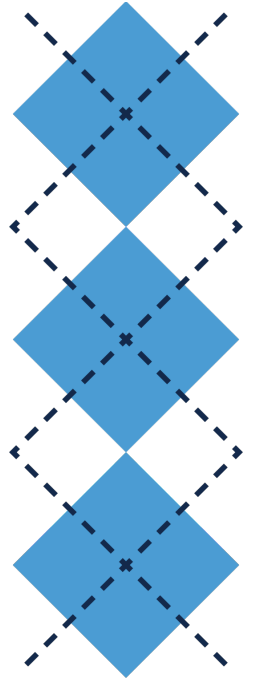


Efficacy and Safety of Orforglipron versus Insulin Glargine in People with Long-standing T2D at Increased Cardiovascular Risk: The ACHIEVE-4 Clinical Trial



Klara Klein, MD, PhD

**Assistant Professor, Division of Endocrinology and Metabolism
University of North Carolina, Chapel Hill, North Carolina, USA**

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



**School of
Medicine**

Disclosures

- I have consulted for Antag Therapeutics, Corxel, Eli Lilly and Company, Novo Nordisk, Pfizer, Roche Pharmaceuticals, and vTv Therapeutics.
- I received research related contracts (paid to the institution) from Bayer, Boehringer-Ingelheim, Carmot, Diasome, Gentibio, Eli Lilly and Company, Novo Nordisk, Rhythm Pharmaceuticals, Roche Pharmaceuticals, and vTv Therapeutics.

ACHIEVE-4 Background



Aim

To compare orforglipron to insulin glargine in individuals with inadequately controlled T2D and overweight/obesity at increased risk for CV events.

Objectives:

- Cardiovascular safety
- Long-term overall safety and efficacy

ACHIEVE-4 Background



Aim

To compare orforglipron to insulin glargine in individuals with inadequately controlled T2D and overweight/obesity at increased risk for CV events.

Objectives:

- Cardiovascular safety
- Long-term overall safety and efficacy



Regulatory Requirements

EMA Guidance on CV Risk¹

- Discharge excess CV risk (upper bound of the 95% CI for the HR <1.8 for MACE-4)

¹. EMA guidance. Reflection paper on assessment of cardiovascular safety profile of medicinal products. 2016 Feb 25. Report No.: EMA/CHMP/50549/2015. ². ORIGIN Trial Investigators, et al. *N Engl J Med*. 2012;367:319-328.

AHM=anti-hyperglycemic medication; CI=confidence interval; EMA=European Medicines Agency

ACHIEVE-4 Background



Aim

To compare orforglipron to insulin glargine in individuals with inadequately controlled T2D and overweight/obesity at increased risk for CV events.

Objectives:

- Cardiovascular safety
- Long-term overall safety and efficacy



Regulatory Requirements

EMA Guidance on CV Risk¹

- Discharge excess CV risk (upper bound of the 95% CI for the HR <1.8 for MACE-4)



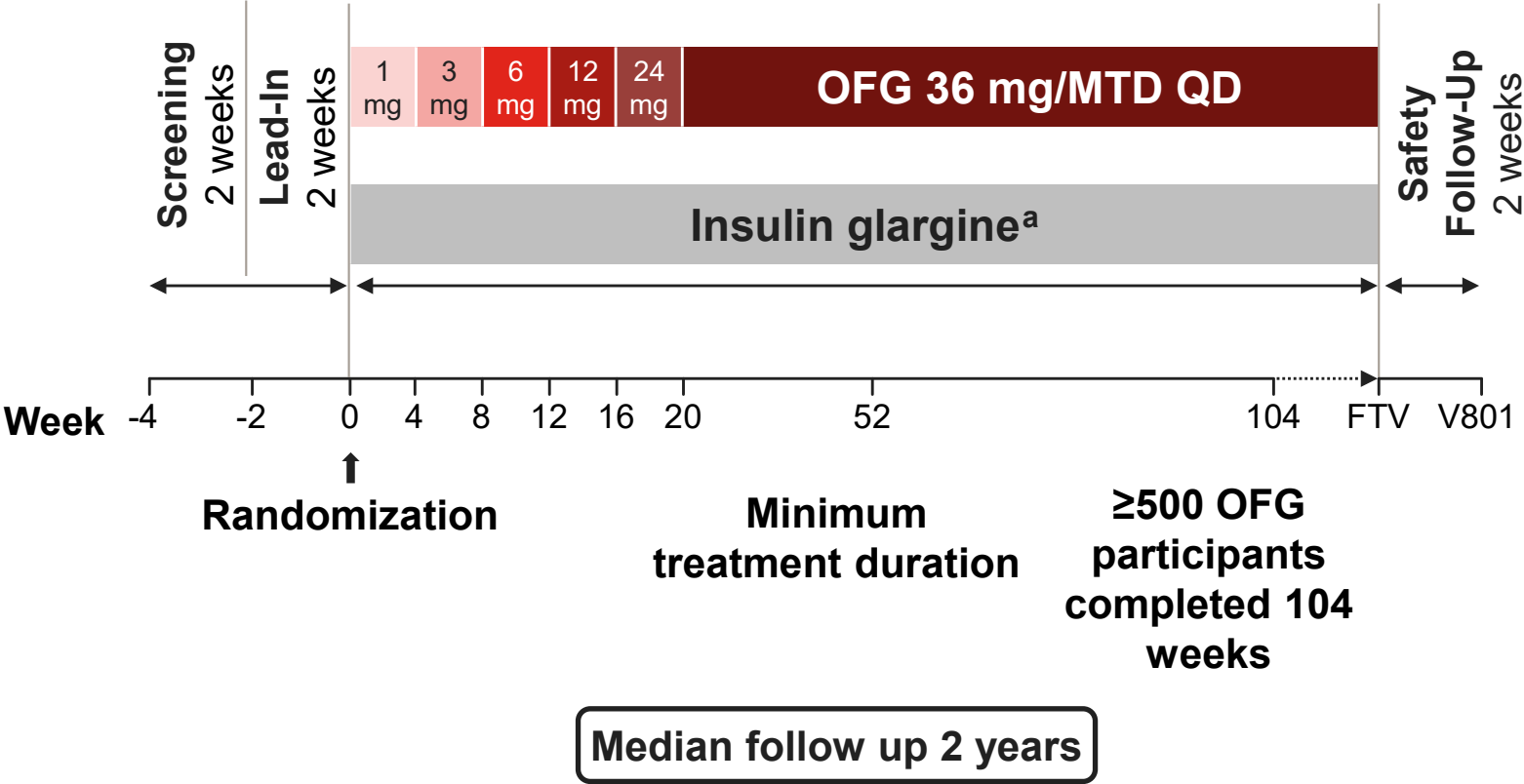
Insulin Glargine as Comparator

- Active control needed to ensure adequate glycemic control in a population with inadequate control
- Insulin glargine shown to have neutral effect on CV outcomes²

1. EMA guidance. Reflection paper on assessment of cardiovascular safety profile of medicinal products. 2016 Feb 25. Report No.: EMA/CHMP/50549/2015. 2. ORIGIN Trial Investigators, et al. *N Engl J Med*. 2012;367:319-328.

AHM=anti-hyperglycemic medication; CI=confidence interval; EMA=European Medicines Agency

ACHIEVE-4 Trial Design



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

^aThe starting dose of insulin glargine will be 10 IU/day, titrated to a fasting blood glucose <100 mg/dL (<5.6 mmol/L) through entire trial via treat-to-target algorithm.
*For matching doses (for example, 36 mg capsule and 17.2 mg tablet), the investigation formulation capsule and tablets were shown to deliver comparable systemic exposure to orforglipron with similar rate and extent of absorption (Ma X, Pharmacokinetic Bioequivalence of Orforglipron Tablets and Capsules in Healthy Participants With Obesity or Overweight. Diabetes, Obesity and Metabolism 2026;28(7):5803-5809. DOI: <https://doi.org/10.1111/dom.70783>) FTV=final treatment visit; MTD=maximum tolerated dose; OFG=orforglipron; QD=once daily;

Key Inclusion/exclusion criteria

Inclusion criteria

- **Adults with T2D**
- **HbA1c:** $\geq 7.0\%$ to $\leq 10.5\%$ (or $\geq 7.5\%$ if using SU)
- **BMI ≥ 25 kg/m²** with stable weight ($\pm 5\%$)
- Using stable doses of **1-3 oral glucose lowering medications** ($\pm$ metformin $\pm$ SGLT-2i $\pm$ SU)^a
- **Increased risk of CV events:**
 - Coronary heart disease
 - Peripheral artery disease
 - Cerebrovascular disease
 - Congestive heart failure
 - Chronic kidney disease

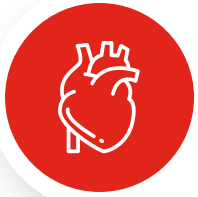
Exclusion criteria

- **eGFR_{cysc} < 15 mL/min/1.73 m²**
- **ALT or AST $> 5 \times$ ULN**
- **Severe hypoglycemia** within the last 6 months or **hypoglycemia unawareness**
- Current or planned treatment of **diabetic retinopathy or diabetic macular edema**
- Use of **insulin, GLP-1 RAs, or weight loss medications** within 90 days prior to screening
- **NYHA class IV CHF**

^aParticipants to continue these medications until end of the study, with dose modifications and/or discontinuations allowed for renal function and/or episodes of hypoglycemia.

AHM=anti-hyperglycemic medication; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CHF=congestive heart failure; eGFR=estimated glomerular filtration rate calculated using CKD-EPI cystatin C equation 2012; NYHA=New York Heart Association; ULN=upper limit of normal.

Primary and Key Secondary Endpoints

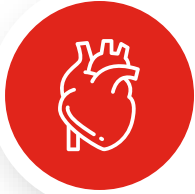


Primary Endpoint^a

Time to first occurrence of any MACE-4^b
(non-inferiority: 95% CI upper bound for HR < 1.8)

^aControlled for family-wise Type I error. ^bMACE-4 includes non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or CV death. ^cMACE-3 includes non-fatal MI, non-fatal stroke, or CV death.

Primary and Key Secondary Endpoints



Primary Endpoint^a

Time to first occurrence of any MACE-4^b
(non-inferiority: 95% CI upper bound for HR < 1.8)

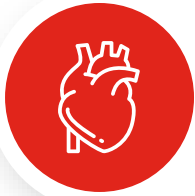


Key Secondary Endpoints^a

- **Time to first occurrence of any MACE-3^c** (superiority)
- **Change from baseline in HbA1c at Week 52** (non-inferiority margin = 0.3%)
- **Change from baseline in HbA1c at Week 52** (superiority)
- **Change from baseline in body weight at Week 52 (% and kg)** (superiority)

^aControlled for family-wise Type I error. ^bMACE-4 includes non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or CV death. ^cMACE-3 includes non-fatal MI, non-fatal stroke, or CV death.

Primary and Key Secondary Endpoints



Primary Endpoint^a

Time to first occurrence of any MACE-4^b
(non-inferiority: 95% CI upper bound for HR < 1.8)



Key Secondary Endpoints^a

- **Time to first occurrence of any MACE-3^c** (superiority)
- **Change from baseline in HbA1c at Week 52** (non-inferiority margin = 0.3%)
- **Change from baseline in HbA1c at Week 52** (superiority)
- **Change from baseline in body weight at Week 52 (% and kg)** (superiority)

HbA1c and body weight were also assessed through 104 weeks as exploratory objectives

^aControlled for family-wise Type I error. ^bMACE-4 includes non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or CV death. ^cMACE-3 includes non-fatal MI, non-fatal stroke, or CV death.

Statistical Methods and Estimands

MACE endpoints

Primary MACE-4 safety endpoint:

- Guided by an estimand comparing orforglipron with insulin glargine based on the ***safety analysis set***.

Key secondary MACE-3 endpoint:

- Superiority assessment from randomization to the end of study based on the ***randomized participants set***.

Statistical Methods and Estimands

MACE endpoints

Primary MACE-4 safety endpoint:

- Guided by an estimand comparing orforglipron with insulin glargine based on the ***safety analysis set***.

Key secondary MACE-3 endpoint:

- Superiority assessment from randomization to the end of study based on the ***randomized participants set***.

Weight and HbA1c endpoints

Population

All randomized participants (ITT). Missing endpoints imputed for both estimands.

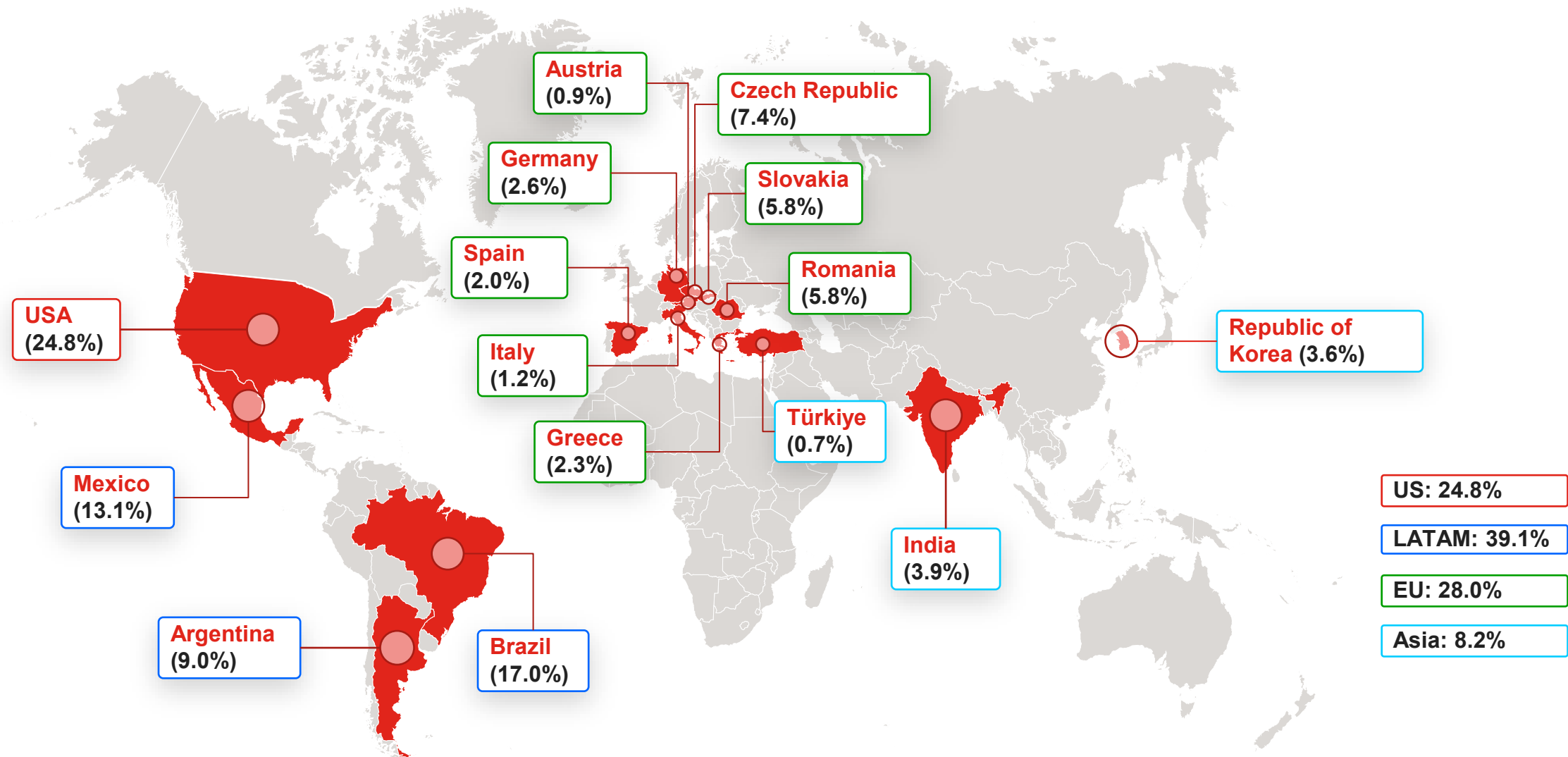
Treatment regimen estimand

Evaluates effect regardless of adherence or initiation of rescue therapy.

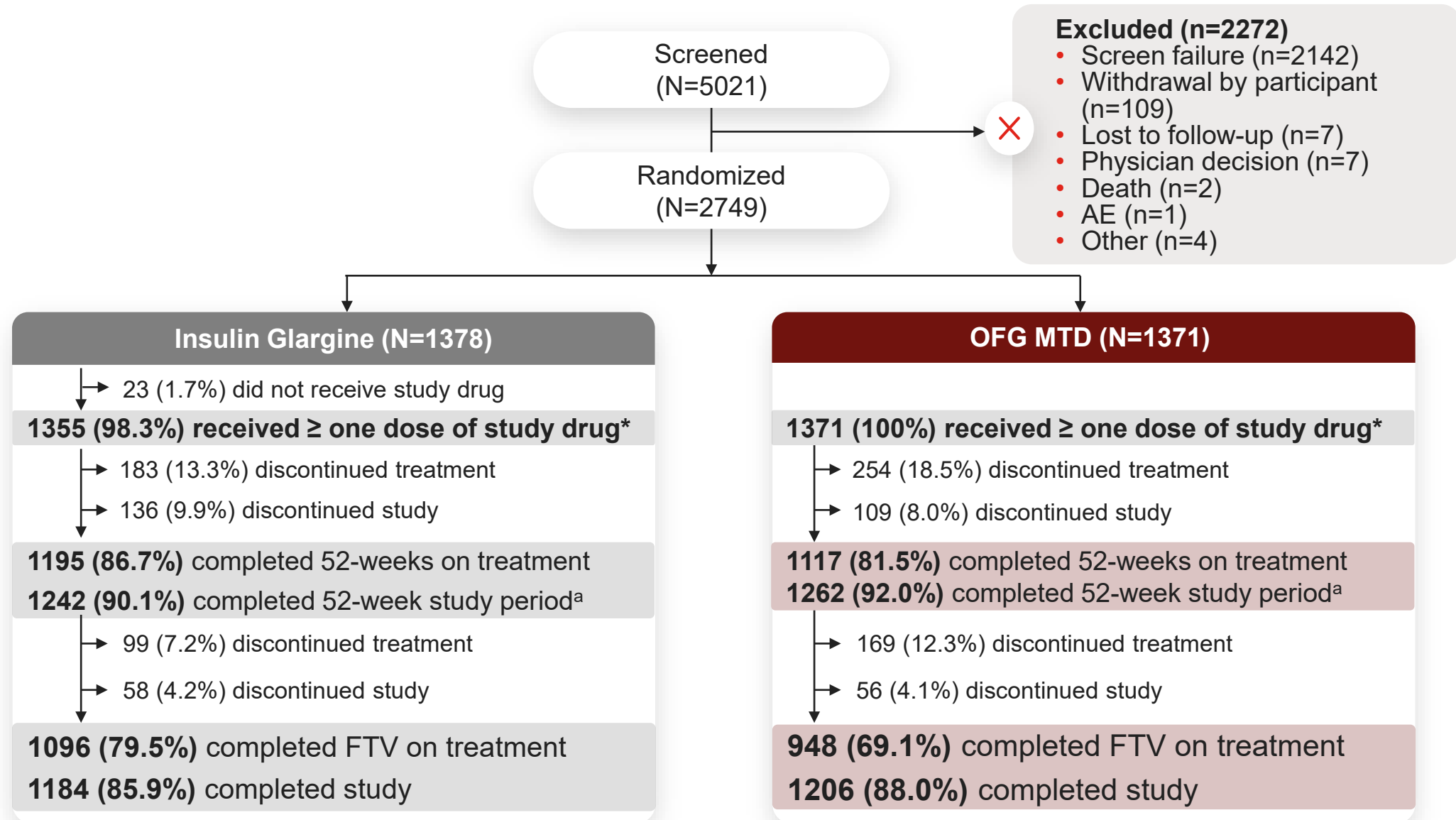
Efficacy estimand

Effect if participants remained on assigned treatment without rescue therapy.

Country-Level Overview (N=2749)



Participant Disposition



* Safety analysis set. ITT analyses include all subjects randomized, regardless of whether study drug was taken. 25 participants (12 insulin glargine, 13 orforglipron) from sites closed during the trial due to GCP non-compliance were excluded from analyses of primary and key secondary endpoints.

^aParticipants are considered to have completed Week 52 treatment or the Week 52 study period if they discontinued treatment after Visit 20 (if it occurred) or more than 52 weeks following the randomization date (if Visit 20 did not occur).

AE=adverse event; FTV=final treatment visit; MTD=maximum tolerated dose; OFG=orforglipron.

Baseline Demographics and Characteristics

Characteristic	Insulin Glargine (N=1378)	OFG MTD (N=1371)	Total (N=2749)
Age, years	63.1 (9.8)	63.2 (10.0)	63.1 (9.9)
Female, n (%)	521 (37.8)	511 (37.3)	1032 (37.5)
Race, n (%)			
American Indian or Alaska Native	137 (10.0)	148 (10.8)	285 (10.4)
Asian	118 (8.6)	114 (8.3)	232 (8.5)
Black or African American	107 (7.8)	120 (8.8)	227 (8.3)
Native Hawaiian or Other Pacific Islander	1 (0.1)	2 (0.1)	3 (0.1)
White	970 (70.7)	944 (69.1)	1914 (69.9)
Ethnicity, n (%)			
Hispanic or Latino	645 (46.8)	631 (46.0)	1276 (46.4)
Duration of T2D, years	12.12 (8.45)	11.94 (8.32)	12.03 (8.38)
HbA _{1c} , %	8.23 (1.00)	8.23 (0.98)	8.23 (0.99)
HbA _{1c} , mmol/mol	66.4 (10.7)	66.4 (11.0)	66.4 (10.9)
BMI, kg/m ²	32.6 (6.1)	32.6 (6.3)	32.6 (6.2)
Baseline eGFR ^a , mL/min/1.73m ²	69.05 (23.64)	69.09 (24.16)	69.07 (23.89)
<60 mL/min/1.73m ²	506 (36.7)	527 (38.4)	1033 (37.6)

Notes: Data are shown as mean (SD) unless stated otherwise. Data from all randomized participants. ^aeGFR was calculated by CKD-EPI cystatin-C equation (Inker et al. 2012).
MTD=maximum tolerated dose; n=number of participants in the specified category; N=number of randomized participants; OFG=orforglipron; SD=standard deviation; BMI=body mass index;

Baseline Cardiovascular and Kidney Disease

Characteristic	Insulin Glargine (N=1378)	OFG MTD (N=1371)	Total (N=2749)
Participants with ≥1 CV disease	1184 (85.9)	1178 (85.9)	2362 (85.9)
Coronary heart disease	668 (48.5)	695 (50.7)	1363 (49.6)
Congestive heart failure	276 (20.0)	276 (20.1)	552 (20.1)
Peripheral arterial disease	251 (18.2)	250 (18.2)	501 (18.2)
Cerebrovascular disease	232 (16.8)	197 (14.4)	429 (15.6)
High or very high-risk CKD	347 (25.2)	362 (26.4)	709 (25.8)

Notes: Data are n (%). Data from all randomized participants with non-missing data.
 CV=cardiovascular; MTD=maximum tolerated dose; n=number of participants in the specified category; N=number of randomized participants;
 NYHA=New York Heart Association OFG=orforglipron.

Baseline Cardiovascular and Kidney Disease

Characteristic	Insulin Glargine (N=1378)	OFG MTD (N=1371)	Total (N=2749)
Participants with ≥1 CV disease	1184 (85.9)	1178 (85.9)	2362 (85.9)
Coronary heart disease	668 (48.5)	695 (50.7)	1363 (49.6)
Congestive heart failure	276 (20.0)	276 (20.1)	552 (20.1)
Peripheral arterial disease	251 (18.2)	250 (18.2)	501 (18.2)
Cerebrovascular disease	232 (16.8)	197 (14.4)	429 (15.6)
High or very high-risk CKD	347 (25.2)	362 (26.4)	709 (25.8)

Notes: Data are n (%). Data from all randomized participants with non-missing data.
 CV=cardiovascular; MTD=maximum tolerated dose; n=number of participants in the specified category; N=number of randomized participants;
 NYHA=New York Heart Association OFG=orforglipron.

Baseline Concomitant Medications

Characteristic	Insulin Glargine (N=1378)	OFG MTD (N=1371)	Total (N=2749)
Concomitant oral AHM use, yes			
Metformin	1209 (87.7)	1211 (88.3)	2420 (88.0)
SGLT-2i	735 (53.3)	731 (53.3)	1466 (53.3)
SU	502 (36.4)	494 (36.0)	996 (36.2)
≥2 AHMs	875 (63.5)	870 (63.5)	1745 (63.5)
Other concomitant medication use, yes			
Blood pressure–lowering	1280 (92.9)	1248 (91.0)	2528 (92.0)
Lipid-lowering	1227 (89.0)	1210 (88.3)	2437 (88.7)

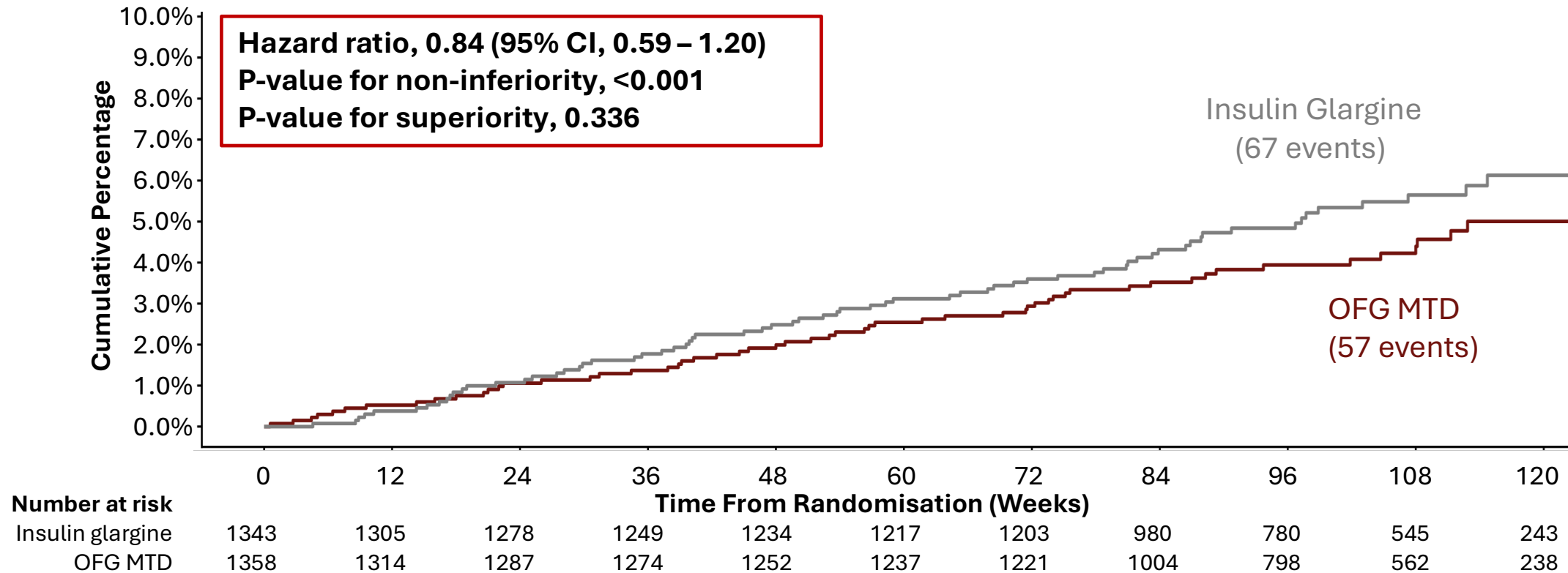
Notes: Data are n (%). Data from all randomized participants with non-missing data.

AHM=anti-hyperglycemic medication; MTD=maximum tolerated dose; n=number of participants in the specified category; N=number of randomized participants;

OFG=orforglipron; SGLT-2i=sodium-glucose co-transporter-2 inhibitor; SU=sulfonylurea.

Orforglipron was Non-inferior to Insulin Glargine in Time to First Occurrence of MACE-4

Primary Endpoint



MACE-4 = composite of non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or CV death

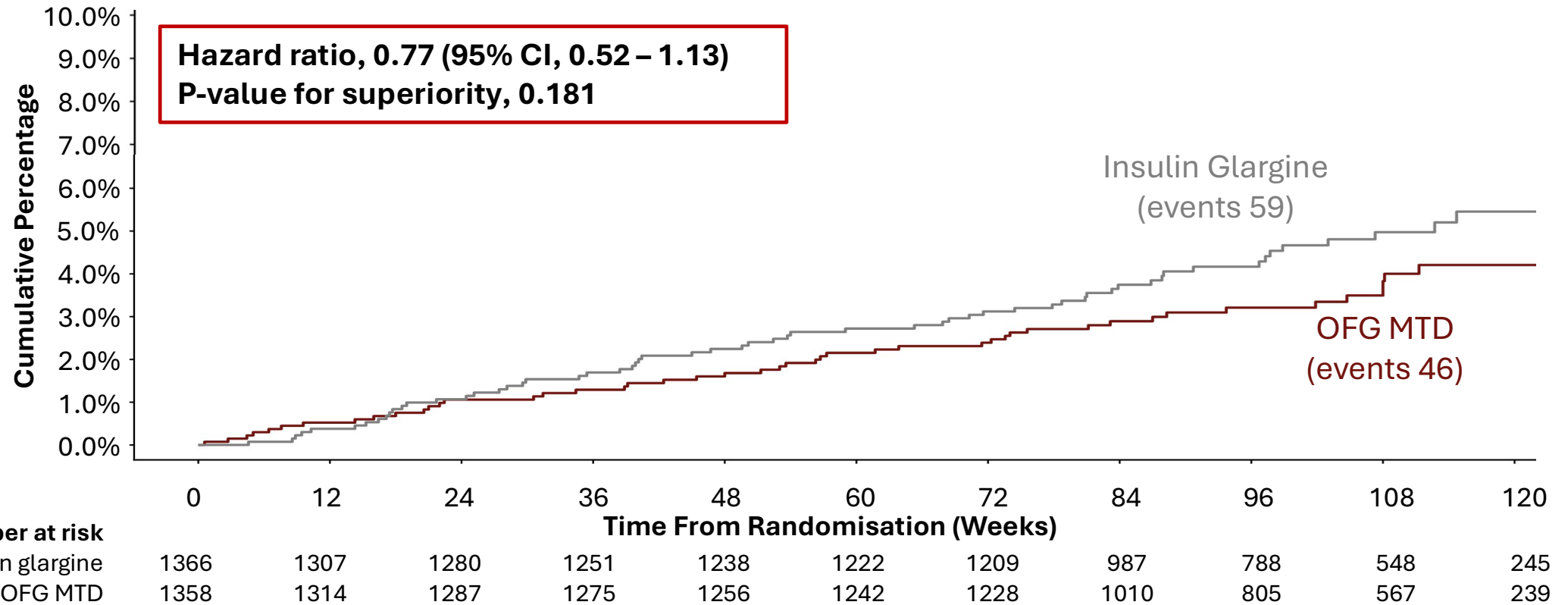
Notes: 1. Safety population used for analysis. 2. All events confirmed by the CEC. 3. Point estimate and 95% CI of HR comparing OFG MTD and insulin glargine obtained from time-to-first-event analysis using Cox proportional hazards model.

CEC=Clinical Endpoint Committee; CI=confidence interval; CV=cardiovascular; HR=hazard ratio; MACE-4=major adverse cardiovascular event-4 point;

MI=myocardial infarction; MTD=maximum tolerated dose; OFG=orforglipron

Orforglipron Did Not Achieve Superiority in Time to First Occurrence of MACE-3

Key Secondary Endpoint



MACE-3 = composite of non-fatal MI, non-fatal stroke, or CV death

Notes: 1. All subjects randomized used for analysis. 2. All events confirmed by the CEC. 3. 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;

CEC=Clinical Endpoint Committee; CI=confidence interval; CV=cardiovascular; HR=hazard ratio; MACE-3=major adverse cardiovascular event-3 point;

MI=myocardial infarction; MTD=maximum tolerated dose; OFG=orforglipron

Summary of MACE Endpoints and Deaths

Endpoint	Insulin Glargine (N=1343)	OFG MTD (N=1358)	HR (95% CI)
Primary^a and components			
MACE-4^b	67 (5.0)	57 (4.2)	0.84 (0.59, 1.20)
Cardiovascular death	29 (2.2)	14 (1.0)	0.47 (0.25, 0.90)
Non-fatal myocardial infarction	22 (1.6)	19 (1.4)	0.85 (0.46, 1.58)
Non-fatal stroke	14 (1.0)	14 (1.0)	0.98 (0.47, 2.06)
Hospitalization for unstable angina	9 (0.7)	14 (1.0)	1.55 (0.67, 3.58)
Key secondary^a			
MACE-3 ^{a,c}	59 (4.3)	46 (3.4)	0.77 (0.52, 1.13)

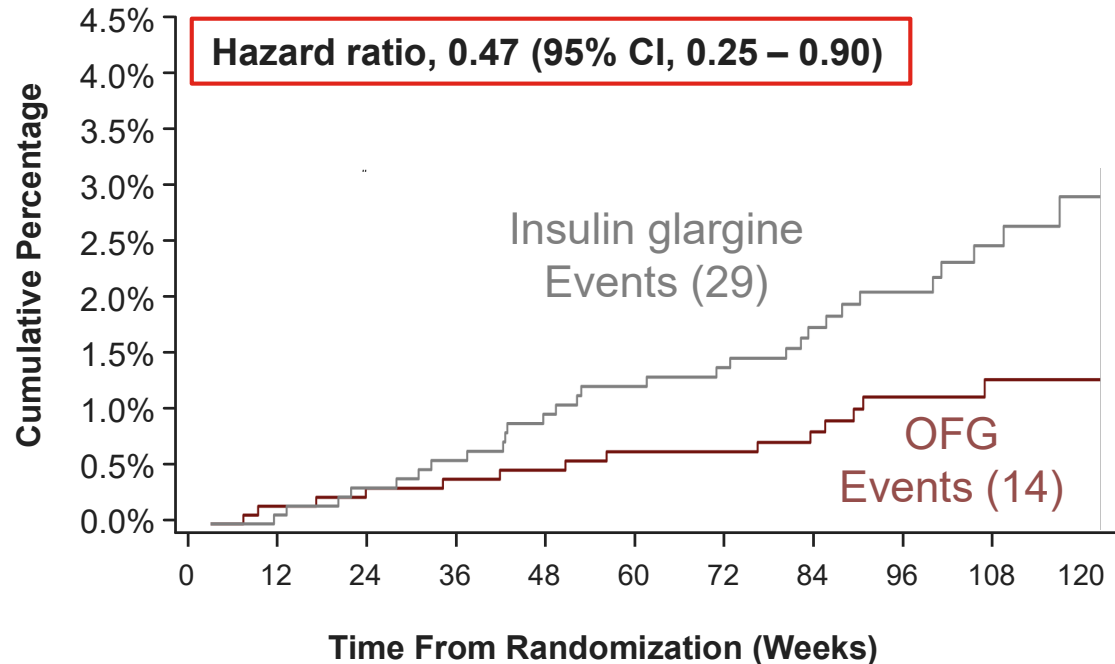
^aControlled for family-wise Type I error. ^bMACE-4 includes deaths due to cardiovascular cause, myocardial infarction, hospitalization for unstable angina, and stroke. Analysis set is all subjects taking ≥ 1 dose of study drug. ^cMACE-3 includes deaths due to cardiovascular cause, myocardial infarction, and stroke. Analysis set is all randomized subjects.

Notes: Data are n (%) unless otherwise stated. All events confirmed by the CEC. 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.

CEC=Clinical Endpoint Committee; CI=confidence interval; HR=hazard ratio; MACE-3=major adverse cardiovascular event-3 point; MACE-4=major adverse cardiovascular event-4 point; MTD=maximum tolerated dose; n=number of participants in the specified category; N=number of participants in the analysis population; OFG=orforglipron.

Numerically Fewer CV Death and All Cause Death Events were Observed in Individuals Randomized to Orforglipron

CV Death



Number at risk												
		0	12	24	36	48	60	72	84	96	108	120
		1343	1308	1287	1263	1252	1240	1229	1009	806	564	250
	Insulin glargine											
	OFG MTD	1358	1319	1297	1287	1271	1262	1251	1033	822	583	248

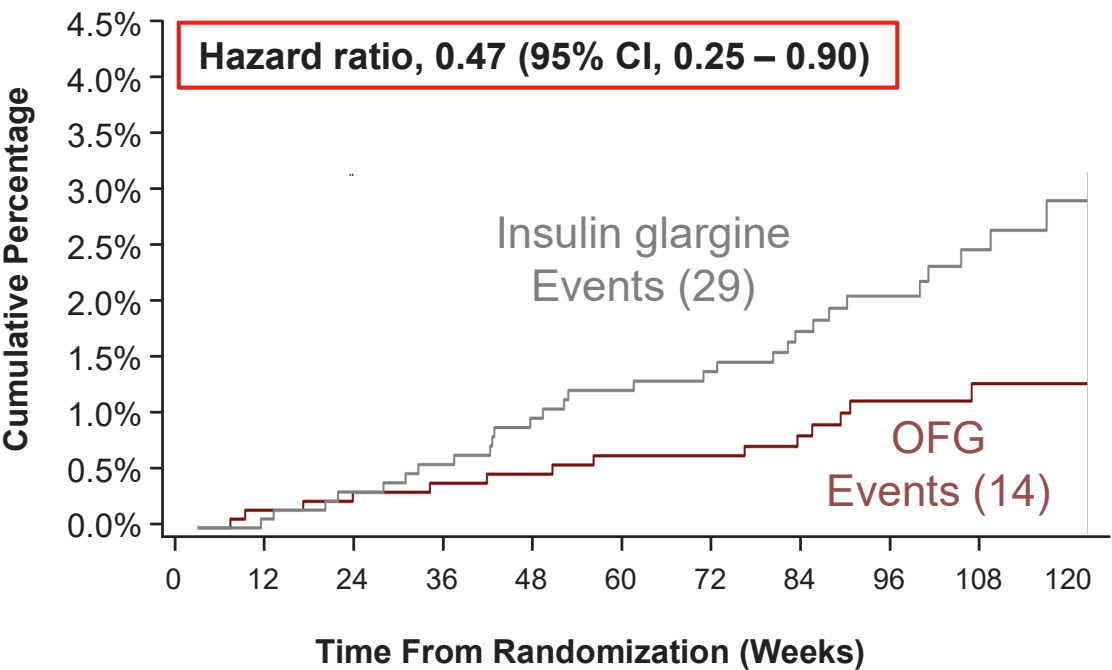
Safety analysis set = all randomized subjects who took ≥ 1 dose of study drug

Notes: 1. All events confirmed by the CEC. 2. 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; safety analysis set. 3. All cause death was an adjudicated outcome but was not a prespecified endpoint controlled for multiplicity.

CEC=Clinical Endpoint Committee; CI=confidence interval; CV=cardiovascular; HR=hazard ratio; MTD=maximum tolerated dose; N=total number of randomized participants in the subgroup; OFG=orforglipron

Numerically Fewer CV Death and All Cause Death Events were Observed in Individuals Randomized to Orforglipron

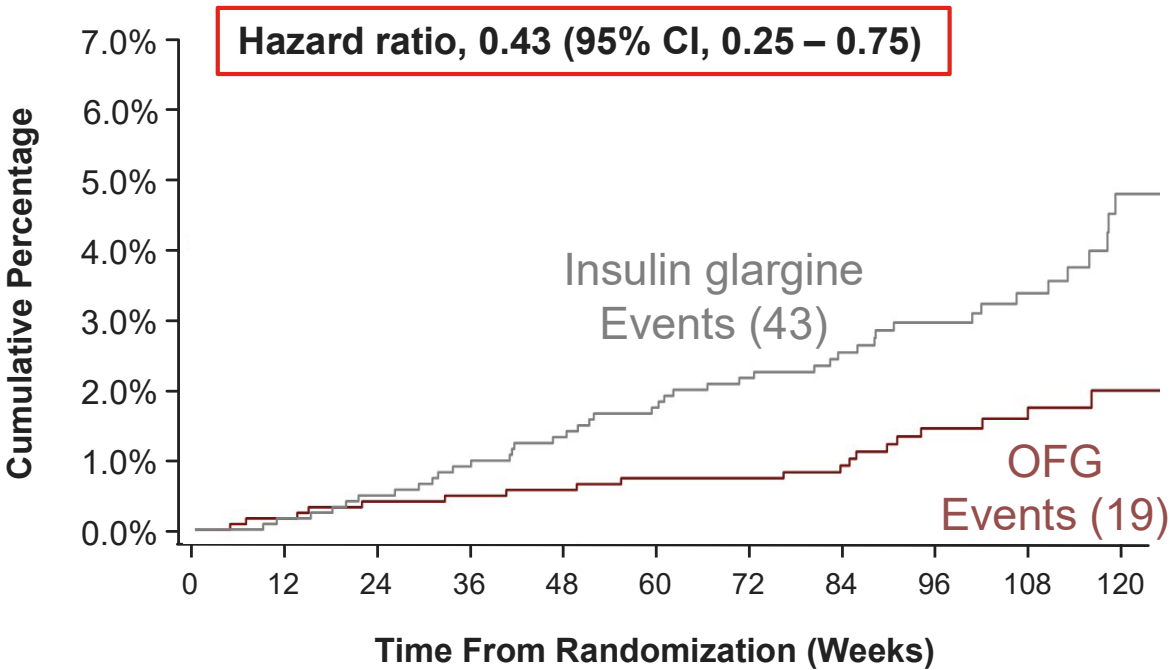
CV Death



Number at risk											
Insulin glargine	1343	1308	1287	1263	1252	1240	1229	1009	806	564	250
OFG MTD	1358	1319	1297	1287	1271	1262	1251	1033	822	583	248

Safety analysis set = all randomized subjects who took ≥ 1 dose of study drug

All Cause Death



Number at risk											
Insulin glargine	1355	1320	1295	1265	1252	1240	1229	1009	806	564	250
OFG MTD	1371	1332	1307	1290	1271	1262	1251	1033	822	583	248

Analysis set = all randomized subjects

Notes: 1. All events confirmed by the CEC. 2. 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; safety analysis set. 3. All cause death was an adjudicated outcome but was not a prespecified endpoint controlled for multiplicity.

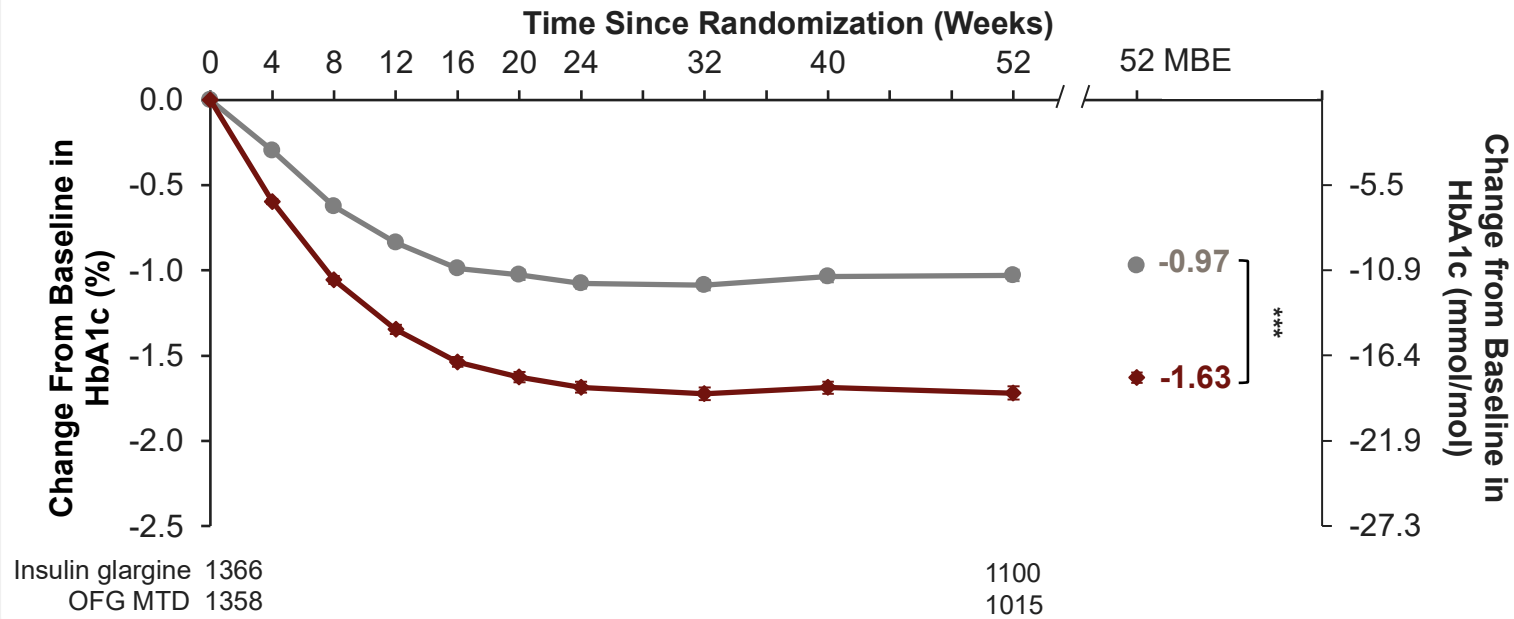
CEC=Clinical Endpoint Committee; CI=confidence interval; CV=cardiovascular; HR=hazard ratio; MTD=maximum tolerated dose; N=total number of randomized participants in the subgroup; OFG=orforglipron

Orforglipron was Superior to Insulin Glargine for Reduction in HbA1c

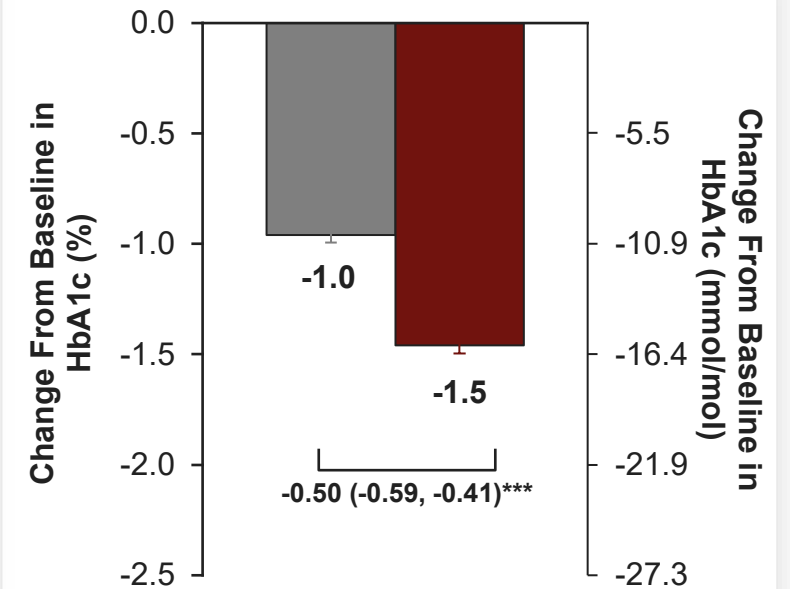
Key Secondary Endpoint

Efficacy Estimand (Observed Mean + MBE)

Mean HbA1c at baseline = 8.23 % [66.4 mmol/mol]



Treatment Regimen Estimand



■ Insulin glargine ■ OFG MTD

OFG MTD vs. insulin glargine: *** $p < 0.001$. p-values are for MBE change difference vs. insulin glargine.

Notes: Data in line plot are raw mean (SE). EE analysis was conducted using MMRM on randomized participants and EE data points set. TRE analysis was conducted using ANCOVA on randomized participants and TRE data points set, with missing data imputed. Family-wise Type I error was controlled for Week 52.

ANCOVA=analysis of covariance; EE=efficacy estimand; HbA1c=hemoglobin A1c; MBE=model-based estimate; MMRM=mixed model for repeated measures;

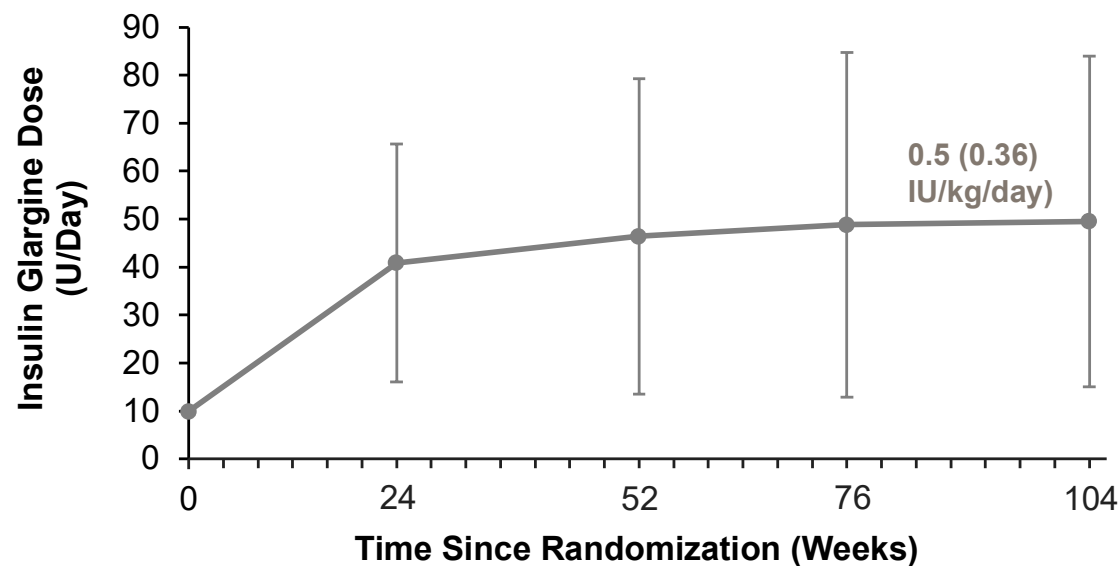
MTD=maximum tolerated dose; N=total number of randomized participants; OFG=orforglipron; SD=standard deviation; SE=standard error;

TRE=treatment regimen estimand.

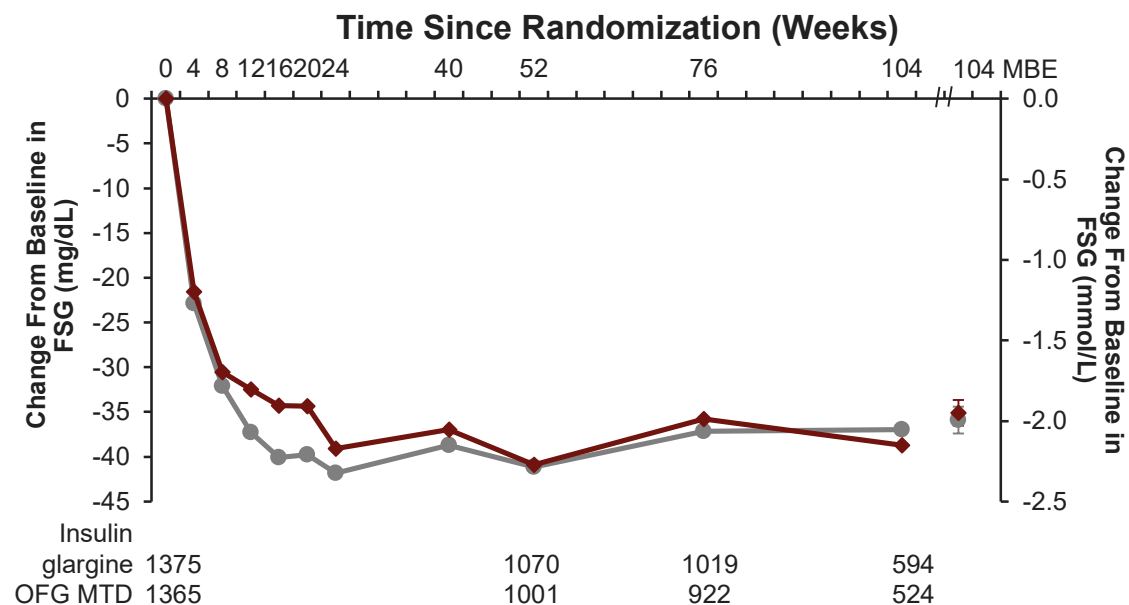
Insulin Glargine was Well-titrated, Achieving Fasting Serum Glucose Reduction Comparable to Orforglipron

Insulin glargine dose

Overall mean FSG at baseline = 154.8 mg/dL [8.6 mmol/L]



FSG



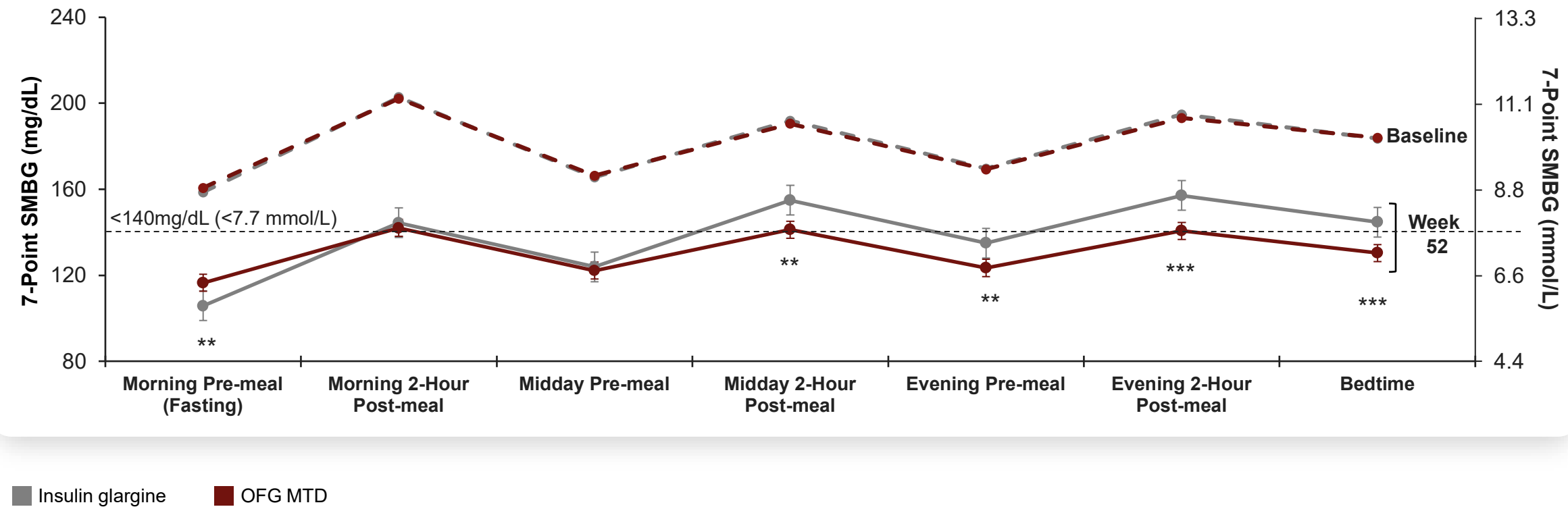
■ Insulin glargine ■ OFG MTD

FSG 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.
EE=efficacy estimand; FSG=fasting serum glucose; 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

Improved Glucose Control Observed Across the 7-point Profile with Both Treatments

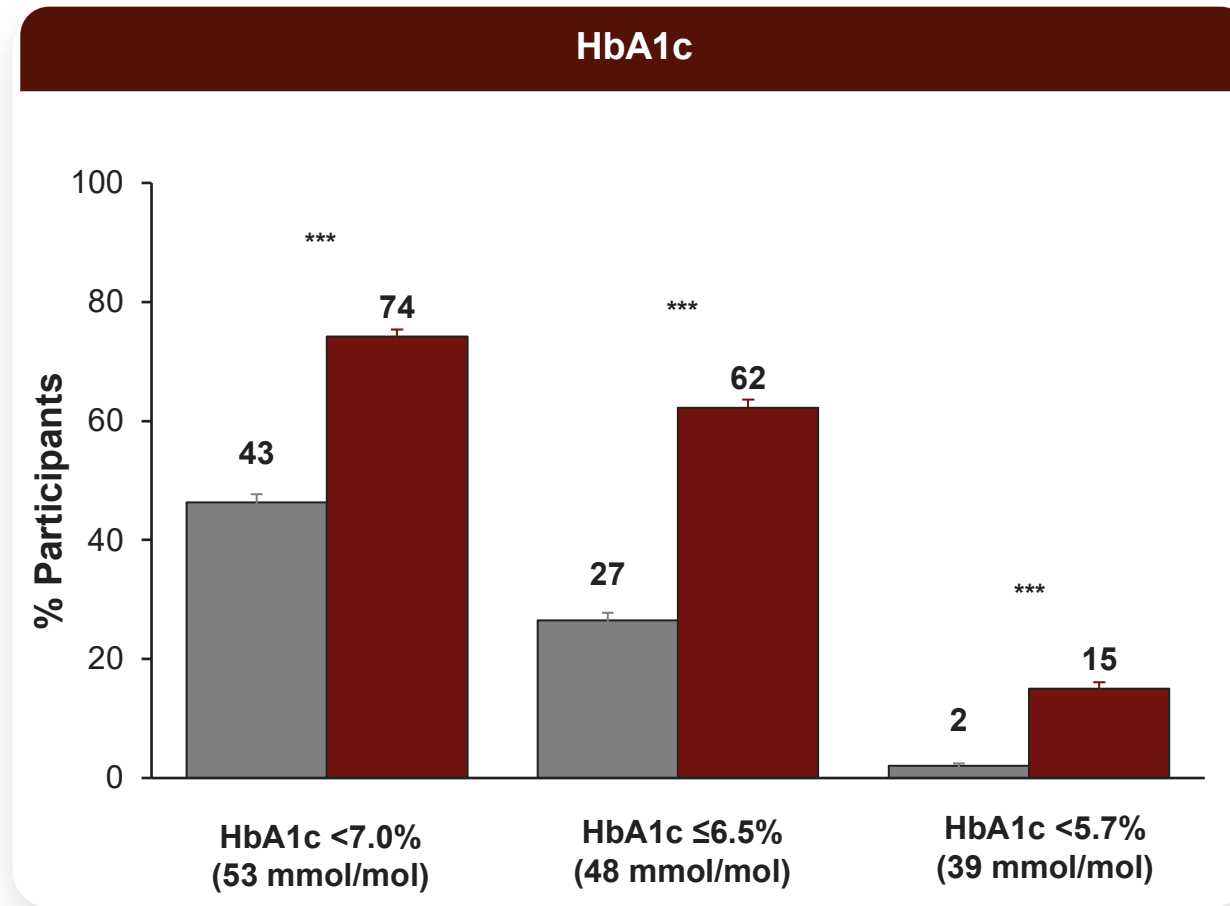
Efficacy Estimand

Daily mean 7-point SMBG at baseline = 180.8 mg/dL [10.0 mmol/L]



OFG MTD vs. insulin glargine: **p<0.01; ***p<0.001. p-values are for MBE change difference vs. insulin glargine. Data are raw mean (SE). EE analysis was conducted using an ANCOVA model with multiple imputation under MAR. ANCOVA = analysis of covariance; EE=efficacy estimand; MAR=missing at random; MTD=maximum tolerated dose; N=total number of randomized participants; OFG=orforglipron; SD=standard deviation; SE=standard error; SMBG=self-monitored blood glucose.

Proportion of Participants Achieving HbA1c Targets at 52 weeks (efficacy estimand)



■ Insulin glargine ■ OFG MTD

OFG vs. insulin glargine: ***p<0.001. p-values are for risk difference vs. insulin glargine.

Notes: Data are MBE (SE). EE analysis was conducted using logistic regression model on randomized participants and EE data points set, with missing data imputed. All analyses were pre-specified. Family-wise Type I error was not controlled.

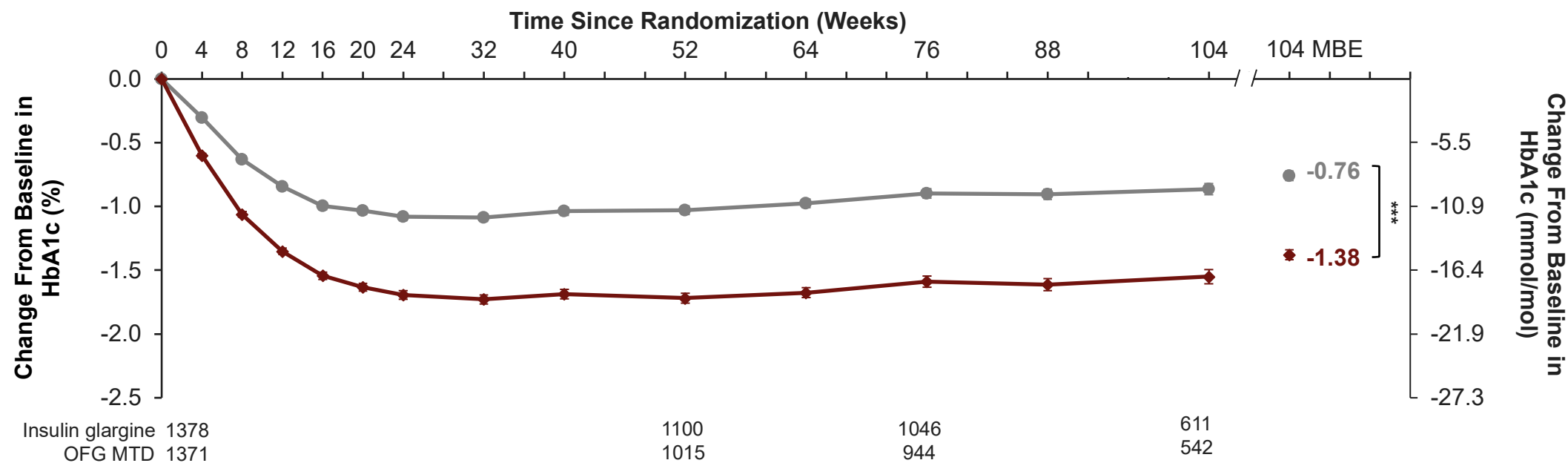
CI=confidence interval; EE=efficacy estimand; HbA1c=hemoglobin A1c; MBE=model-based estimate; MTD=maximum tolerated dose;

N=total number of randomized participants; OFG=orforglipron; SE=standard error.

Maintenance of Clinically Meaningful Glycemic Control Observed Through 2 years

Efficacy Estimand

Mean HbA1c at baseline = 8.23 % [66.4 mmol/mol]



■ Insulin glargine ■ OFG MTD

OFG MTD vs. insulin glargine: *** $p < 0.001$, p-values are for MBE change difference vs. insulin glargine.

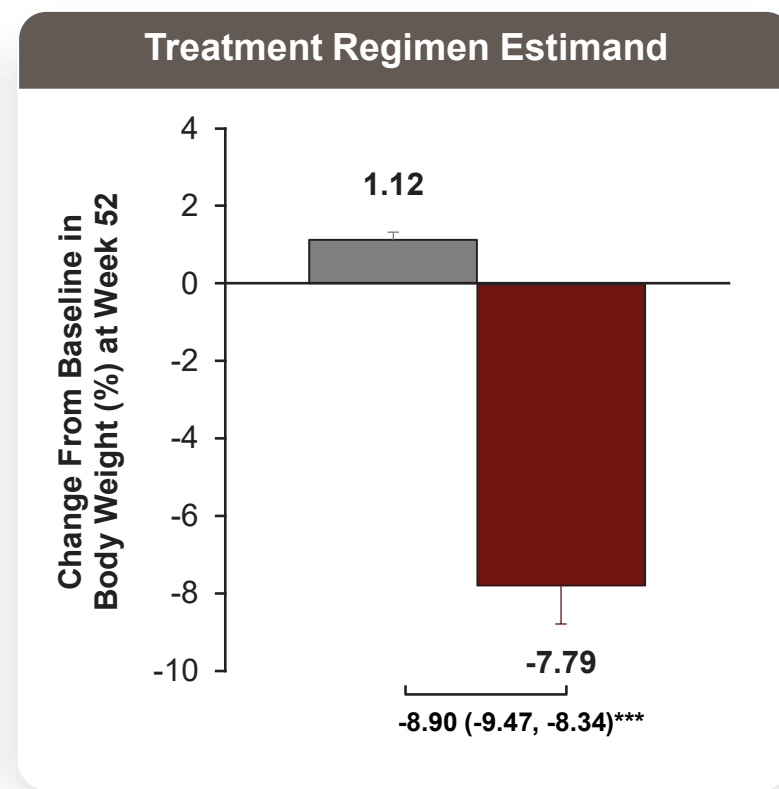
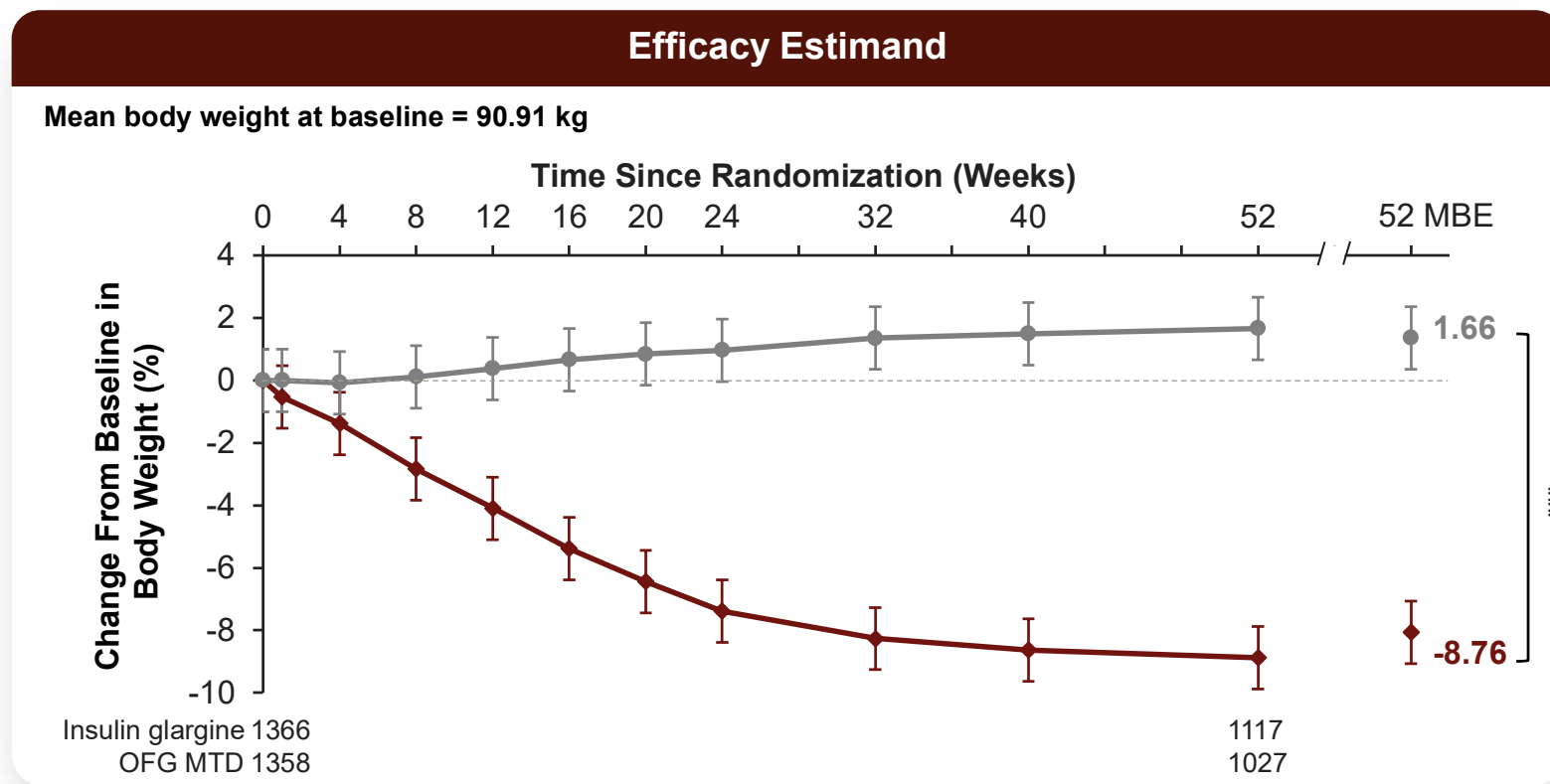
Notes: Data in line plot are raw mean (SE); other data are MBE (SE) unless stated otherwise. EE analysis was conducted using MMRM on randomized participants and EE data points set. Family-wise Type I error was not controlled for Week 76.

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

Orforglipron was Superior to Insulin Glargine for bodyweight reduction

Key Secondary Endpoint



■ Insulin glargine ■ OFG MTD

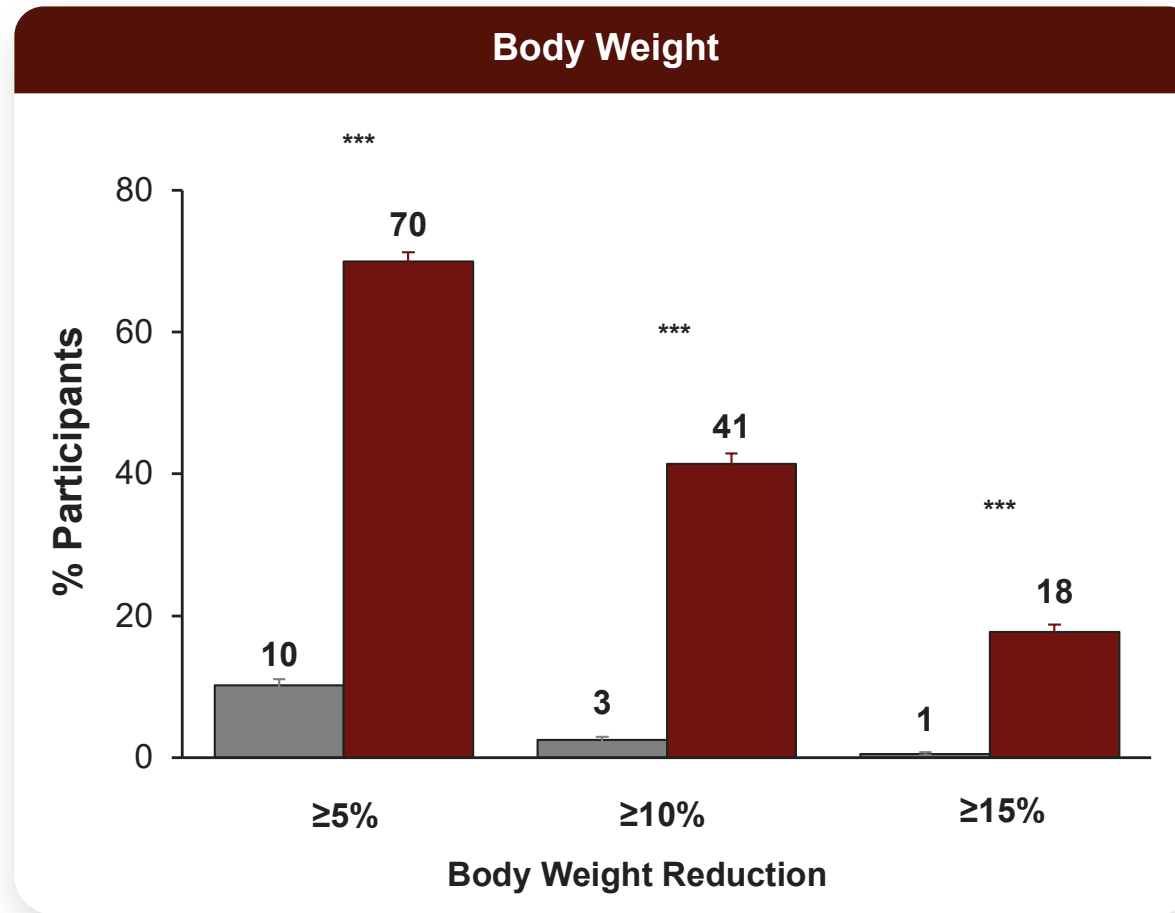
OFG MTD vs. insulin glargine: *** $p < 0.001$. p-values are for MBE change difference vs. insulin glargine.

Notes: Data in line plot are raw mean (SE); all other data are MBE (SE) unless stated otherwise. EE analysis was conducted using MMRM on randomized participants and EE data points set. TRE analysis was conducted using ANCOVA on randomized participants and TRE data points set, with missing data imputed. All analyses were pre-specified. Family-wise Type I error was controlled for Week 52.

ANCOVA=analysis of covariance; EE=efficacy estimand; 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; TRE=treatment regimen estimand.

Proportion of Participants Achieving Body Weight Targets at 52 weeks (efficacy estimand)



■ Insulin glargine ■ OFG MTD

OFG vs. insulin glargine: *** $p < 0.001$. p-values are for risk difference vs. insulin glargine.

Notes: Data are MBE (SE). EE analysis was conducted using logistic regression model on randomized participants and EE data points set, with missing data imputed. All analyses were pre-specified. Family-wise Type I error was not controlled.

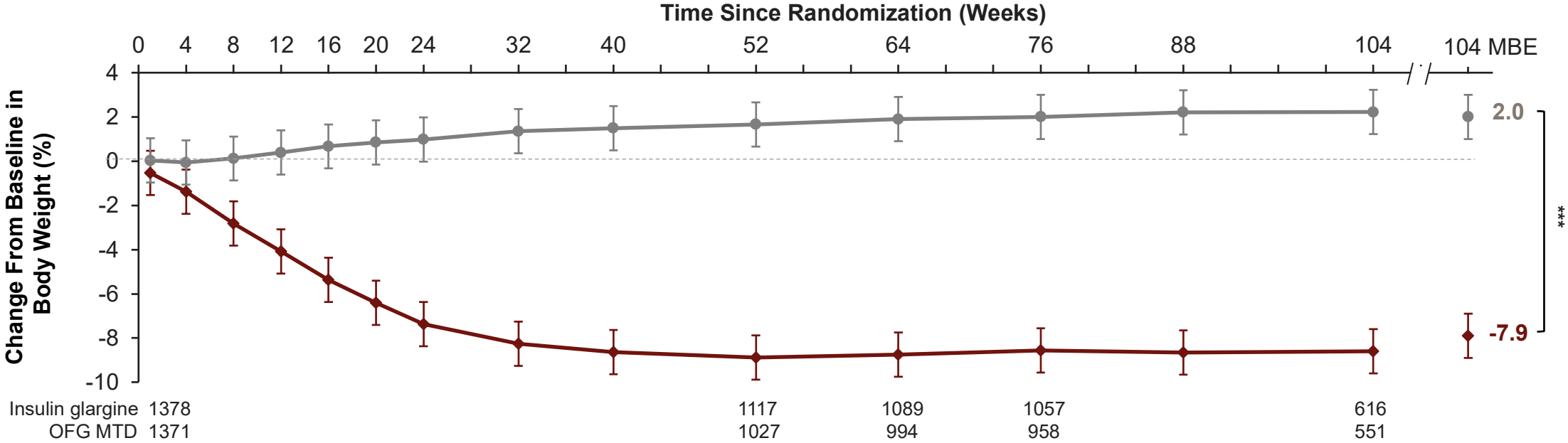
CI=confidence interval; EE=efficacy estimand; HbA1c=hemoglobin A1c; MBE=model-based estimate; MTD=maximum tolerated dose;

N=total number of randomized participants; OFG=orforglipron; SE=standard error.

Maintenance of Clinically Meaningful Weight Loss Observed Through 2 years with Orforglipron

Efficacy Estimand

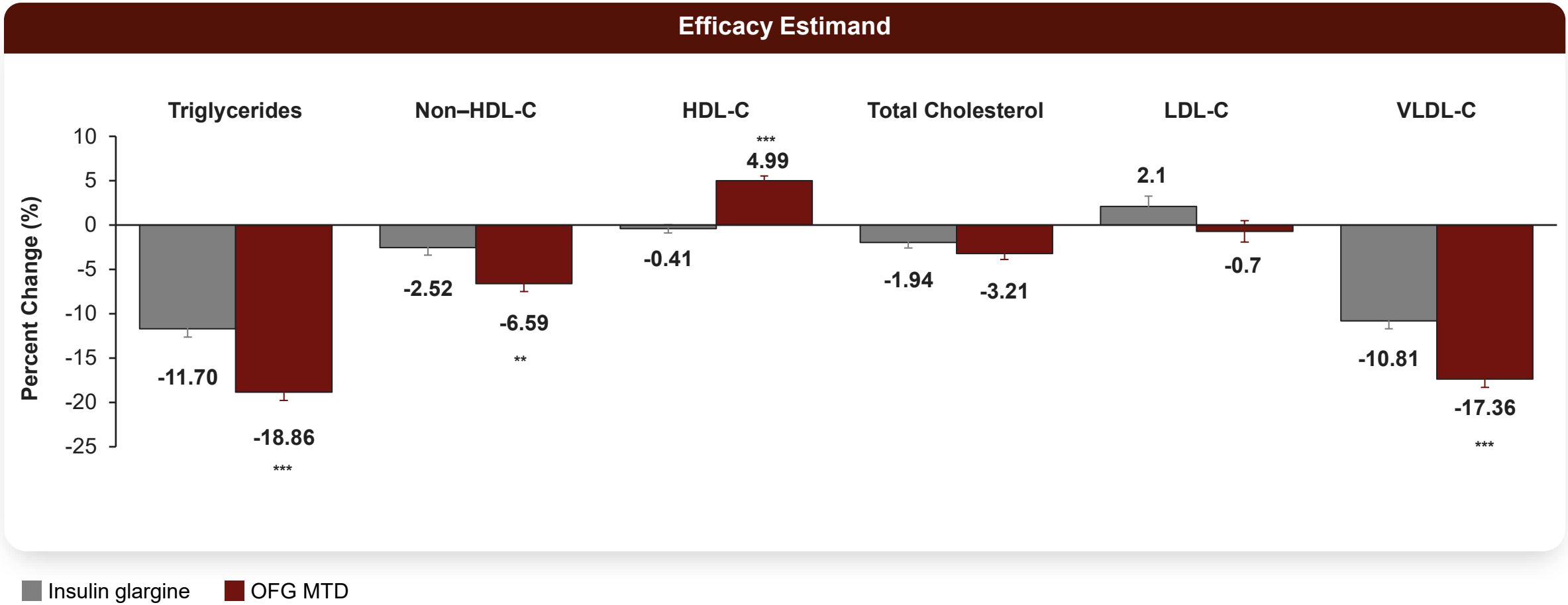
Overall mean body weight at baseline = 90.91 (20.04) kg



■ Insulin glargine ■ OFG MTD

OFG MTD vs. insulin glargine: ***p<0.001. p-values are for MBE change difference vs. insulin glargine.
Notes: Data in line plot are raw mean (SE); all other data are MBE (SE) unless stated otherwise. EE analysis was conducted using MMRM on randomized participants and EE data points set. All analyses were pre-specified. Family-wise Type I error was not controlled for Week 76. More details in slide notes.
EE=efficacy estimand; 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.

Favorable Lipid Profile Changes were Sustained Through Week 52

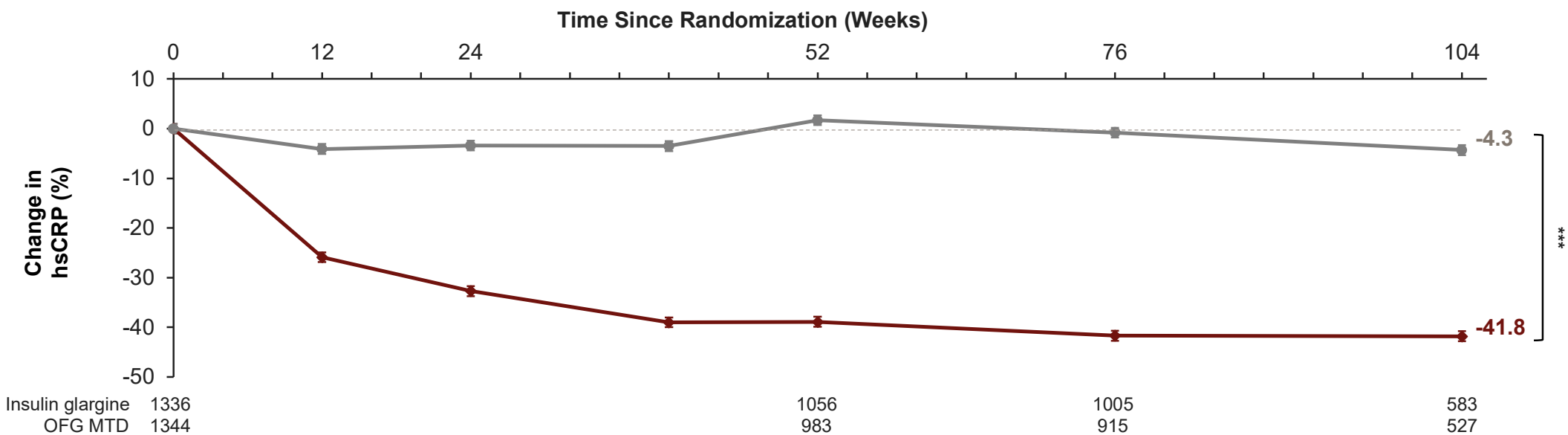


OFG MTD vs. insulin glargine: **p<0.01, ***p<0.001. p-values are for MBE change difference vs. insulin glargine.
Note: Data are MBE (SE).
HDL-C=high-density lipoprotein-cholesterol; LDL-C=low-density lipoprotein-cholesterol; MBE=model-based estimate;
MTD=maximum tolerated dose; N=total number of randomized participants; OFG=orforglipron; SD=standard deviation; SE=standard error;
VLDL-C=very low-density lipoprotein-cholesterol.

Reductions in Inflammatory Markers were Observed with Orforglipron

Efficacy Estimand

Overall geometric mean (CV[%]) hsCRP at baseline = 2.24 (183.449) mg/L



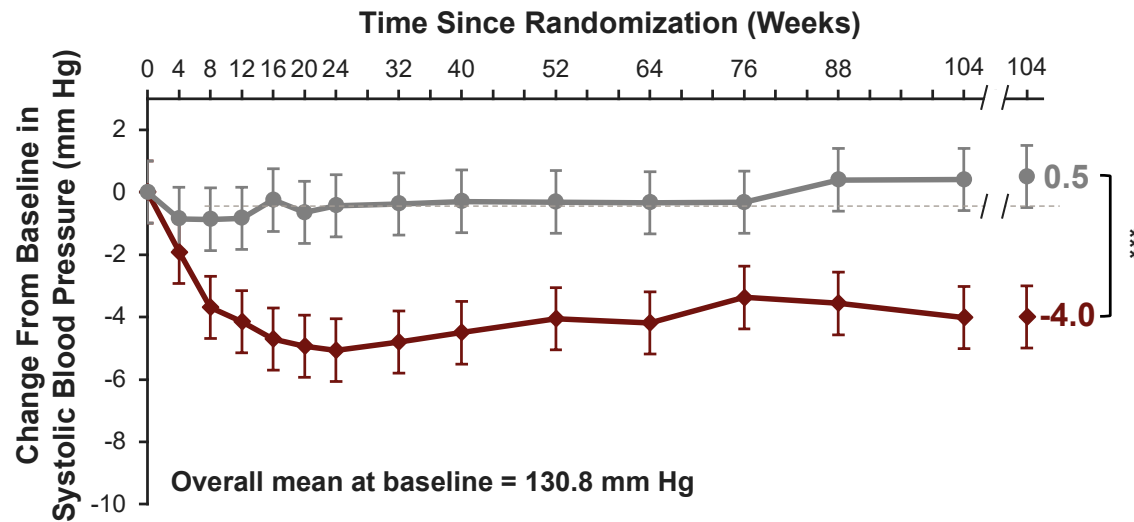
■ Insulin glargine ■ OFG MTD

OFG MTD vs. insulin glargine: ***p<0.001. p-values are for MBE change difference vs. insulin glargine.
Data in line plot are MBE (SE). EE analysis was conducted using MMRM on randomized participants and EE data points set. Family-wise Type I error was not controlled.
EE=efficacy estimand; hsCRP=high-sensitivity C-reactive protein; MBE=model-based estimate; MMRM=mixed model for repeated measures; MTD=maximum tolerated dose; N=total number of randomized participants; OFG=orforglipron

Changes in Blood Pressure

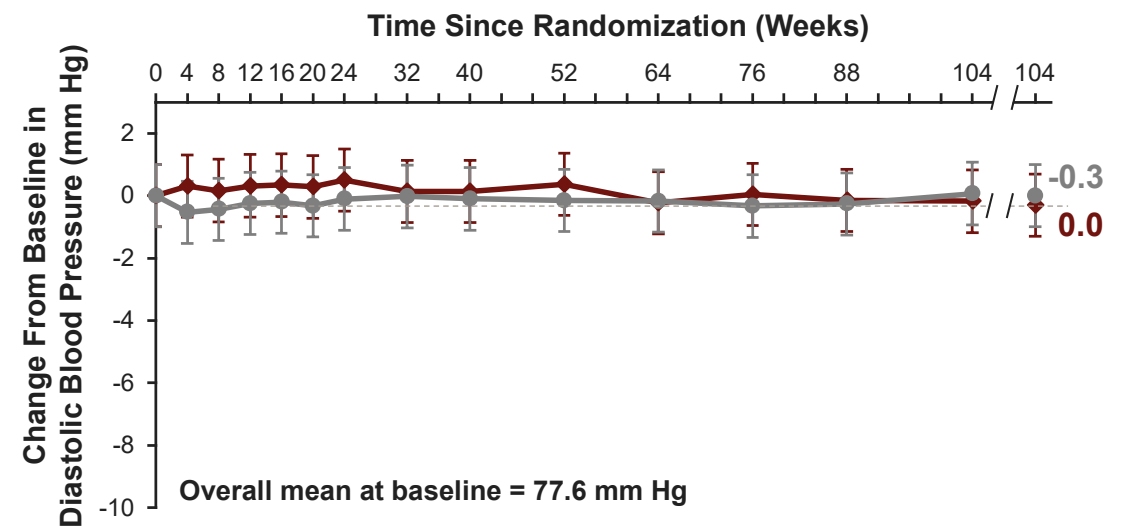
Efficacy Estimand

Systolic Blood Pressure



Insulin glargine	1378	1118	1090	1059	616
OFG MTD	1371	1027	994	959	551

Diastolic Blood Pressure



Insulin glargine	1378	1118	1090	1059	616
OFG MTD	1371	1027	994	959	551

■ Insulin glargine ■ OFG MTD

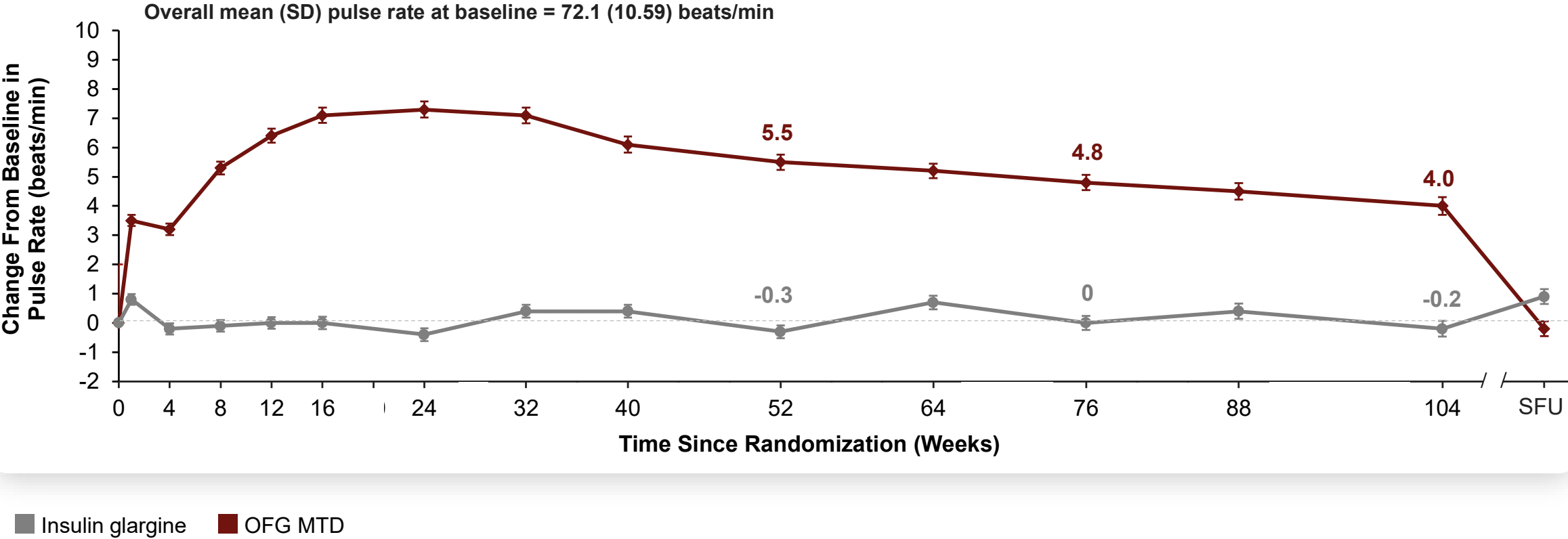
OFG MTD vs. insulin glargine: *** $p < 0.001$. p-values are for MBE change difference vs. insulin glargine.

Notes: Data in line plots are raw mean (SE); all other data are MBE (SE) unless stated otherwise. Analysis was conducted using MMRM on randomized participants and EE data points set. Family-wise Type I error was not controlled.

EE=efficacy estimand; MBE=model-based estimate; MMRM=mixed model for repeated measures; MTD=maximum tolerated dose; N=number of participants; OFG=orforglipron

Pulse Rate Changes

Estimand Guiding Safety (N=2726)



Notes: Data are MBE (SE) unless stated otherwise. Safety analysis was conducted using MMRM on safety participants and safety data points set. MBE=model-based estimate; MMRM=mixed model for repeated measures; MTD=maximum tolerated dose; N=total number of participants in the estimand guiding safety data set; OFG=orforglipron; SD=standard deviation; SE=standard error; SFU=safety follow-up visit.

Safety Overview

Safety Event, n (%)	Insulin Glargine (N=1355)	OFG MTD (N=1371)
Death ^a	43 (3.2)	19 (1.4)
Participants with ≥1 TEAE	922 (68.0)	1129 (82.3)
Participants with ≥1 serious AE	255 (18.8)	222 (16.2)
Discontinuation from study treatment due to AE	73 (5.4)	211 (15.4)
Discontinuation from study due to AE	49 (3.6)	42 (3.1)

^aDeath is also included as serious AE and discontinuations due to AE.
Notes: Data are reported for the safety data points set. Safety population defined as all participants who were randomly assigned a study intervention and who received ≥1 dose of study intervention.
AE=adverse event; MTD=maximum tolerated dose; n=number of participants with events meeting specified criteria;
N=number of participants in analysis population; OFG=orforglipron; TEAE=treatment-emergent AE.

Safety Overview

Safety Event, n (%)	Insulin Glargine (N=1355)	OFG MTD (N=1371)
Death ^a	43 (3.2)	19 (1.4)
Participants with ≥1 TEAE	922 (68.0)	1129 (82.3)
Participants with ≥1 serious AE	255 (18.8)	222 (16.2)
Discontinuation from study treatment due to AE	73 (5.4)	211 (15.4)
Discontinuation from study due to AE	49 (3.6)	42 (3.1)

^aDeath is also included as serious AE and discontinuations due to AE.
Notes: Data are reported for the safety data points set. Safety population defined as all participants who were randomly assigned a study intervention and who received ≥1 dose of study intervention.
AE=adverse event; MTD=maximum tolerated dose; n=number of participants with events meeting specified criteria;
N=number of participants in analysis population; OFG=orforglipron; TEAE=treatment-emergent AE.

Safety Overview

Safety Event, n (%)	Insulin Glargine (N=1355)	OFG MTD (N=1371)
Death ^a	43 (3.2)	19 (1.4)
Participants with ≥1 TEAE	922 (68.0)	1129 (82.3)
Participants with ≥1 serious AE	255 (18.8)	222 (16.2)
Discontinuation from study treatment due to AE	73 (5.4)	211 (15.4)
Discontinuation from study due to AE	49 (3.6)	42 (3.1)

^aDeath is also included as serious AE and discontinuations due to AE.
Notes: Data are reported for the safety data points set. Safety population defined as all participants who were randomly assigned a study intervention and who received ≥1 dose of study intervention.
AE=adverse event; MTD=maximum tolerated dose; n=number of participants with events meeting specified criteria;
N=number of participants in analysis population; OFG=orforglipron; TEAE=treatment-emergent AE.

Safety Overview

Safety Event, n (%)	Insulin Glargine (N=1355)	OFG MTD (N=1371)
Death ^a	43 (3.2)	19 (1.4)
Participants with ≥1 TEAE	922 (68.0)	1129 (82.3)
Participants with ≥1 serious AE	255 (18.8)	222 (16.2)
Discontinuation from study treatment due to AE	73 (5.4)	211 (15.4)
Discontinuation from study due to AE	49 (3.6)	42 (3.1)

^aDeath is also included as serious AE and discontinuations due to AE.
Notes: Data are reported for the safety data points set. Safety population defined as all participants who were randomly assigned a study intervention and who received ≥1 dose of study intervention.
AE=adverse event; MTD=maximum tolerated dose; n=number of participants with events meeting specified criteria;
N=number of participants in analysis population; OFG=orforglipron; TEAE=treatment-emergent AE.

GI-related Treatment Emergent AEs were common with Orforglipron

Safety Event, n (%)	Insulin Glargine (N=1355)	OFG MTD (N=1371)
TEAEs in ≥5% of participants		
Nausea	19 (1.4)	438 (31.9)
Vomiting	22 (1.6)	288 (21.0)
Diarrhea	66 (4.9)	280 (20.4)
Decreased appetite	5 (0.4)	175 (12.8)
Constipation	19 (1.4)	174 (12.7)
Dyspepsia	13 (1.0)	146 (10.6)
Abdominal distension	6 (0.4)	93 (6.8)
Diabetic retinopathy	86 (6.3)	79 (5.8)
Hypertension	73 (5.4)	59 (4.3)

Notes: Data are reported for the safety data points set. Safety population defined as all participants who were randomly assigned a study intervention and who received ≥1 dose of study intervention.
MTD=maximum tolerated dose; n=number of participants with events meeting specified criteria; N=number of participants in analysis population; OFG=orforglipron; TEAE=treatment-emergent adverse event.

GI-related Treatment Emergent AEs were common with Orforglipron

Safety Event, n (%)	Insulin Glargine (N=1355)	OFG MTD (N=1371)
TEAEs in ≥5% of participants		
Nausea	19 (1.4)	438 (31.9)
Vomiting	22 (1.6)	288 (21.0)
Diarrhea	66 (4.9)	280 (20.4)
Decreased appetite	5 (0.4)	175 (12.8)
Constipation	19 (1.4)	174 (12.7)
Dyspepsia	13 (1.0)	146 (10.6)
Abdominal distension	6 (0.4)	93 (6.8)
Diabetic retinopathy	86 (6.3)	79 (5.8)
Hypertension	73 (5.4)	59 (4.3)

Notes: Data are reported for the safety data points set. Safety population defined as all participants who were randomly assigned a study intervention and who received ≥1 dose of study intervention.
MTD=maximum tolerated dose; n=number of participants with events meeting specified criteria; N=number of participants in analysis population; OFG=orforglipron; TEAE=treatment-emergent adverse event.

GI-related Treatment Emergent AEs were common with Orforglipron

Safety Event, n (%)	Insulin Glargine (N=1355)	OFG MTD (N=1371)
TEAEs in ≥5% of participants		
Nausea	19 (1.4)	438 (31.9)
Vomiting	22 (1.6)	288 (21.0)
Diarrhea	66 (4.9)	280 (20.4)
Decreased appetite	5 (0.4)	175 (12.8)
Constipation	19 (1.4)	174 (12.7)
Dyspepsia	13 (1.0)	146 (10.6)
Abdominal distension	6 (0.4)	93 (6.8)
Diabetic retinopathy	86 (6.3)	79 (5.8)
Hypertension	73 (5.4)	59 (4.3)

Notes: Data are reported for the safety data points set. Safety population defined as all participants who were randomly assigned a study intervention and who received ≥1 dose of study intervention.
MTD=maximum tolerated dose; n=number of participants with events meeting specified criteria; N=number of participants in analysis population; OFG=orforglipron; TEAE=treatment-emergent adverse event.

GI-related Treatment Emergent AEs were common with Orforglipron

Safety Event, n (%)	Insulin Glargine (N=1355)	OFG MTD (N=1371)
TEAEs in ≥5% of participants		
Nausea	19 (1.4)	438 (31.9)
Vomiting	22 (1.6)	288 (21.0)
Diarrhea	66 (4.9)	280 (20.4)
Decreased appetite	5 (0.4)	175 (12.8)
Constipation	19 (1.4)	174 (12.7)
Dyspepsia	13 (1.0)	146 (10.6)
Abdominal distension	6 (0.4)	93 (6.8)
Diabetic retinopathy	86 (6.3)	79 (5.8)
Hypertension	73 (5.4)	59 (4.3)

Notes: Data are reported for the safety data points set. Safety population defined as all participants who were randomly assigned a study intervention and who received ≥1 dose of study intervention.
MTD=maximum tolerated dose; n=number of participants with events meeting specified criteria; N=number of participants in analysis population; OFG=orforglipron; TEAE=treatment-emergent adverse event.

GI-related Treatment Emergent AEs were common with Orforglipron

Safety Event, n (%)	Insulin Glargine (N=1355)	OFG MTD (N=1371)
TEAEs in ≥5% of participants		
Nausea	19 (1.4)	438 (31.9)
Vomiting	22 (1.6)	288 (21.0)
Diarrhea	66 (4.9)	280 (20.4)
Decreased appetite	5 (0.4)	175 (12.8)
Constipation	19 (1.4)	174 (12.7)
Dyspepsia	13 (1.0)	146 (10.6)
Abdominal distension	6 (0.4)	93 (6.8)
Diabetic retinopathy	86 (6.3)	79 (5.8)
Hypertension	73 (5.4)	59 (4.3)

Notes: Data are reported for the safety data points set. Safety population defined as all participants who were randomly assigned a study intervention and who received ≥1 dose of study intervention.
MTD=maximum tolerated dose; n=number of participants with events meeting specified criteria; N=number of participants in analysis population; OFG=orforglipron; TEAE=treatment-emergent adverse event.

GI-related Treatment Emergent AEs were common with Orforglipron

Safety Event, n (%)	Insulin Glargine (N=1355)	OFG MTD (N=1371)
TEAEs in ≥5% of participants		
Nausea	19 (1.4)	438 (31.9)
Vomiting	22 (1.6)	288 (21.0)
Diarrhea	66 (4.9)	280 (20.4)
Decreased appetite	5 (0.4)	175 (12.8)
Constipation	19 (1.4)	174 (12.7)
Dyspepsia	13 (1.0)	146 (10.6)
Abdominal distension	6 (0.4)	93 (6.8)
Diabetic retinopathy	86 (6.3)	79 (5.8)
Hypertension	73 (5.4)	59 (4.3)

Notes: Data are reported for the safety data points set. Safety population defined as all participants who were randomly assigned a study intervention and who received ≥1 dose of study intervention.
MTD=maximum tolerated dose; n=number of participants with events meeting specified criteria; N=number of participants in analysis population; OFG=orforglipron; TEAE=treatment-emergent adverse event.

Other AEs of Special Interest were Balanced Across the Groups

Safety Event, n (%)	Insulin Glargine (N=1355)	OFG MTD (N=1371)
All GI TEAEs	193 (14.2)	851 (62.1)
Other TEAEs of interest		
Thyroid malignancy	0	1 (0.1) ^b
Adjudicated pancreatitis	3 (0.2)	2 (0.1)
Gallbladder and biliary disorders	22 (1.6)	21 (1.5)
Cholelithiasis	11 (0.8)	12 (0.9)
Cholecystitis acute	5 (0.4)	3 (0.2)
Diabetic retinopathy, macular edema, and related complications ^a	124 (9.2)	127 (9.3)
Ischemic optic neuropathy	2 (0.1)	0
Acute renal failure	32 (2.4)	28 (2.0)

^aBased on standardized MedDRA queries. ^bAnaplastic thyroid cancer.

Notes: Data are reported for the safety data points set. Safety population defined as all participants who were randomly assigned a study intervention and who received ≥1 dose of study intervention.

GI=gastrointestinal;; MedDRA=Medical Dictionary for Regulatory Activities; MTD=maximum tolerated dose; n=number of participants with events meeting specified criteria; N=number of participants in analysis population; OFG=orforglipron; TEAE=treatment-emergent AE.

Hypoglycemia was More Frequently Observed with Insulin Glargine

Safety Event, n (%)	Insulin Glargine (N=1355)	OFG MTD (N=1371)
Hypoglycemia <54 mg/dL (Level 2) or severe hypoglycemia (Level 3)^a		
All participants	260 (19.2)	93 (6.8)
Participants on sulfonylurea at baseline	127 (25.7)	63 (12.8)
Participants not on sulfonylurea at baseline	133 (15.5)	30 (3.4)
Severe hypoglycemia (Level 3)^a		
All participants	12 (0.9)	1 (0.1)
Nocturnal hypoglycemia^b (Level 2 or Level 3)	143 (10.6)	37 (2.7)

^aSevere hypoglycemia is characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. Numbers for hypoglycemia exclude hypoglycemic events occurring after initiation of any new anti-hyperglycemic therapy. ^bHypoglycemia event (including severe hypoglycemia) that occurs at night and presumably during sleep.

Notes: Data are reported for the safety data points set. Safety population defined as all participants who were randomly assigned a study intervention and who received ≥1 dose of study intervention.

AE=adverse event; MTD=maximum tolerated dose; n=number of participants with events meeting specified criteria; N=number of participants in analysis population; OFG=orforglipron

Hypoglycemia was More Frequently Observed with Insulin Glargine

Safety Event, n (%)	Insulin Glargine (N=1355)	OFG MTD (N=1371)
Hypoglycemia <54 mg/dL (Level 2) or severe hypoglycemia (Level 3)^a		
All participants	260 (19.2)	93 (6.8)
Participants on sulfonylurea at baseline	127 (25.7)	63 (12.8)
Participants not on sulfonylurea at baseline	133 (15.5)	30 (3.4)
Severe hypoglycemia (Level 3)^a		
All participants	12 (0.9)	1 (0.1)
Nocturnal hypoglycemia^b (Level 2 or Level 3)	143 (10.6)	37 (2.7)

^aSevere hypoglycemia is characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. Numbers for hypoglycemia exclude hypoglycemic events occurring after initiation of any new anti-hyperglycemic therapy. ^bHypoglycemia event (including severe hypoglycemia) that occurs at night and presumably during sleep.

Notes: Data are reported for the safety data points set. Safety population defined as all participants who were randomly assigned a study intervention and who received ≥1 dose of study intervention.

AE=adverse event; MTD=maximum tolerated dose; n=number of participants with events meeting specified criteria; N=number of participants in analysis population; OFG=orforglipron

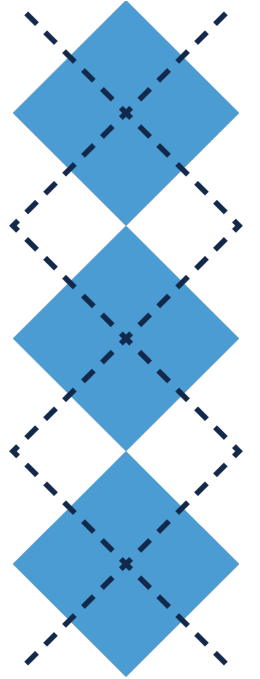
Summary of ACHIEVE-4

- Orforglipron was non-inferior to insulin glargine for MACE-4: HR 0.84 (95% CI, 0.59 – 1.20)
- Superiority for MACE-3 not achieved: HR 0.77 (95% CI, 0.52 – 1.13)
- Orforglipron provided superior HbA1c and body weight reductions at 52 weeks with sustained improvements for ≥ 2 years
- Cardiometabolic markers (lipids, hsCRP) improved compared to insulin glargine
- Overall safety profile generally consistent with the GLP-1 receptor agonists

Orforglipron, the first small molecule GLP-1 RA, was not associated with a higher incidence of cardiovascular events versus insulin glargine and showed clinically relevant improvements in glycemia and bodyweight.

Thank you!

We would like to send gratitude to all the trial participants, investigators, and site staff.



**School of
Medicine**