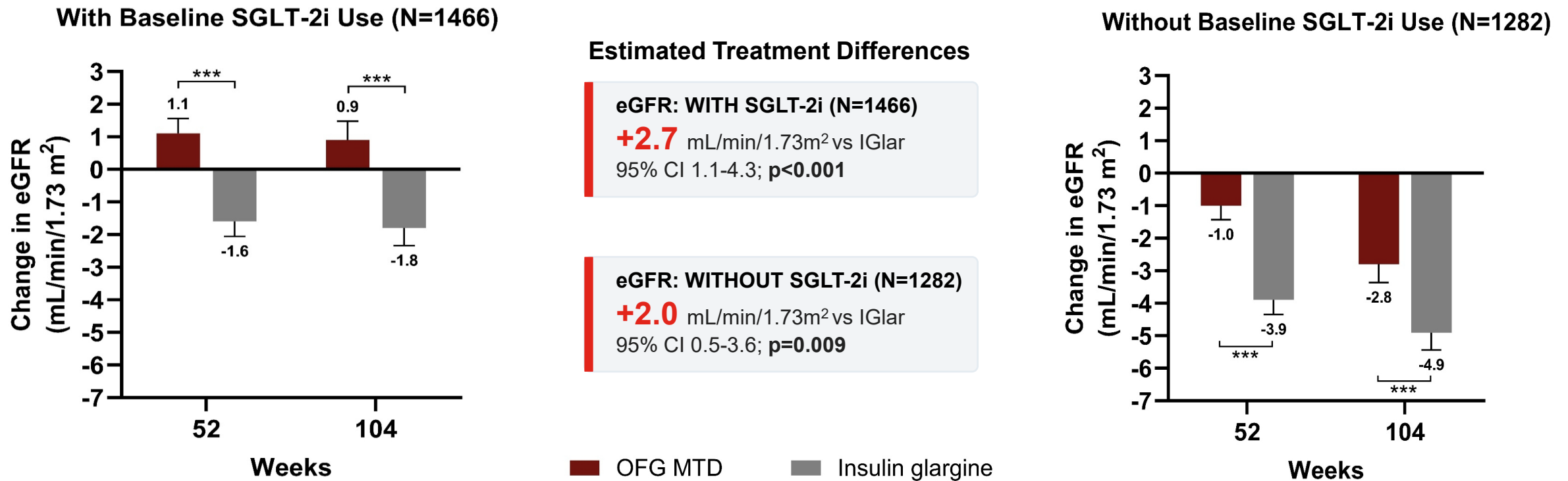
Number of participants

Orforglipron MTD	361	317	295	265	250	235	126
Insulin glargine	347	313	298	278	271	255	150

Data are MBE (SE). ***p<0.001. p-values are for MBE change difference of OFG MTD vs. insulin glargine. eGFR values over time were reported using mixed-effects model for repeated measures. Slope analysis was conducted for the randomized participants who completed 104 weeks of study participation, using the efficacy estimand data points set. eGFR was calculated by CKD-EPI Cystatin C equation. CKD=chronic kidney disease; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; eGFR=estimated glomerular filtration rate; KDIGO=Kidney Disease Improving Global Outcomes; MBE=model-based estimate; MTD=maximum tolerated dose; OFG=orforglipron; SE=standard error.

Change in eGFR in Participants With/Without Baseline SGLT-2i Use

Kidney benefits of OFG were **consistent regardless of baseline SGLT-2i use**: Change from baseline in eGFR was less pronounced with OFG vs IGlar in both subgroups



Data are MBE (SE). ***p<0.001. p-values are for MBE change difference of OFG MTD versus insulin glargine.

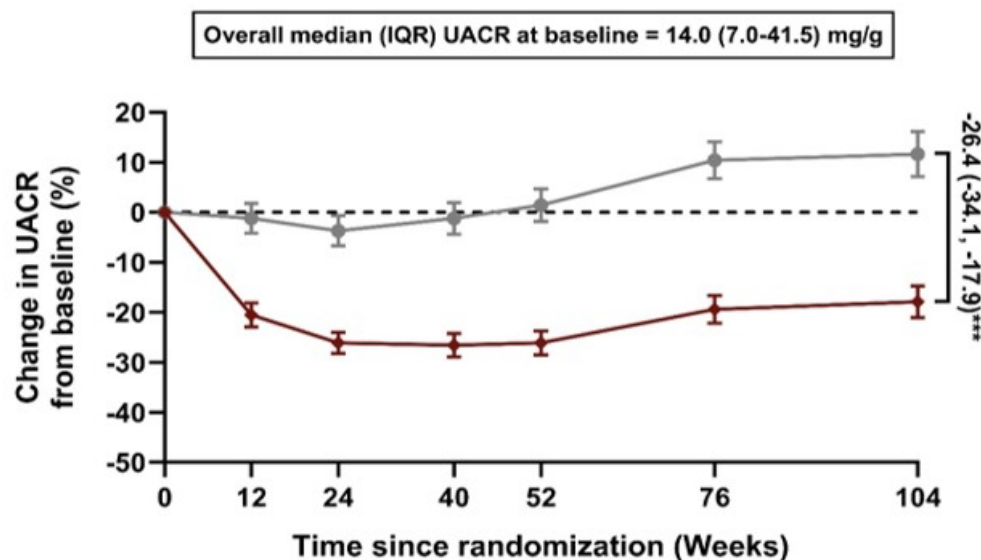
CI=confidence interval; eGFR=estimated glomerular filtration rate; IGlar=insulin glargine; MBE=model-based estimate; MTD=maximum tolerated dose; OFG=orforglipron; SE=standard error; SGLT-2i=sodium-glucose cotransporter-2 inhibitor.

Percent Change in UACR from Baseline

(A) Overall population

-26.4% (95% CI -34.1 to -17.9); $p<0.001$

(A)



Number of participants

Orforglipron MTD	1263	1096	1052	974	936	874	490
Insulin glargine	1258	1119	1084	1020	1002	959	542

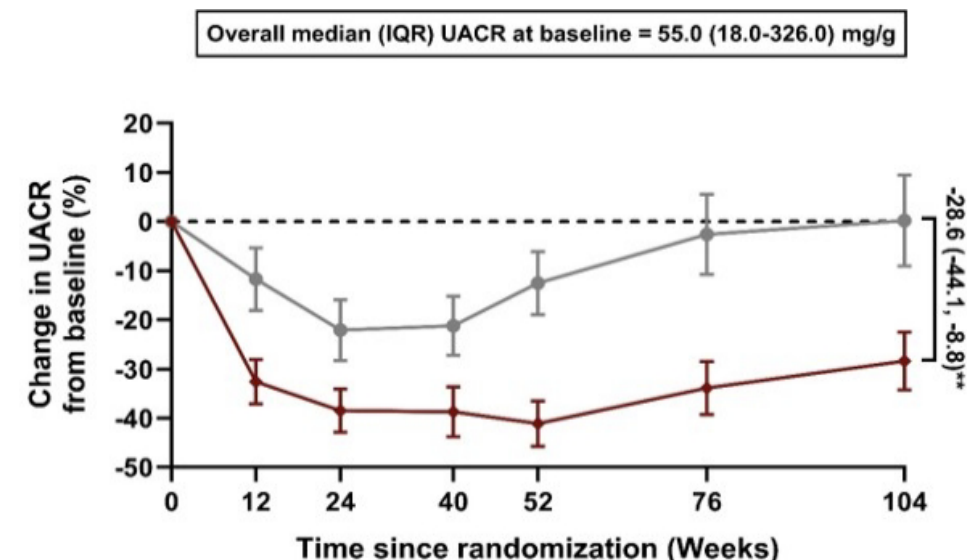
◆ OFG MTD

● Insulin glargine

(B) High/very high KDIGO risk

-28.6% (95% CI -44.1 to -8.8); $p=0.007$

(B)



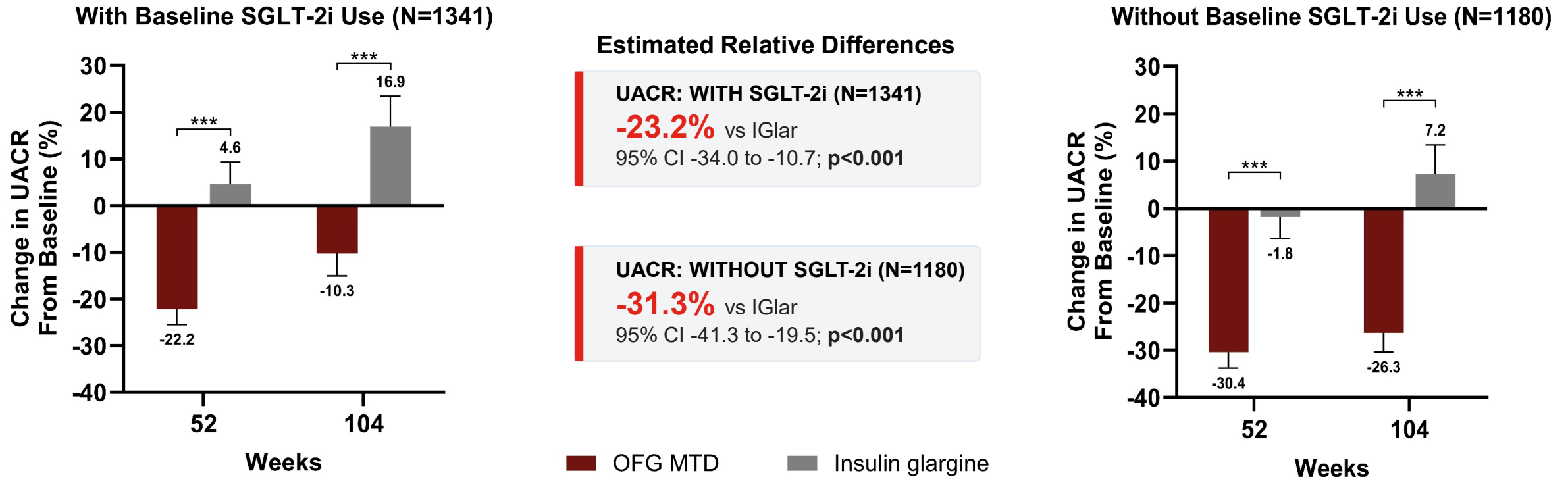
Number of participants

Orforglipron MTD	332	285	269	244	233	219	114
Insulin glargine	329	288	275	254	253	236	135

Data are MBE (SE). ** $p<0.01$; *** $p<0.001$. p-values are for MBE change difference of OFG MTD vs. IGlar. EE analysis was conducted using MMRM with log-transformation on randomized participants and EE data points set. CI=confidence interval; EE=efficacy estimand; IGlar=insulin glargine; IQR=interquartile range; KDIGO=Kidney Disease Improving Global Outcomes; MBE=model-based estimate; MMRM=mixed-effects model for repeated measures; MTD=maximum tolerated dose; OFG=orforglipron; SE=standard error; UACR=urinary albumin-creatinine ratio.

Change in UACR in Participants With/Without Baseline SGLT-2i Use

Kidney benefits of OFG were **generally consistent regardless of baseline SGLT-2i use**: Reduction in albuminuria vs insulin glargine in both subgroups through Week 104



EE analysis was conducted using MMRM on randomized participants and EE data points set. Data are MBE (SE). *** $p < 0.001$. p-values are for MBE change difference of OFG MTD versus insulin glargine. CI=confidence interval; EE=efficacy estimand; IGlar=insulin glargine; MBE=model-based estimate; MMRM=mixed-effects model for repeated measures; MTD=maximum tolerated dose; OFG=orforglipron; SE=standard error; SGLT-2i=sodium-glucose cotransporter-2 inhibitor; UACR=urinary albumin-creatinine ratio.

Conclusion



In a prespecified analysis of participants with T2D, overweight or obesity and at increased CV risk, daily OFG compared with titrated insulin glargine:

1

Reduced the relative risk of a 4-component major kidney composite outcome by 26% (9.3% vs 12.3%; median follow-up of 103.6 weeks), mainly driven by new-onset macroalbuminuria

2

Preserved eGFR over 104 weeks

3

Reduced UACR by 26-29% over 104 weeks

4

Exhibited significant results in the overall population and directionally consistent results in the subgroup with high or very high KDIGO risk

5

Demonstrated generally consistent benefits on eGFR and UACR regardless of baseline SGLT-2i use



Scan the QR code to access this eposter/presentation.
Other company and product names are trademarks of their respective owners.