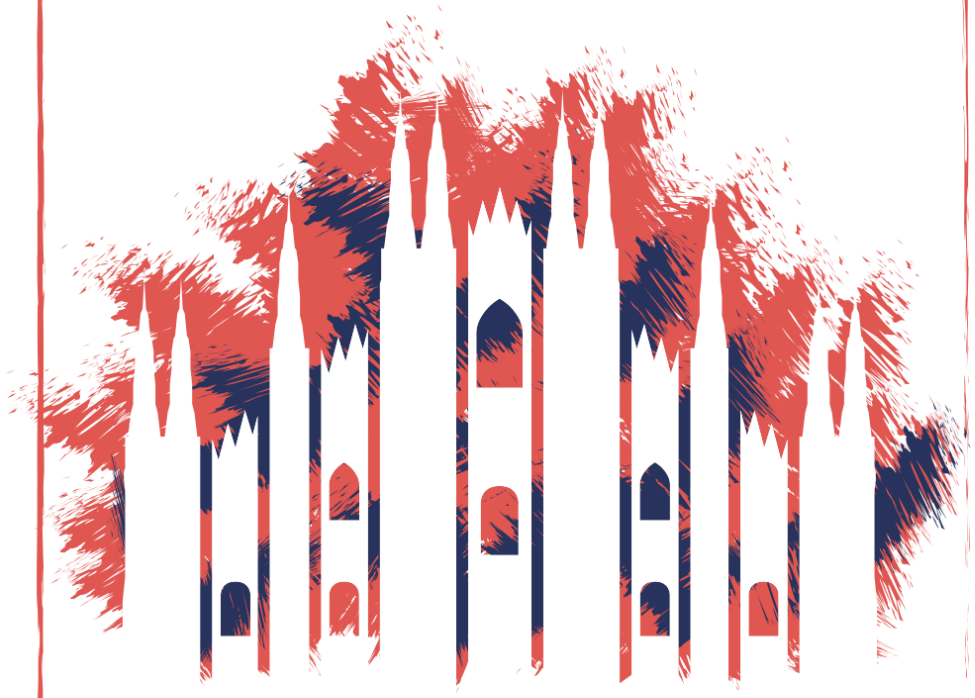
62nd Annual Meeting

European Association for the Study of Diabetes



EASD 2026

28 September
02 October

Milan
Italy

Tirzepatide Improved Markers of β-Cell Function and Insulin Sensitivity in Early Type 2 Diabetes: Pre-Specified Analysis of the 2-Year Results of SURPASS-EARLY

Steven E. Kahn,[1] Vivian Thieu,[2] Robert J. Heine,[2] Andrea Mari,[3] Palash Sharma,[2] Meltem Zeytinoglu,[2] Jacek Kiljanski,[2] Elizabeth LaBell,[2] Francesco Giorgino[4]

[1]University of Washington, Seattle, WA, USA; [2]Eli Lilly and Company, Indianapolis, IN, USA; [3]CNR Institute of Neuroscience, Padova, Italy; [4]University of Bari Aldo Moro, Bari, Italy

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

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BACKGROUND AND OBJECTIVES

- T2D is driven by two core defects: β-cell dysfunction and insulin resistance;[1] more than 80% of β-cell function is already lost at diagnosis.[2]
- In SURPASS-EARLY, tirzepatide treatment resulted in higher rates of normoglycaemia and greater or superior weight reduction vs optimized intensified conventional care (ICC) at 2 years in people with type 2 diabetes for <4 years.[3]
  - ICC included DPP-4 inhibitors, insulin, sulfonylureas, SGLT2 inhibitors, and GLP-1 RAs.
  - ICC treatments were used in accordance with the standard of care with the aim of achieving non-diabetic blood glucose levels.
- This pre-specified analysis asks the mechanistic question:

1. Kahn SE. *Diabetologia*. 2003;46:3-19. 2. Esser N, et al.. *Diabetologia*. 2020;63:2007-2021. 3. Del Prato S, et al. *Ann Intern Med.* 2026; 179(7):917-928

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BACKGROUND AND OBJECTIVES

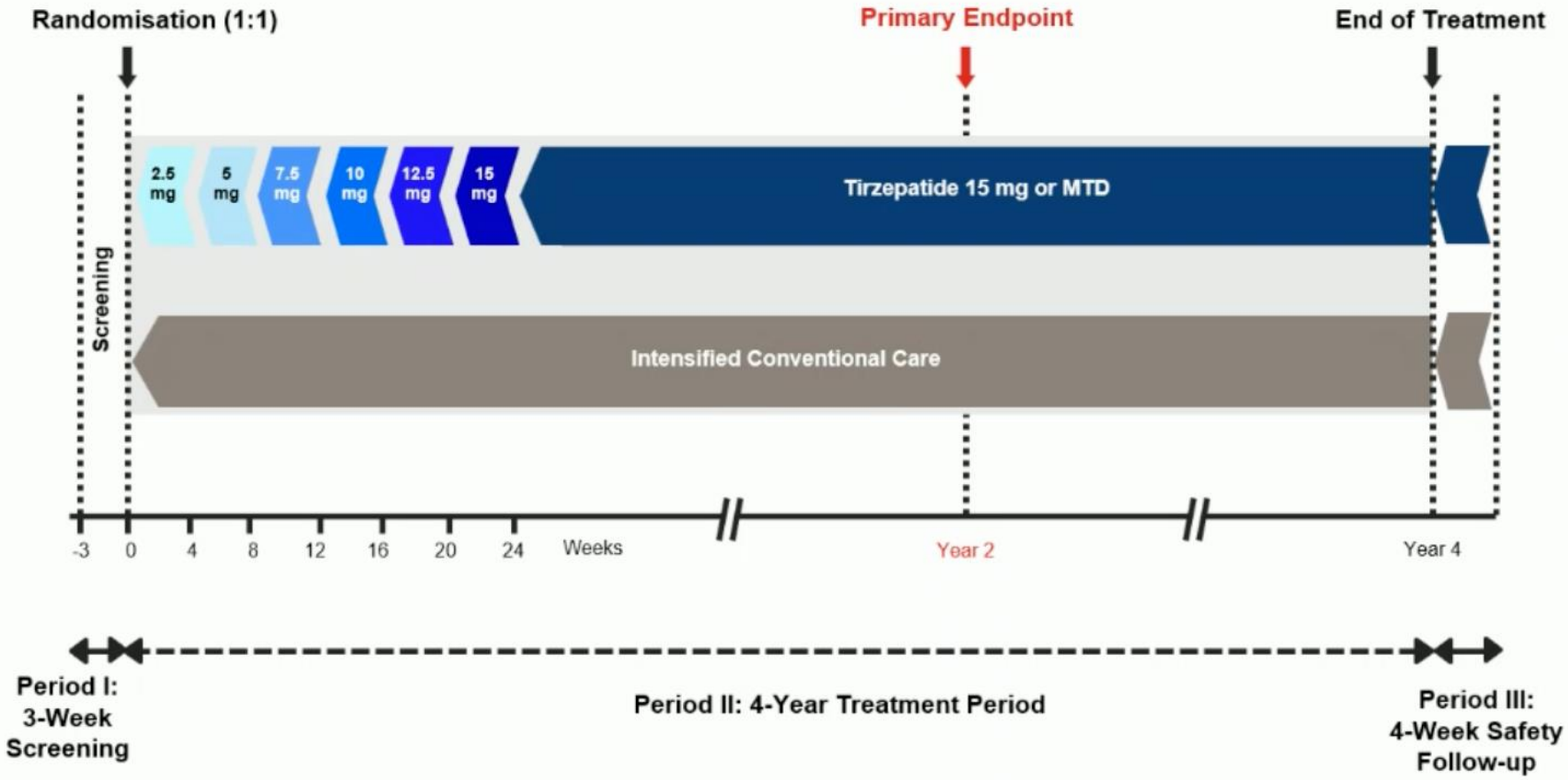
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- In SURPASS-EARLY, tirzepatide treatment resulted in higher rates of normoglycaemia and greater or superior weight reduction vs optimized intensified conventional care (ICC) at 2 years in people with type 2 diabetes for <4 years.[3]
  - ICC included DPP-4 inhibitors, insulin, sulfonylureas, SGLT2 inhibitors, and GLP-1 RAs.
  - ICC treatments were used in accordance with the standard of care with the aim of achieving non-diabetic blood glucose levels.
- This pre-specified analysis asks the mechanistic question:

Can the superior and durable (2 yr) glycaemic control be attributed to improvements in β-cell function and/or insulin sensitivity?

1. Kahn SE. *Diabetologia*. 2003;46:3-19. 2. Esser N, et al.. *Diabetologia*. 2020;63:2007-2021. 3. Del Prato S, et al. *Ann Intern Med*. 2026; 179(7):917-928

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SURPASS-EARLY STUDY DESIGN

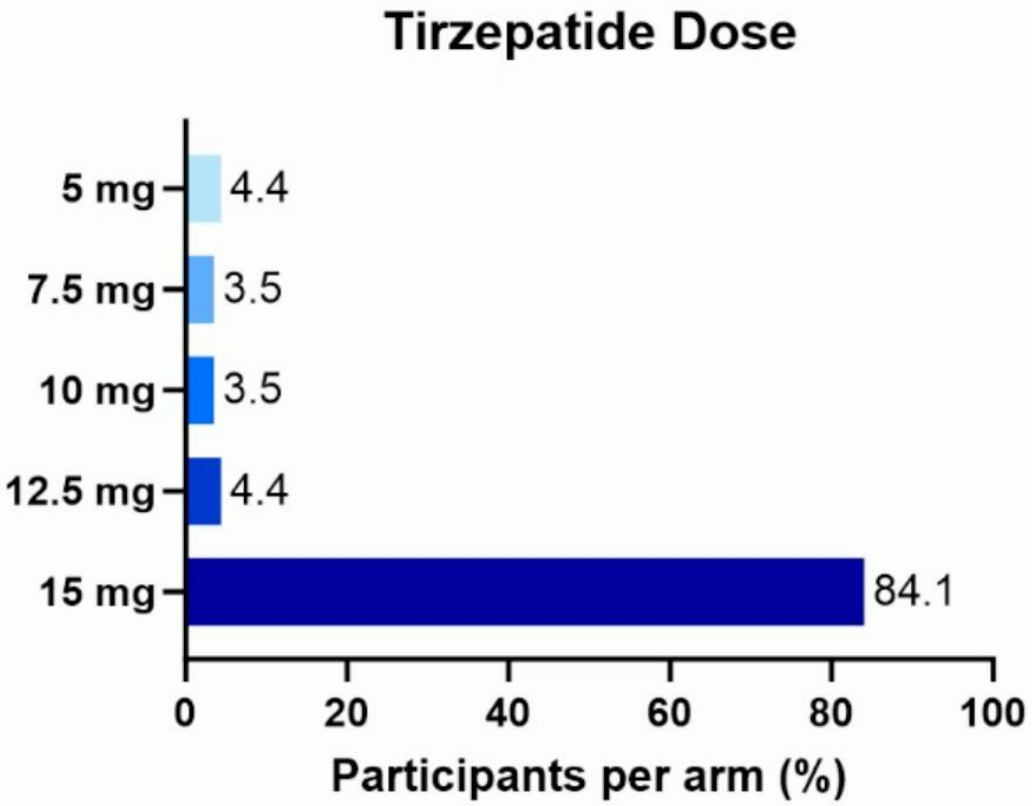


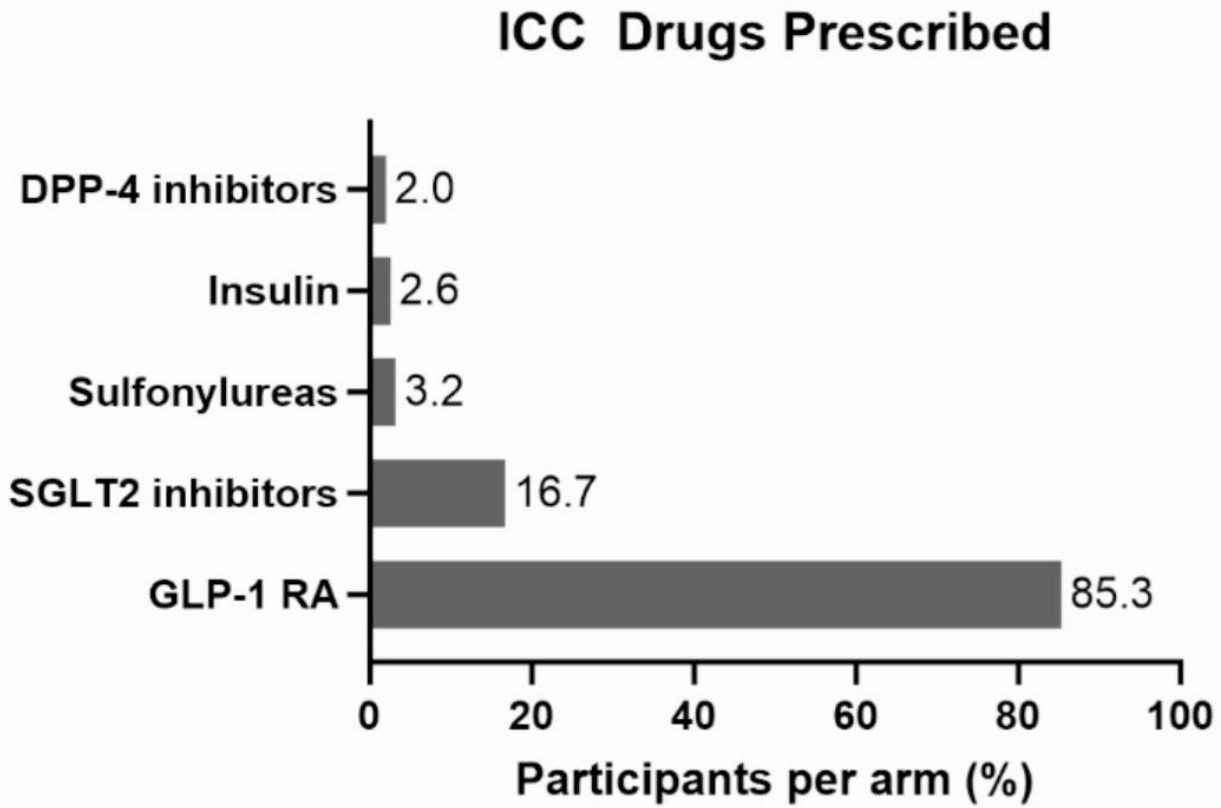
Key eligibility criteria: diagnosed with T2D in the last 4 years, on stable metformin treatment only ≥90 days preceding Visit 1, no history of cardiovascular conditions or at high-risk for cardiovascular disease. Mean diabetes duration=2.6 years (tirzepatide 15 mg or MTD=2.5 years, ICC=2.7 years).

Del Prato S, et al. *Ann Intern Med.* 2026; 179(7):917-928

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TREATMENT EXPOSURE AT WEEK 104 WITH METFORMIN AS BACKGROUND THERAPY



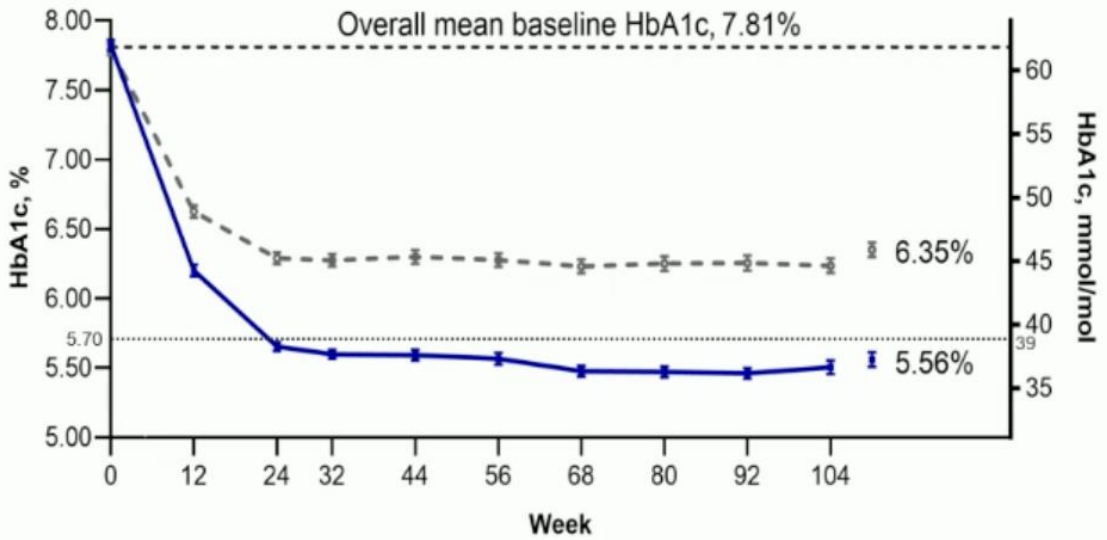


Composition of GLP-1 RAs: Injectable semaglutide =55.6%, oral semaglutide=18.2%, injectable dulaglutide=11.8%.
Results do not include metformin, since metformin is considered background therapy. Percentages may not sum to total due to rounding or use of >1 drug.
Del Prato S, et al. Ann Intern Med. 2026; 179(7):917-928

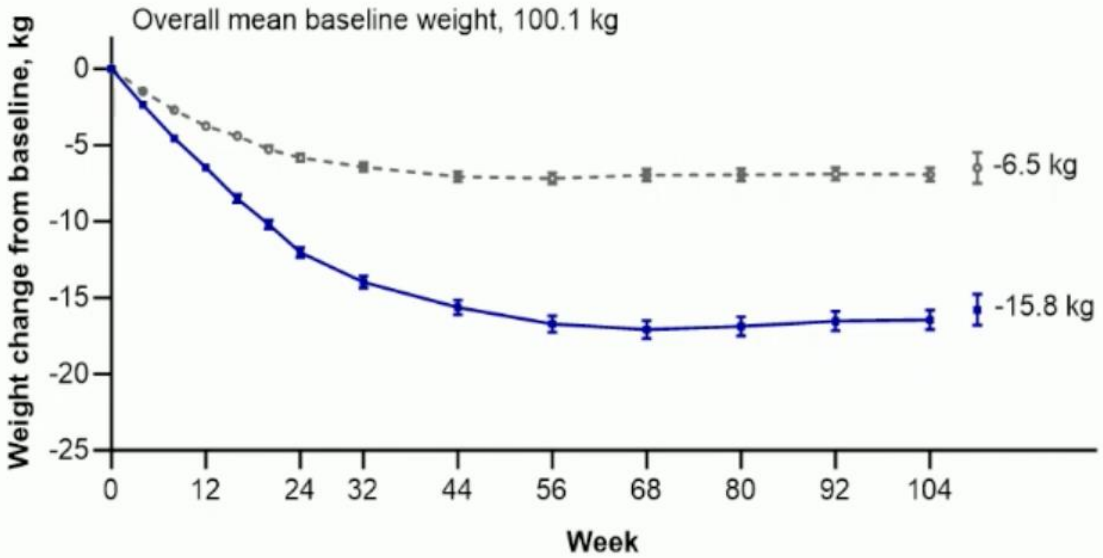
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HBA1C AND WEIGHT CHANGE OVER TIME

HbA1c



Weight



TZP 15 mg or MTD ICC

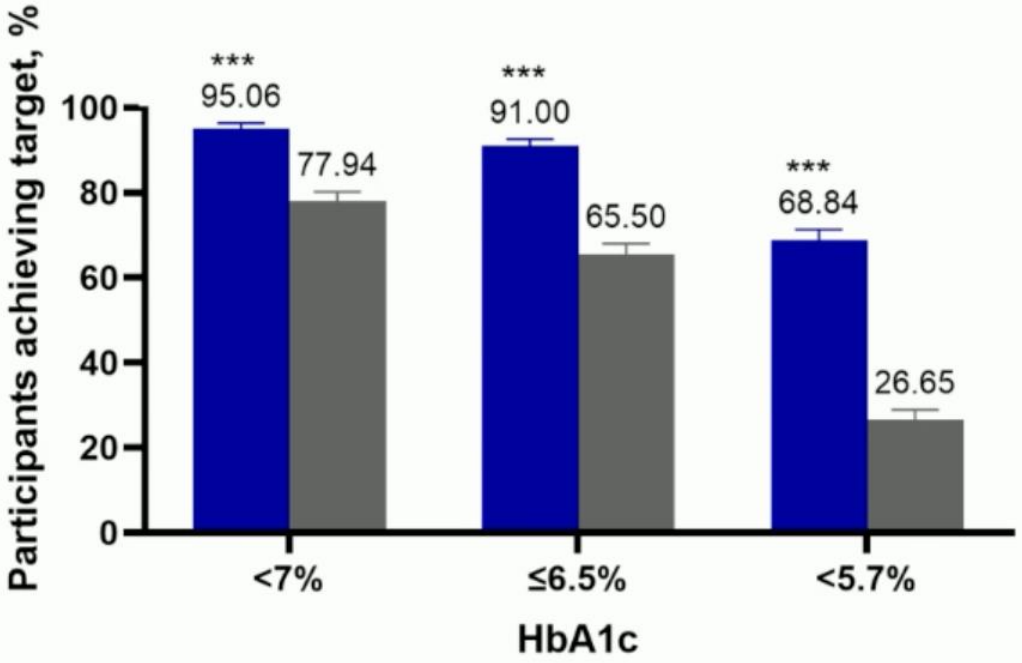
Data are raw mean (SE). All other data are MBE (SE) unless stated otherwise. EE analysis was conducted using MMRM on randomized participants and EE data points set. Pairwise comparisons are MBE (95% CI). MBE=model-based estimate.

Del Prato S, et al. Ann Intern Med. 2026; 179(7):917-928

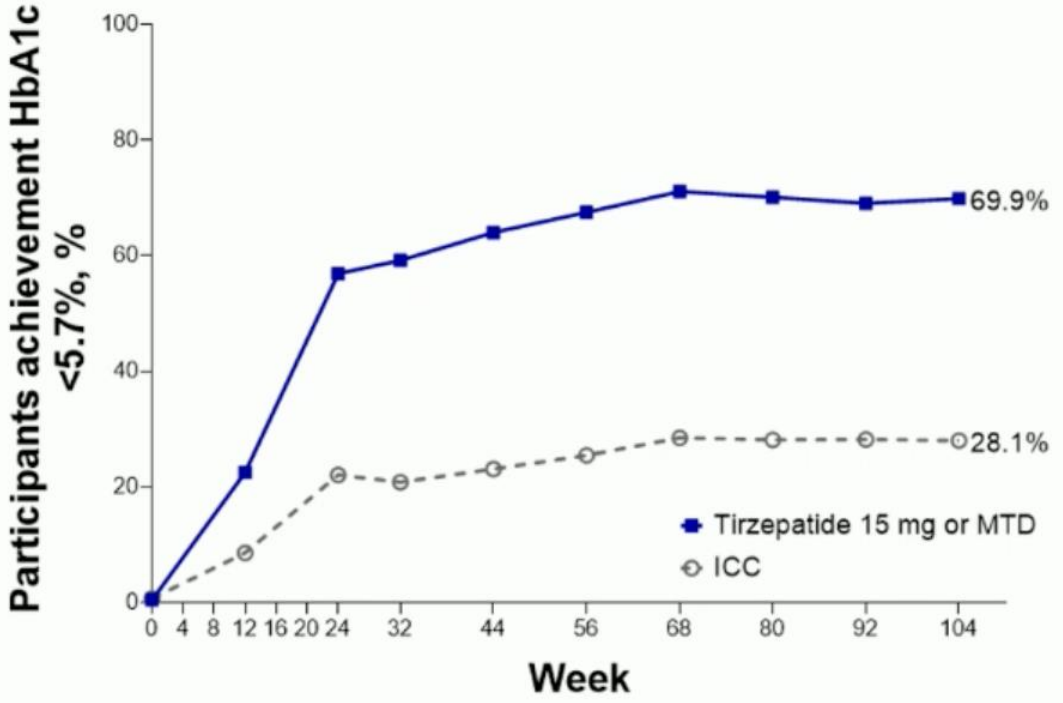
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GLYCAEMIC CONTROL AT YEAR 2

HbA1c Goals



HbA1c <5.7%



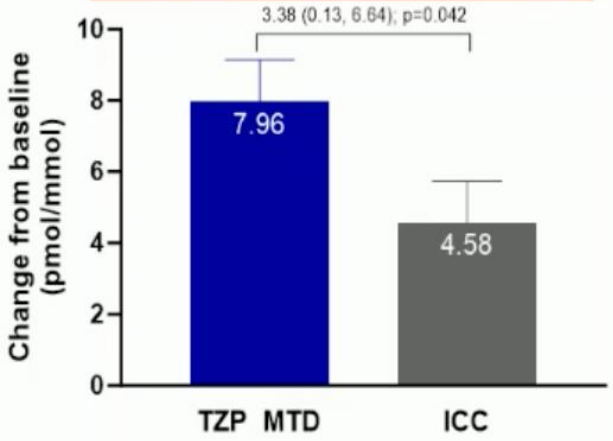
***p<0.001. p-values are for risk difference.

Notes: Data are group mean (%) (SE). EE analysis was conducted using logistic regression model on randomized participants and EE data points set. Data in right panel are observed data. HbA1 <5.7% analysis was conducted using the observed EE data point set

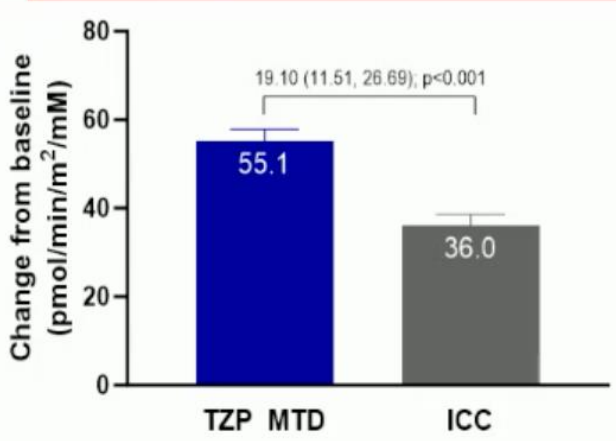
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OGTT-BASED MARKERS OF β-CELL FUNCTION AND INSULIN SENSITIVITY AT 2 YEARS

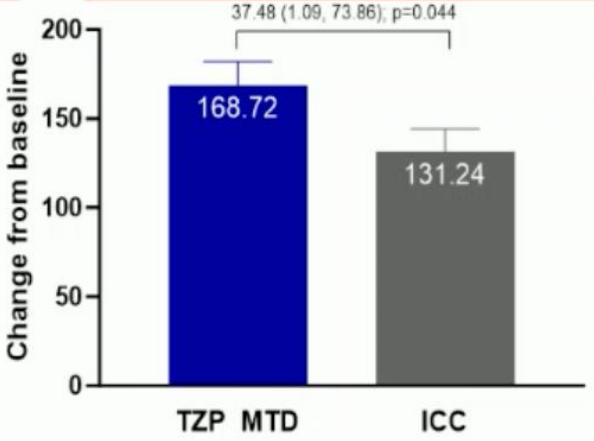
Insulinogenic Index



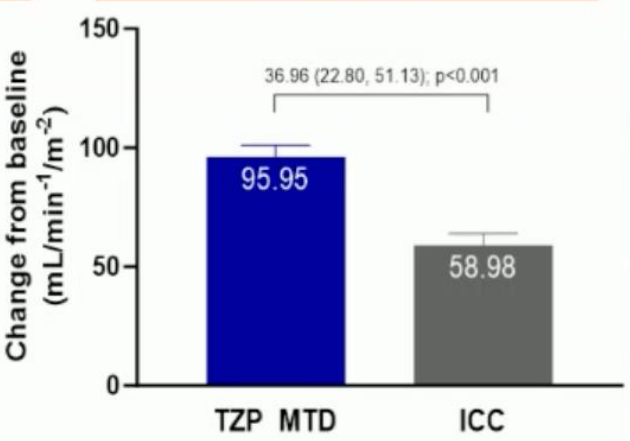
β-cell Glucose Sensitivity



ISR at 9.2 mM/l glucose



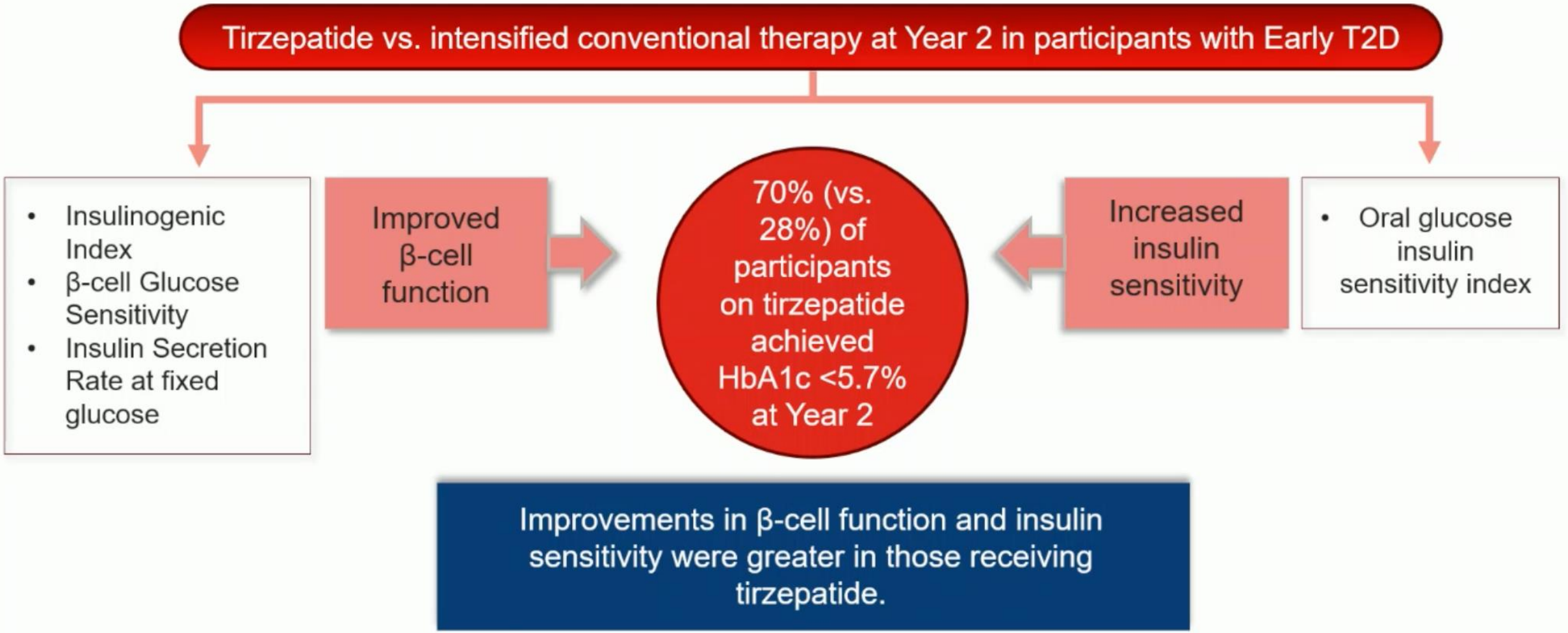
OGIS Index



Data are MBE (SE) unless stated otherwise. Pairwise comparisons are MBE (95% CI). EE analysis was conducted using ANCOVA on randomized participants and EE data points set. Some parameters are log transformed if deemed appropriate. MBE=model-based estimate

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SUMMARY



TZP was tested against an ICC arm that was 85% GLP-1 RAs, suggesting effects are beyond GLP-1 RA use alone. Open label, indirect OGTT measures, no multiplicity adjustment. Del Prato 2026 (NCT05433584).

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CONCLUSION

In this pre-specified analysis of SURPASS-EARLY, tirzepatide improved markers of beta-cell function and insulin sensitivity compared to ICC. These results suggest that tirzepatide may have an increased ability to achieve and sustain normoglycaemia for two years and suggest considering initiation of tirzepatide early in the course of the type 2 diabetes disease process.

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

Clinically Meaningful Composite Glycaemic and Weight Benefits of Tirzepatide in Youth With Type 2 Diabetes: Results From SURPASS-PEDS

Margarita Barrientos-Pérez[1], Melanie J. Davies[2], Clare Lee[3], Karthik C. Pamidipati[3], Megan O. Bensignor[4], Juan M. Maldonado[5]

[1]Hospital Angeles Puebla, Puebla City, Mexico, [2]University of Leicester, Leicester, UK; Diabetes Research Centre, University of Leicester, Leicester, UK; NIHR Leicester Biomedical Research Centre, Leicester, UK, [3]Eli Lilly and Company, Indianapolis, USA, [4]Department of Endocrinology and Diabetes, Children's National Hospital, Washington DC, USA, [5]Eli Lilly S.A., San Juan, Puerto Rico

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BACKGROUND

- Youth-onset type 2 diabetes (T2D) progresses more rapidly than adult-onset T2D, with a tendency toward rapid β-cell dysfunction and reduced response to available therapies[1-3]
- Achievement of both glycaemic and obesity-related targets is important in the treatment of youth-onset T2D[1]; however, there are limited approved glucose-lowering therapies for youths[2]
- In the SURPASS-PEDS Phase 3 trial (NCT05260021)[4] in children and adolescents with youth-onset T2D, at Week 30 tirzepatide vs. placebo demonstrated:
  - Significant improvements in glycaemic control (glycated haemoglobin [HbA1c] -2.23% vs. 0.05% [-24.4 vs. 0.5 mmol/mol])
  - Improvements in obesity-related measures (body mass index [BMI] and body weight)
  - Safety generally consistent with the established adult safety profile

1. Rodriquez IM, O'Sullivan KL. *Curr Diab Rep*. 2023;23:59-67. 2. La Grasta Sabolic L, et al. *World J Diabetes*. 2024;15:876-885.
3. Chung ST, et al. *J Clin Endocrinol Metabol*. 2024;109:e870-e872. 4. Hannon TS, et al. *Lancet*. 2025;406:1484-1496.

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SURPASS-PEDS Study Design

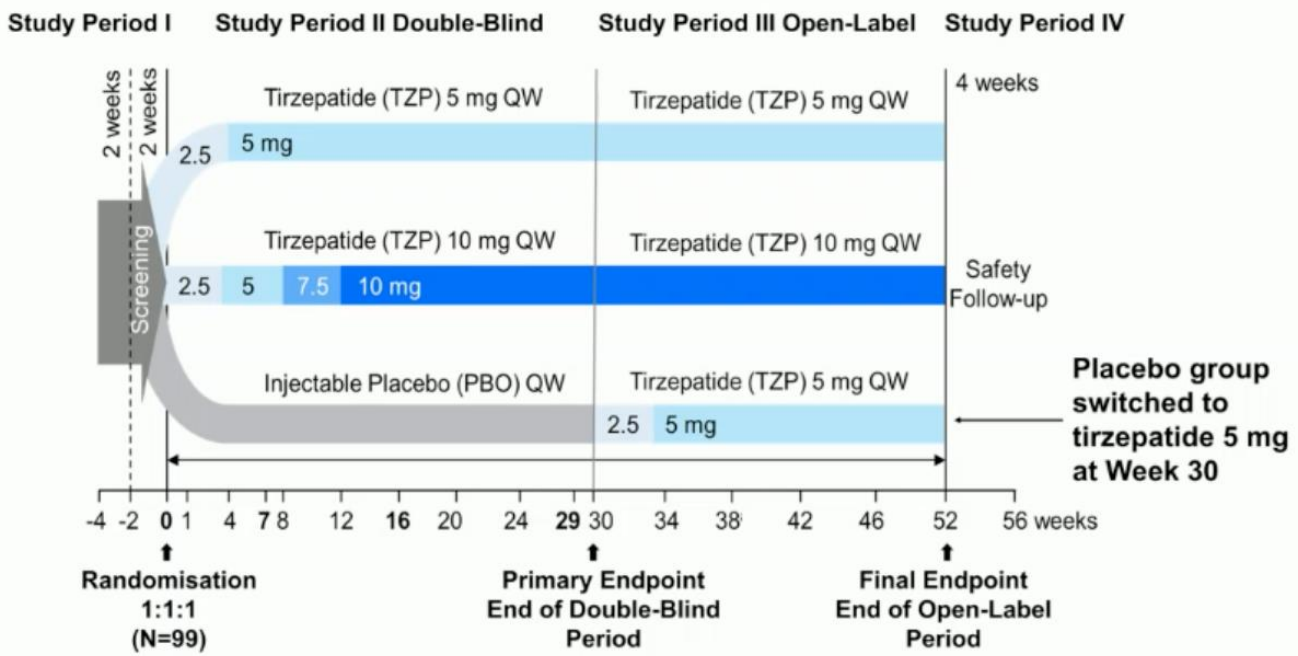
A Phase 3, double-blind, placebo-controlled, multicentre, multinational trial over 30 weeks, followed by an open-label extension for 22 weeks[1]

Key Inclusion Criteria

- Participants with youth-onset T2D (age 10 to <18 years)
- Body weight ≥50 kg and BMI >85th percentile
- HbA1c >6.5% to ≤11% at screening

Key Exclusion Criteria

- Type 1 diabetes
- History of diabetic ketoacidosis or hyperosmolar syndrome after T2D diagnosis
- ≥1 episode of hypoglycaemic unawareness within the last 6 months



1. Hannon TS, et al. *Lancet*. 2025;406:1484-1496.

BMI=body mass index; HbA1c=glycated haemoglobin; QW=once weekly; T2D=type 2 diabetes.

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OBJECTIVE

This post hoc analysis of SURPASS-PEDS assesses the achievement of composite glycaemic and weight goals in individuals with youth-onset T2D treated with tirzepatide vs. placebo

T2D=type 2 diabetes.

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Objectives of This Post hoc Analysis

- Achievement of composite outcomes at Weeks 30 and 52:
  - **HbA1c ≤6.5% without clinically significant or severe hypoglycaemia PLUS**
  - **≥5% or ≥10% reductions in BMI or body weight from baseline**
- Achievement of composite endpoints was calculated by utilising G-computation method from logistic regression model using imputed data with baseline age group, baseline anti-hyperglycaemic medication and treatment as factors

BMI=body mass index; HbA1c=glycated haemoglobin.

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Baseline Demographic Characteristics

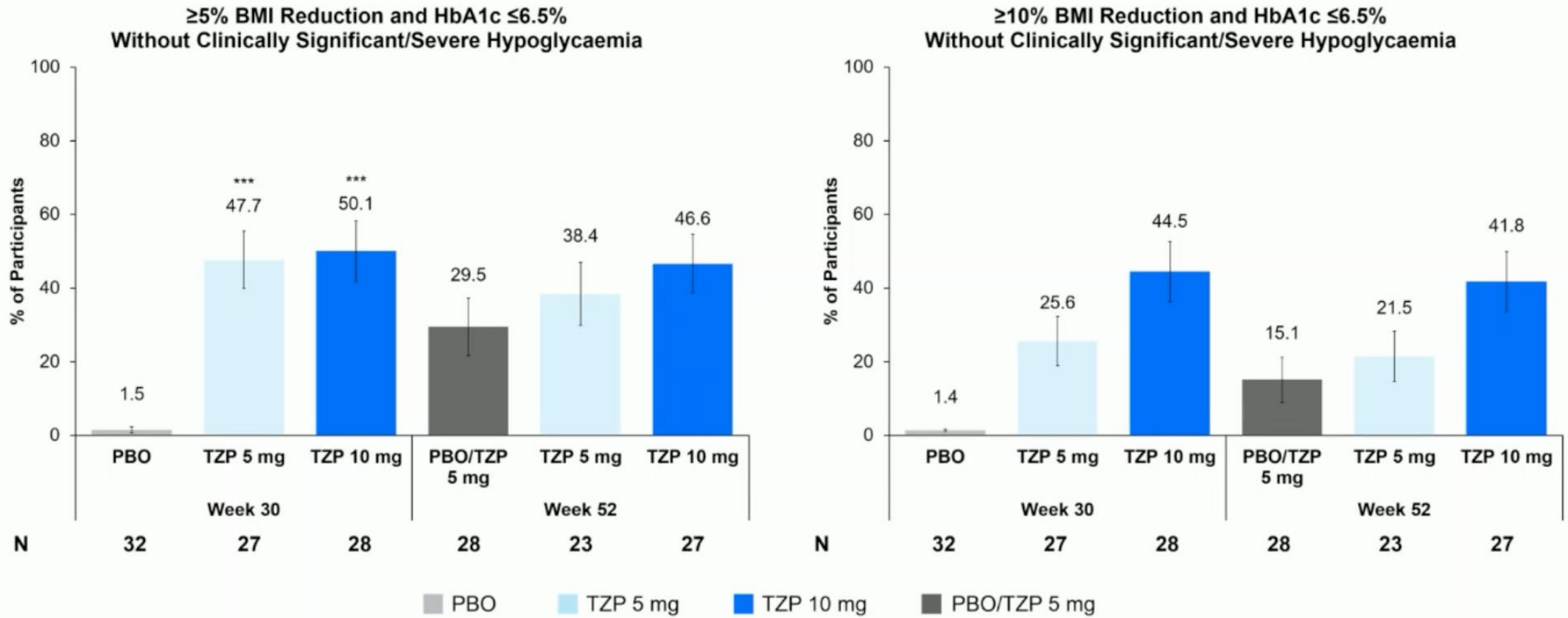
- Baseline demographics were generally well balanced across treatment groups

Characteristic	PBO/TZP 5 mg (N=34)	TZP 5 mg (N=32)	TZP 10 mg (N=33)
Age, years	14.6 (1.8)	15.0 (1.9)	14.6 (1.8)
Female, n (%)	21 (61.8)	21 (65.6)	18 (54.5)
Race, n (%)			
American Indian or Alaska Native	8 (23.5)	7 (21.9)	5 (15.2)
Asian	3 (8.8)	1 (3.1)	2 (6.1)
Black or African American	2 (5.9)	5 (15.6)	4 (12.1)
Native Hawaiian or Other Pacific Islander	0	1 (3.1)	2 (6.1)
White	21 (61.8)	17 (53.1)	19 (57.6)
Multiple	0	1 (3.1)	1 (3.0)
Ethnicity, n (%)			
Hispanic or Latino	24 (70.6)	24 (75.0)	17 (51.5)

Note: Data are mean (SD) unless stated otherwise.
PBO=placebo; SD=standard deviation; TZP=tirzepatide.

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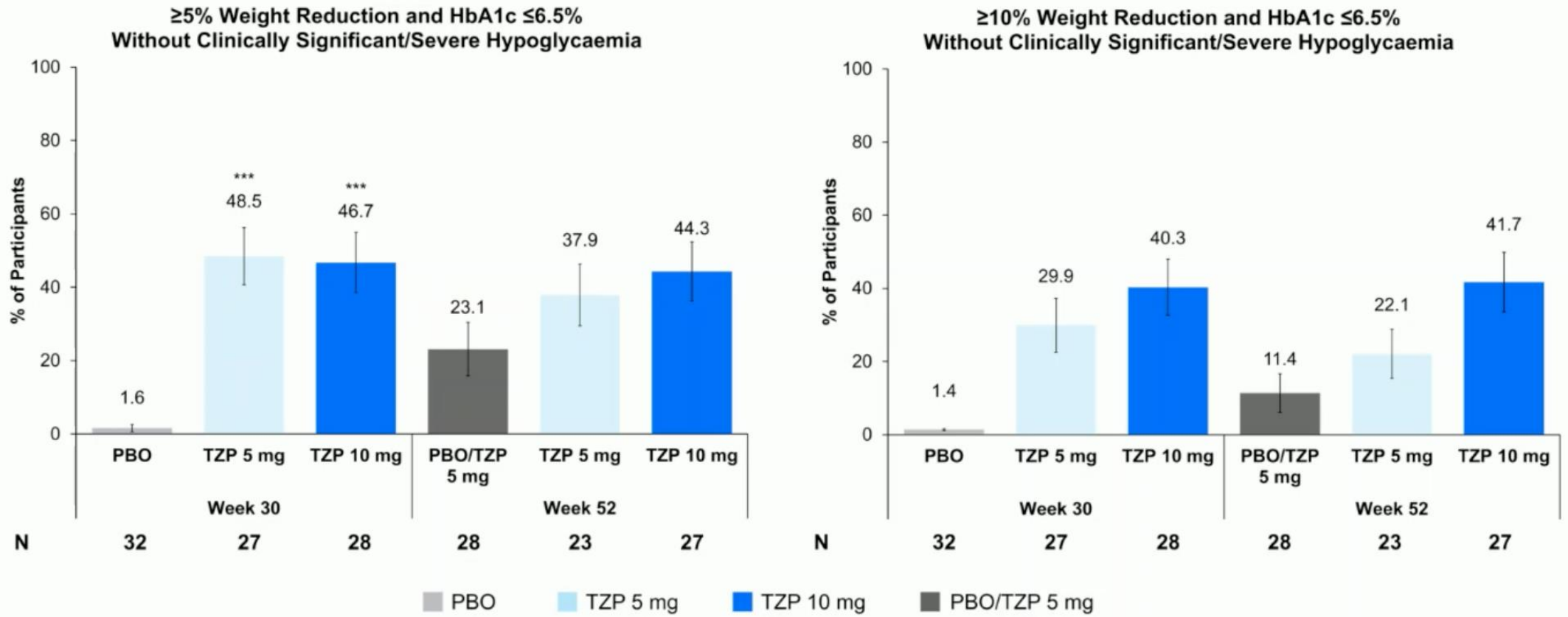
Tirzepatide Was Associated With Composite BMI Reduction Thresholds (≥5% or ≥10%) and HbA1c ≤6.5% at Week 30 With Sustained Benefits Through Week 52



***p<0.001 vs. PBO at Week 30 for the ≥5% threshold. p-value not estimable for the ≥10% threshold at Week 30 due to 0% observed response in the PBO group; no significance testing displayed for that panel.
Notes: Data are adjusted % (SE) calculated utilising G-computation method from logistic regression model using imputed data with baseline age group, baseline anti-hyperglycaemic medication and treatment as factors. The PBO/TZP 5 mg group includes participants who were switched from PBO to TZP 5 mg at Week 30.
BMI=body mass index; HbA1c=glycated haemoglobin; N=number of participants with baseline value and ≥1 non-missing post-baseline value at Week 30 or Week 52 in observed data; PBO=placebo; SE=standard error; TZP=tirzepatide.

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Tirzepatide Was Associated With Composite Weight Reduction Thresholds (≥5% or ≥10%) and HbA1c ≤6.5% at Week 30 With Sustained Benefits Through Week 52



***p<0.001 vs. PBO at Week 30 for the ≥5% threshold. p-value not estimable for the ≥10% threshold at Week 30 due to 0% observed response in the PBO group; no significance testing displayed for that panel.
Notes: Data are adjusted % (SE) calculated utilising G-computation method from logistic regression model using imputed data with baseline age group, baseline anti-hyperglycaemic medication and treatment as factors. The PBO/TZP 5 mg group includes participants who were switched from PBO to TZP 5 mg at Week 30.
HbA1c=glycated haemoglobin; N=number of participants with baseline value and ≥1 non-missing post-baseline value at Week 30 or Week 52 in observed data; PBO=placebo; SE=standard error; TZP=tirzepatide.

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CONCLUSIONS

- In participants with youth-onset T2D from the SURPASS-PEDS trial, tirzepatide was associated with an increase in the proportion of youths with T2D achieving clinically meaningful composite glycaemic (HbA1c ≤6.5%) and weight-related goals compared with placebo at Week 30, with benefits sustained through Week 52
- Week 30 composite endpoint achievement:
  - **BMI reduction (≥5% vs. placebo, p<0.001; ≥10% not estimable)**
    - ≥5%: 48% (5 mg), 50% (10 mg) vs. 2% (placebo)
    - ≥10%: 26% (5 mg), 45% (10 mg) vs. 1% (placebo)
  - **Weight reduction (≥5% vs. placebo, p<0.001; ≥10% not estimable)**
    - ≥5%: 49% (5 mg), 47% (10 mg) vs. 2% (placebo)
    - ≥10%: 30% (5 mg), 40% (10 mg) vs. 1% (placebo)
- These findings suggest the potential of tirzepatide to help youths with T2D achieve clinically meaningful improvements in glycaemic control and weight-related outcomes

BMI=body mass index; HbA1c=glycated haemoglobin; T2D=type 2 diabetes.

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EASD
September 30, 2026

TRIUMPH-2: Study Design, Baseline Characteristics, and Efficacy Results

Juan Pablo Frías, MD

Medical Director and Principal Investigator
Los Angeles Institute for Metabolic Research
Los Angeles, CA, USA

GLP-1, GIP, and Glucagon – Potential Roles in Obesity

Brain

Appetite regulation[1-6]

↓ Nausea[1,2,4]

Pancreas

↑ Insulin secretion[1-5]

↓ Glucagon secretion[1,3,4]

↑ Glucagon secretion[a,1-3]

Liver

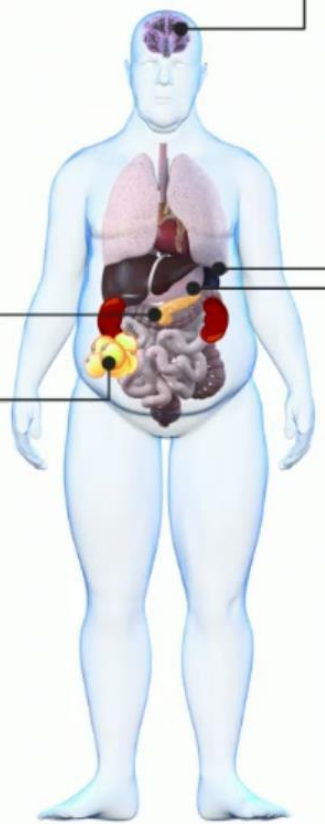
- ↑ Glycogenolysis[2,5]
- ↑ Gluconeogenesis[2,3,5]
- Improvements in lipid metabolism[2,3,5]
- ↑ Energy expenditure[2,3,6,7]

Adipose tissue

- ↑ Insulin sensitivity[1]
- Improvements in lipid metabolism[2-4]

Stomach

Delayed gastric emptying[1-4,8]



GLP-1
GIP
Glucagon

[a]GIP increases glucagon only in the hypoglycemic state; Indirect effect.
GIP=Glucose-Dependent Insulinotropic Polypeptide; GLP-1=Glucagon-Like Peptide-1.

1. Samms RJ, et al. *Trends Endocrinol Metab.* 2020;31(6):410-421. 2. Kusminski CM, et al. *Cell.* 2024;187(15):3829-3853. 3. Nogueiras R, et al. *Nat Metab.* 2023;5(6):933-944. 4. Hammoud R, Drucker DJ. *Nat Rev Endocrinol.* 2023;19(4):201-216. 5. Hædersdal S, et al. *Nat Rev Endocrinol.* 2023;19(6):321-335. 6. Novikoff A, Müller TD. *Peptides.* 2023;165:171003. 7. Klein T, et al. *Diabetes Res Clin Pract.* 2024;207:110779. 8. Urva S, et al. *Diabetes Obes Metab.* 2023;25(9):2784-2788.

Retatrutide: A Novel GIP, GLP-1, and Glucagon Receptor Agonist

Molecular Design[1]

- Novel synthetic molecule
- C-20 fatty diacid moiety enables albumin binding and prolongs half-life

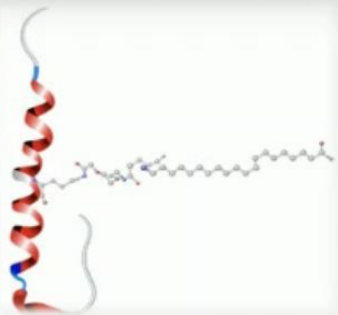
Pharmacokinetics[1,2]

- Mean half-life: **~6 days**
- Enables **weekly** SC dosing

Mechanism of Action[1]

- Agonist of **GIPR**, **GLP-1R**, and **GCGR**
  - Greater potency vs native GIP
  - Lower potency vs native GLP-1 and GCG

RETATRUTIDE[1]



1. Coskun T, et al. *Cell Metab*. 2022;34:1234-1247.e9. 2. Urva S, et al. *Lancet*. 2022;400:1869-1881.
GCGR=glucagon receptor; GIP=glucose-dependent insulinotropic polypeptide; GIPR=GIP receptor; GLP-1R=glucagon-like peptide-1 receptor; SC=subcutaneous.

Retatrutide: A Novel GIP, GLP-1, and Glucagon Receptor Agonist

Molecular Design[1]

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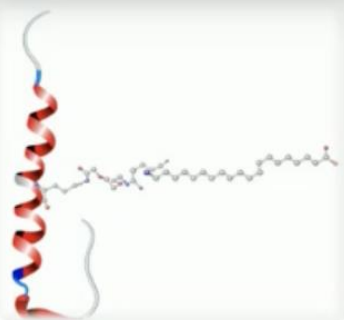
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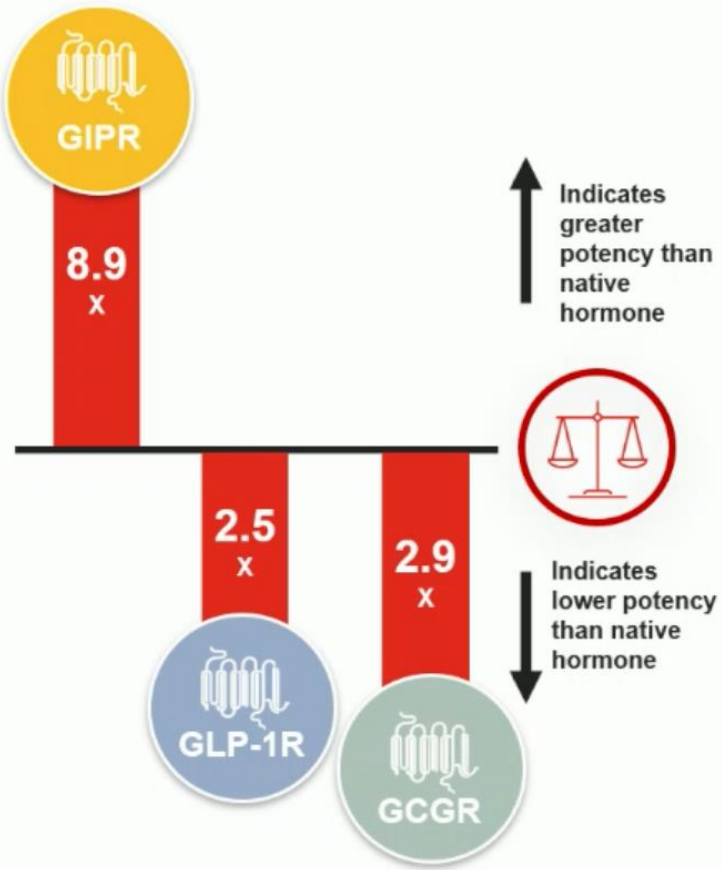
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- Agonist of **GIPR**, **GLP-1R**, and **GCGR**
  - Greater potency vs native GIP
  - Lower potency vs native GLP-1 and GCG

RETATRUTIDE[1]



A Balanced Tri-Agonism by Design

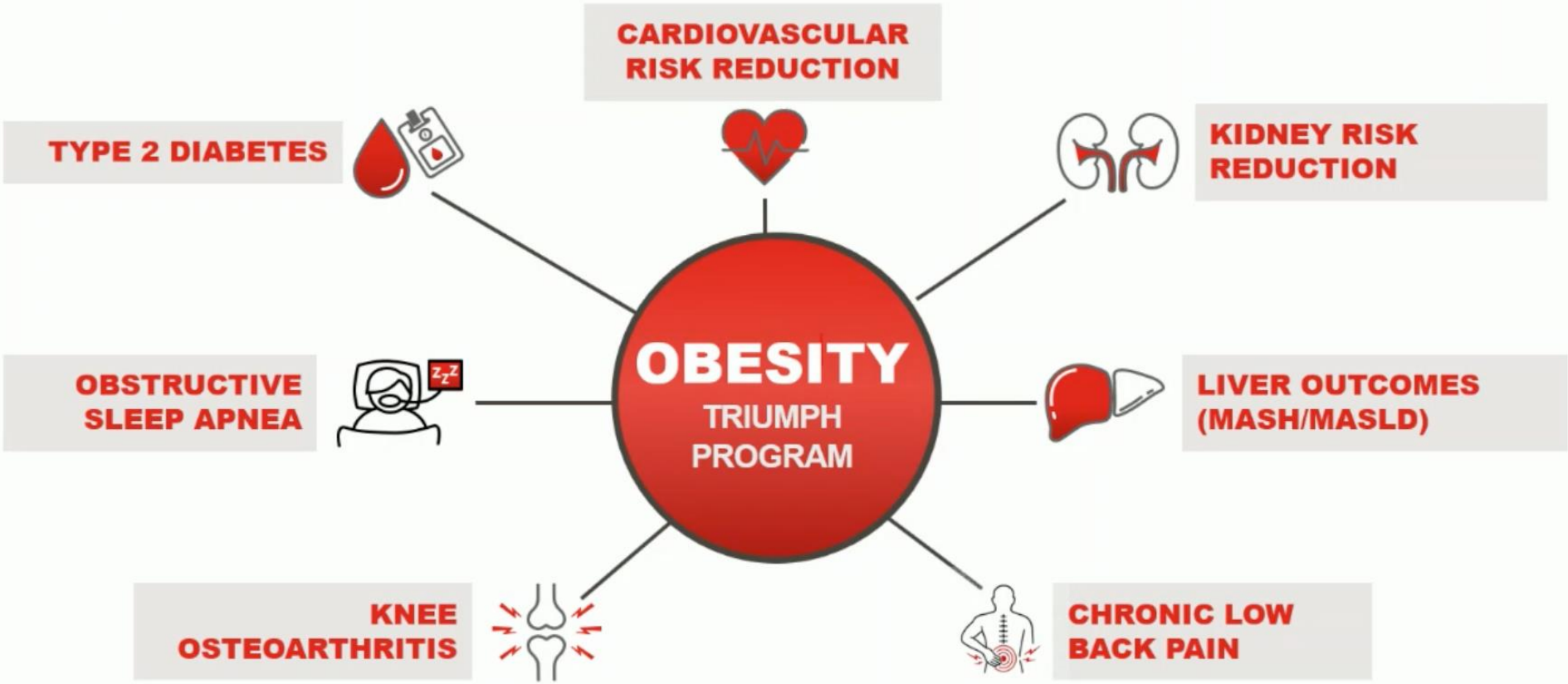


1. Coskun T, et al. *Cell Metab*. 2022;34:1234-1247.e9. 2. Urva S, et al. *Lancet*. 2022;400:1869-1881.
GCGR=glucagon receptor; GIP=glucose-dependent insulinotropic polypeptide; GIPR=GIP receptor; GLP-1R=glucagon-like peptide-1 receptor; SC=subcutaneous.

TRIUMPH-2
OBESITY+T2D

Retatrutide Phase 3 Program Across Obesity & Complications

~22,000 Participants Supporting 8 Potential Indications

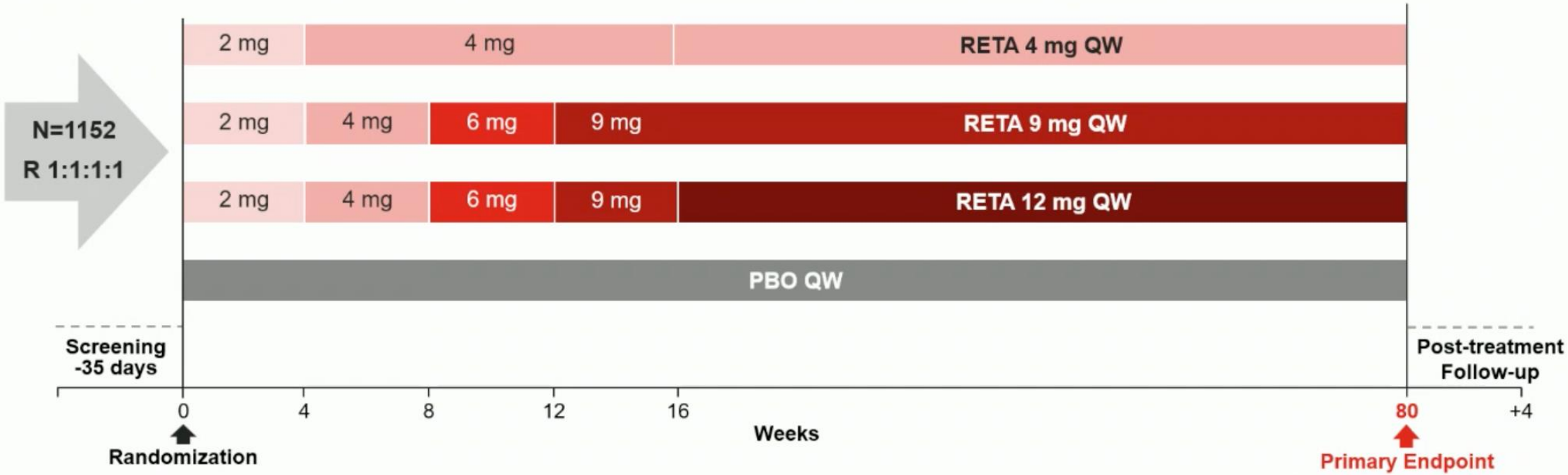


TRIUMPH-2 is one of the 4 registrational trials supporting the obesity indication

MASLD=metabolic dysfunction-associated steatotic liver disease, MASH=metabolic dysfunction-associated steatohepatitis; OA=osteoarthritis; OSA=obstructive sleep apnea; T2D=type 2 diabetes.

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TRIUMPH-2 Study Design:
Phase 3 study in Participants with Overweight / Obesity and T2D



Key Inclusion Criteria

- Adults with T2D
- HbA1c ≥6.5% to ≤10.5%
- BMI ≥27 kg/m^2
- No incretin agents or insulin for ≥90 days prior to screening; no basal insulin allowed

Two dose reductions allowed for

- Intolerable GI symptoms (during first 20 weeks only)
- Poor nutrition or dehydration
- Reaching BMI ≤22 kg/m^2
- Perceived excessive body weight loss

Lifestyle intervention: Ongoing individualized counseling for healthy diet & ≥150 minutes/week physical activity

BMI=body mass index; GI=gastrointestinal; HbA1c=glycated hemoglobin; PBO=placebo; QW=once weekly; R=randomized; RETA=retatrutide; SU=sulfonylurea; T2D=type 2 diabetes.

TRIUMPH-2
OBESITY+T2D

Multinational Trial:
N=1152 Participants Randomized at 92 Study Sites Across 8 Countries



TRIUMPH-2
OBESITY+T2D

Primary and Key Secondary Endpoints

Primary Endpoint

% change in body weight from baseline at Week 80 for RETA 9 mg and 12 mg

Key Secondary Endpoints[a]

BODY WEIGHT AND OTHER ANTHROPOMETRIC ENDPOINTS

- % change in body weight from baseline for RETA 4 mg
- Proportion of participants achieving weight reduction of ≥5%, ≥10%, ≥15%, ≥20%, and ≥25%
- % change in body weight and achievement of weight reduction thresholds among participants with BMI ≥35 kg/m^2
- Change in waist circumference

OTHER CV RISK FACTORS AND SYSTEMIC INFLAMMATION

- % change in TG, non-HDL-cholesterol, and hsCRP
- Change in SBP

GLYCEMIC MEASURES

- Change in HbA1c and fasting glucose
- Achievement of HbA1c ≤6.5%

PATIENT-REPORTED OUTCOMES

- Change in IWQOL-Lite-CT Physical Function composite scores

[a]Change from baseline at Week 80 for continuous endpoints, and status at Week 80 for categorical endpoints.

BMI=body mass index; CV=cardiovascular; HbA1c=glycated hemoglobin; HDL=high-density lipoprotein; hsCRP=high-sensitivity C-reactive protein; IWQOL-Lite-CT=Impact of Weight on Quality of Life-Lite Clinical Trials Version; QW=once weekly; RETA=retatrutide; SBP= systolic blood pressure; TG=triglycerides

TRIUMPH-2
OBESITY+T2D

Key Demographics and Baseline Characteristics

Body weight	BMI	Waist circumference	HbA1c	Duration of T2D/Obesity
106.4 kg	38.2 kg/m^2	119.7 cm	7.7%	7.5 yrs/22 yrs

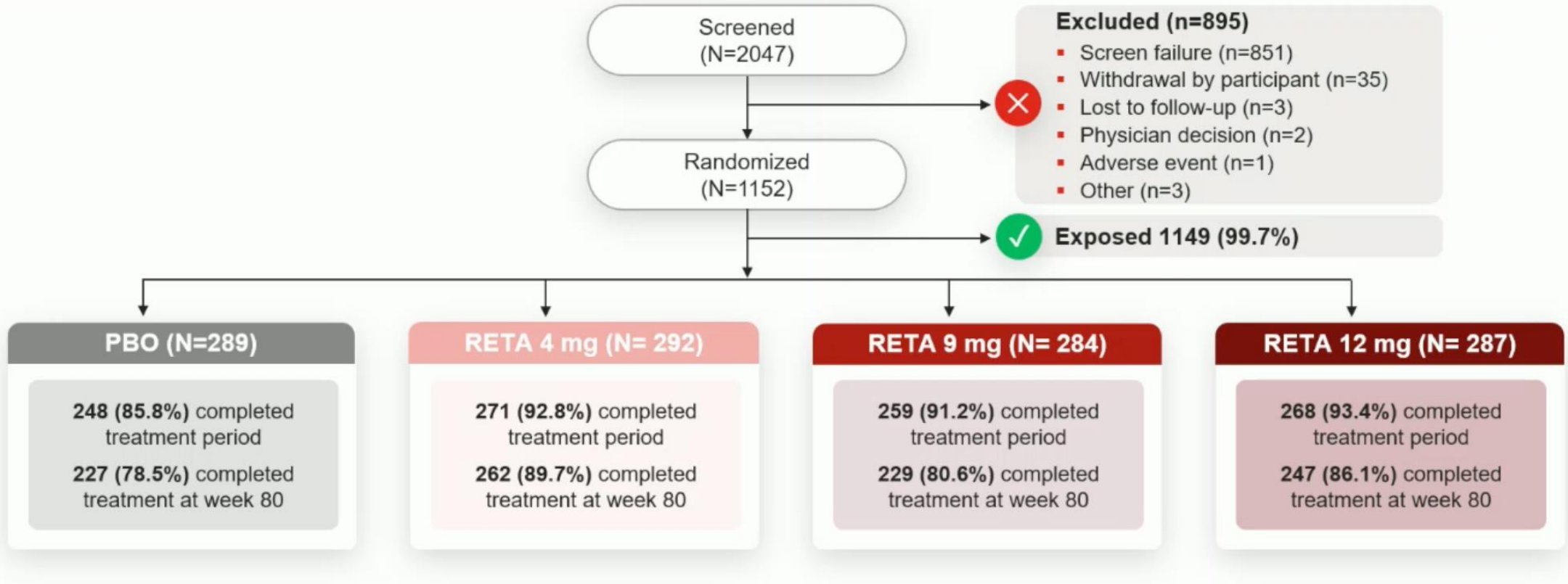
Female	Age	White / American Indian or Alaska Native / Asian / Black or African American / Others	T2D Medications
48%	55 yr	58.3% / 18.6% / 14.8% / 3.9% / 4.4%	• Metformin 87.2% • SGLT2i: 26.0% • Sulfonylurea: 25.3%

Baseline Characteristics Were Well Balanced Across Treatment Arms

Note: all values are reported as mean values at baseline unless indicated otherwise.
BMI=body mass index; HbA1c=glycated hemoglobin; SGLT2i=sodium glucose co-transporter-2 inhibitor; T2D=type 2 diabetes.

TRIUMPH-2
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Participant Disposition



Across doses, 81% to 90% of retatrutide-treated participants remained on treatment through Week 80

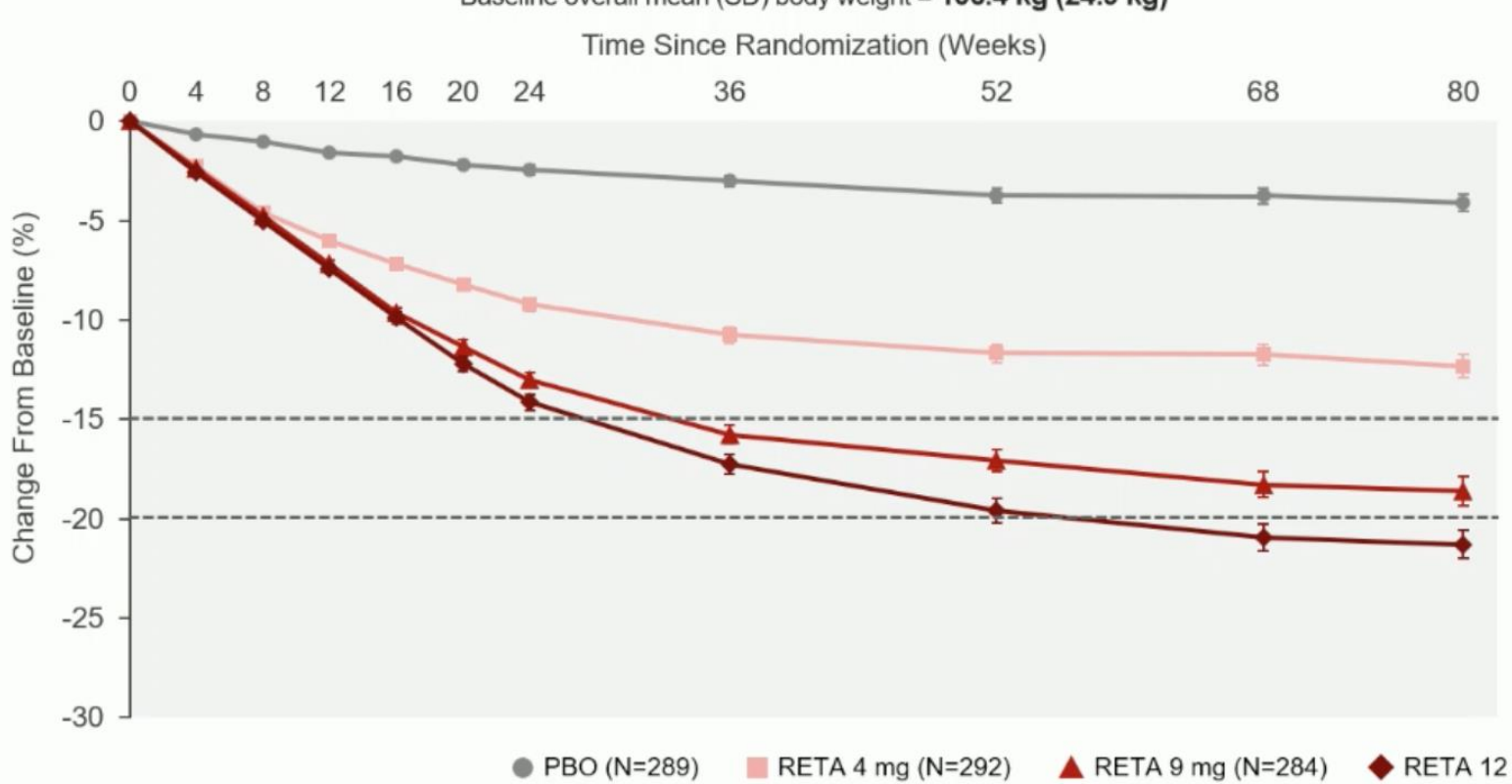
N=all randomly assigned participants who took ≥1 dose of study drug; n=number of participants in the specified category/reason; PBO=placebo; RETA=retatrutide.

TRIUMPH-2
OBESITY+T2D

Percent Change in Body Weight Over 80 Weeks

Mean Observed Data

Baseline overall mean (SD) body weight = **106.4 kg (24.9 kg)**



	Efficacy Estimand	Treatment Regimen Estimand	EE Weight Change (kg)
PBO (N=289)	-4.0%	-5.1%	-4.2 kg
RETA 4 mg (N=292)	-12.7%***	-11.9%***	-13.5 kg
RETA 9 mg (N=284)	-19.1%***	-16.8%***	-20.6 kg
RETA 12 mg (N=287)	-20.8%***	-18.8%***	-22.5 kg

RETA vs. PBO: ***p<0.001. p-values are for MBE change difference vs. PBO.

[a]Percent change in body weight from baseline to Week 80 is the primary endpoint for the comparison of RETA 9 mg and RETA 12 mg groups only vs. PBO (RETA 4 mg vs. PBO is a key secondary endpoint).

Notes: Data in time course plot are shown as mean (SE). Data for EE and TRE are MBE (SE) unless otherwise stated. EE analysis was conducted using MMRM. TRE analysis was conducted using ANCOVA. Data are from all randomized participants.

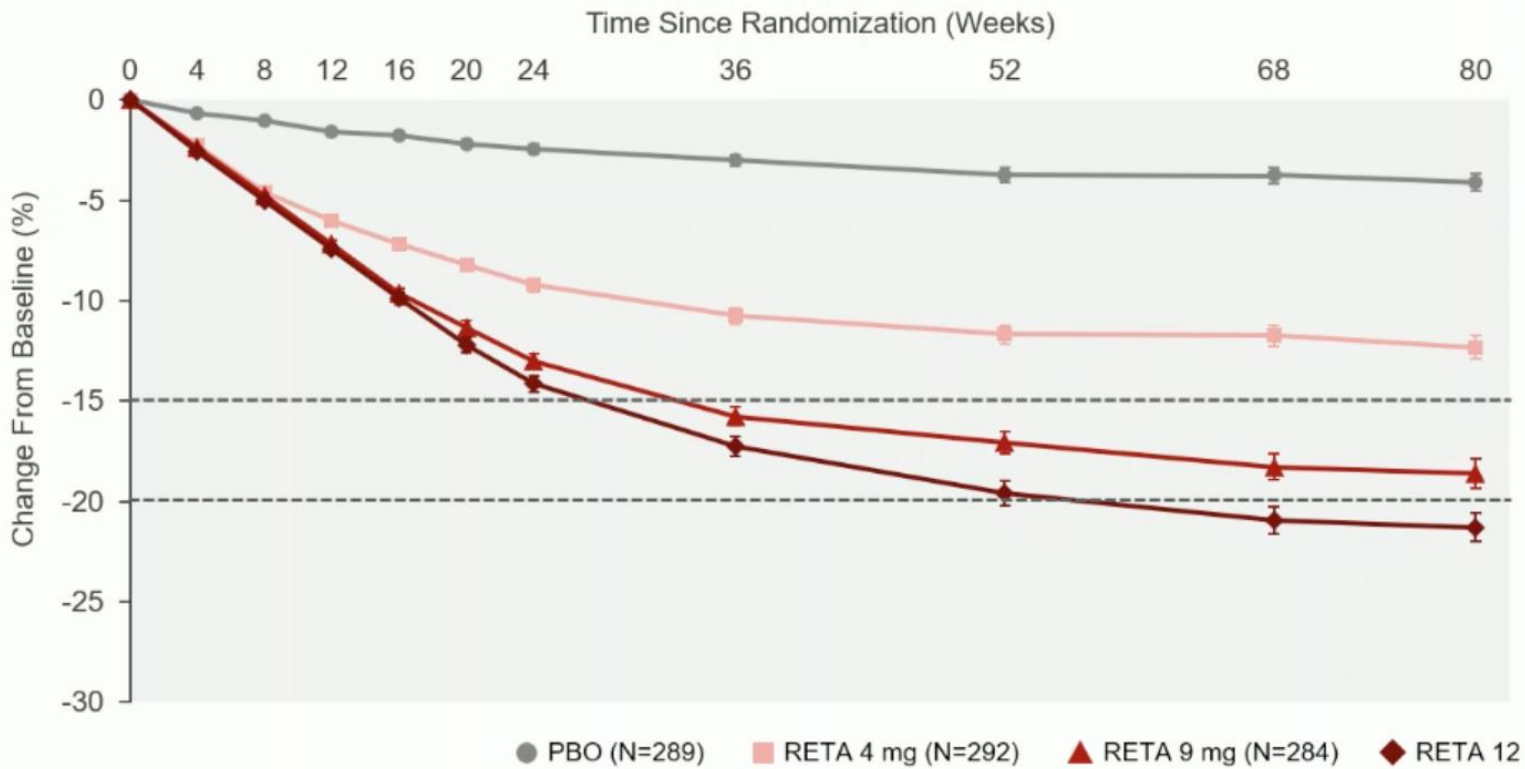
ANCOVA=analysis of covariance; EE=efficacy estimand; MBE=model-based estimate; MMRM=mixed model for repeated measures; N=number of participants in the population; PBO=placebo; RETA=retatrutide; SD=standard deviation; SE=standard error; TRE=treatment regimen estimand.

TRIUMPH-2
OBESITY+T2D

Percent Change in Body Weight Over 80 Weeks

Mean Observed Data

Baseline overall mean (SD) body weight = **106.4 kg (24.9 kg)**



	Efficacy Estimand	Treatment Regimen Estimand	EE Weight Change (kg)
PBO (N=289)	-4.0%	-5.1%	-4.2 kg
RETA 4 mg (N=292)	-12.7%***	-11.9%***	-13.5 kg
RETA 9 mg (N=284)	-19.1%***	-16.8%***	-20.6 kg
RETA 12 mg (N=287)	-20.8%***	-18.8%***	-22.5 kg

With RETA 4 mg, which requires a single dose escalation, mean body weight decreased by 12.7%;
With RETA 12 mg, mean body weight decreased by 20.8%

RETA vs. PBO: ***p<0.001. p-values are for MBE change difference vs. PBO.

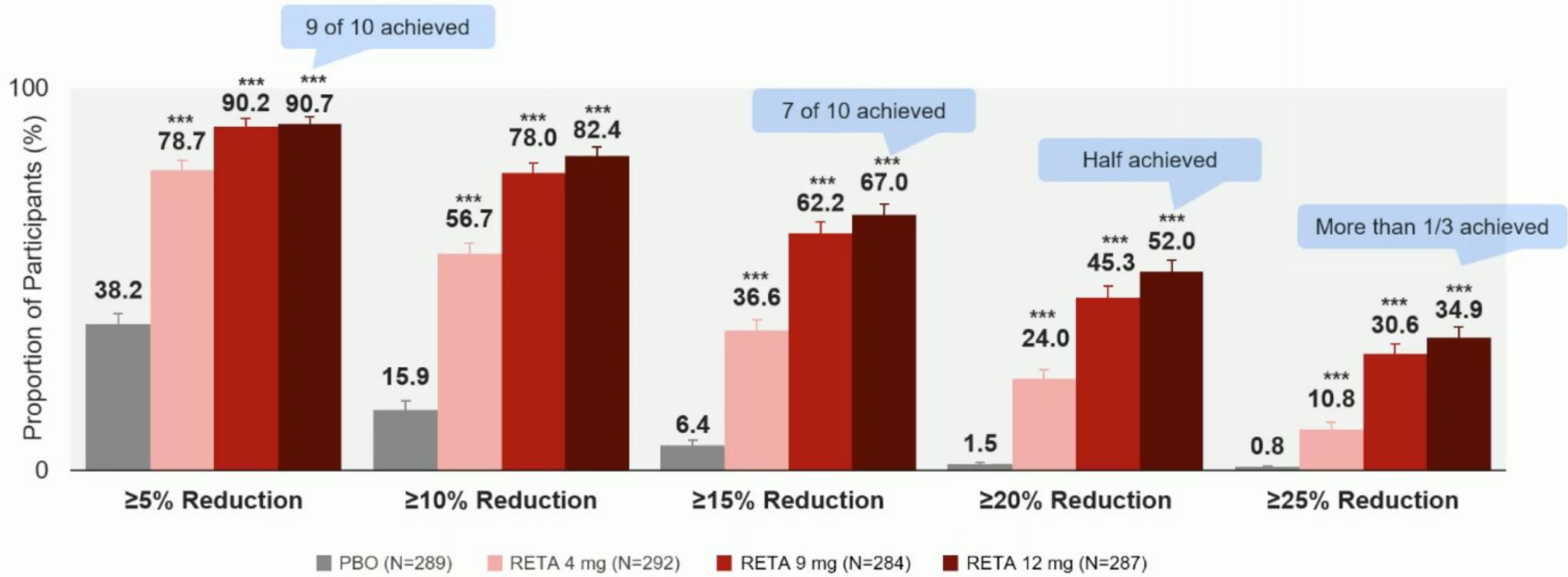
[a]Percent change in body weight from baseline to Week 80 is the primary endpoint for the comparison of RETA 9 mg and RETA 12 mg groups only vs. PBO (RETA 4 mg vs. PBO is a key secondary endpoint).

Notes: Data in time course plot are shown as mean (SE). Data for EE and TRE are MBE (SE) unless otherwise stated. EE analysis was conducted using MMRM. TRE analysis was conducted using ANCOVA. Data are from all randomized participants.

ANCOVA=analysis of covariance; EE=efficacy estimand; MBE=model-based estimate; MMRM=mixed model for repeated measures; N=number of participants in the population; PBO=placebo; RETA=retatrutide; SD=standard deviation; SE=standard error; TRE=treatment regimen estimand.

Achievement of Body Weight Reduction Thresholds at 80 Weeks

Efficacy Estimand

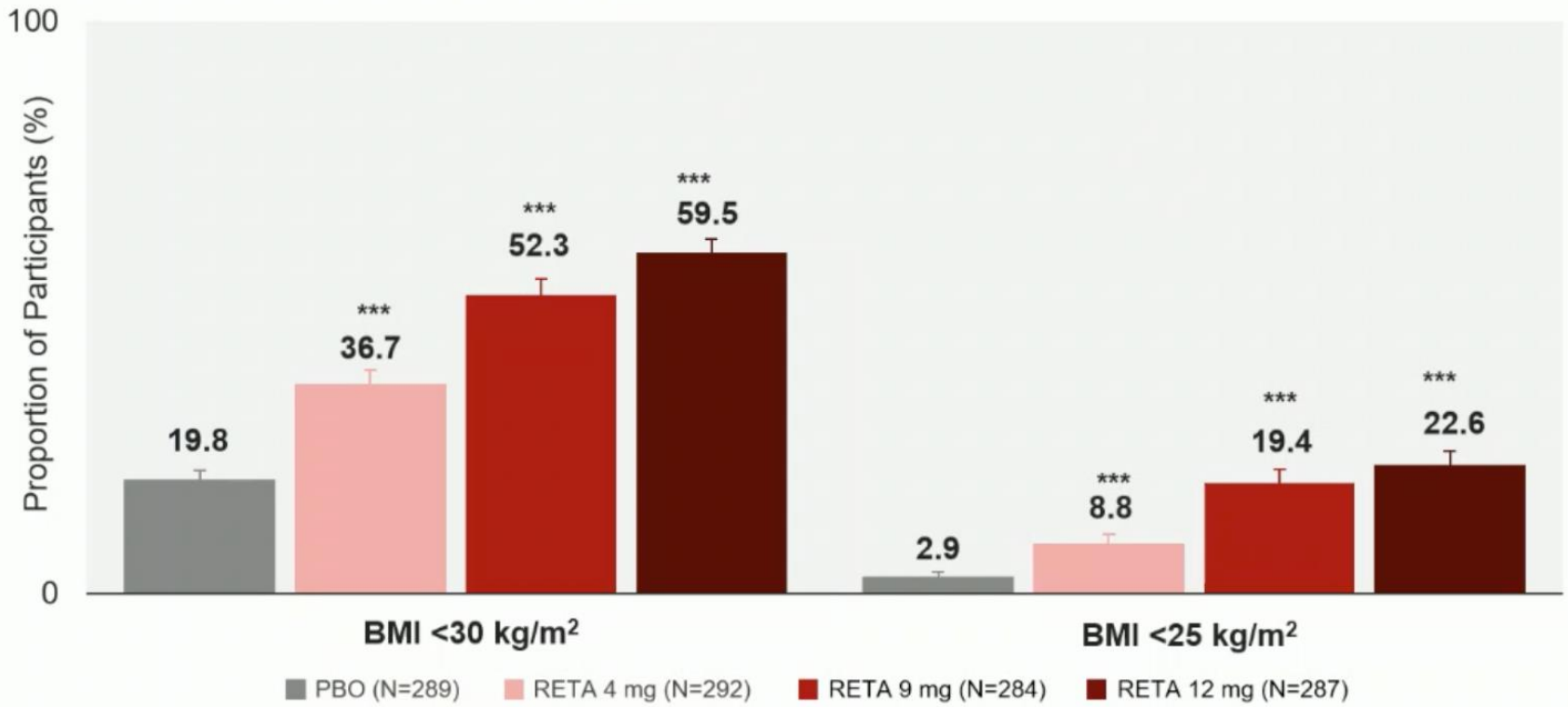


RETA vs. PBO: *p<0.05, **p<0.01, and ***p<0.001. p-values are for MBE (SE) risk difference vs. PBO.
Notes: Data are shown as MBE (SE) unless otherwise stated. EE analysis was conducted using logistic regression with multiple imputation. Data are from all randomized participants.
BW=body weight; EE=efficacy estimand; MBE=model-based estimate; N=number of participants in the population; PBO=placebo; RETA=retatrutide; SE=standard error.

TRIUMPH-2
OBESITY+T2D

Proportion of Participants Achieving BMI Targets at Week 80

Efficacy Estimand



With RETA 9 mg and 12 mg, >50% of participants achieved a BMI <30 kg/m^2 and ~20% achieved a BMI <25 kg/m^2

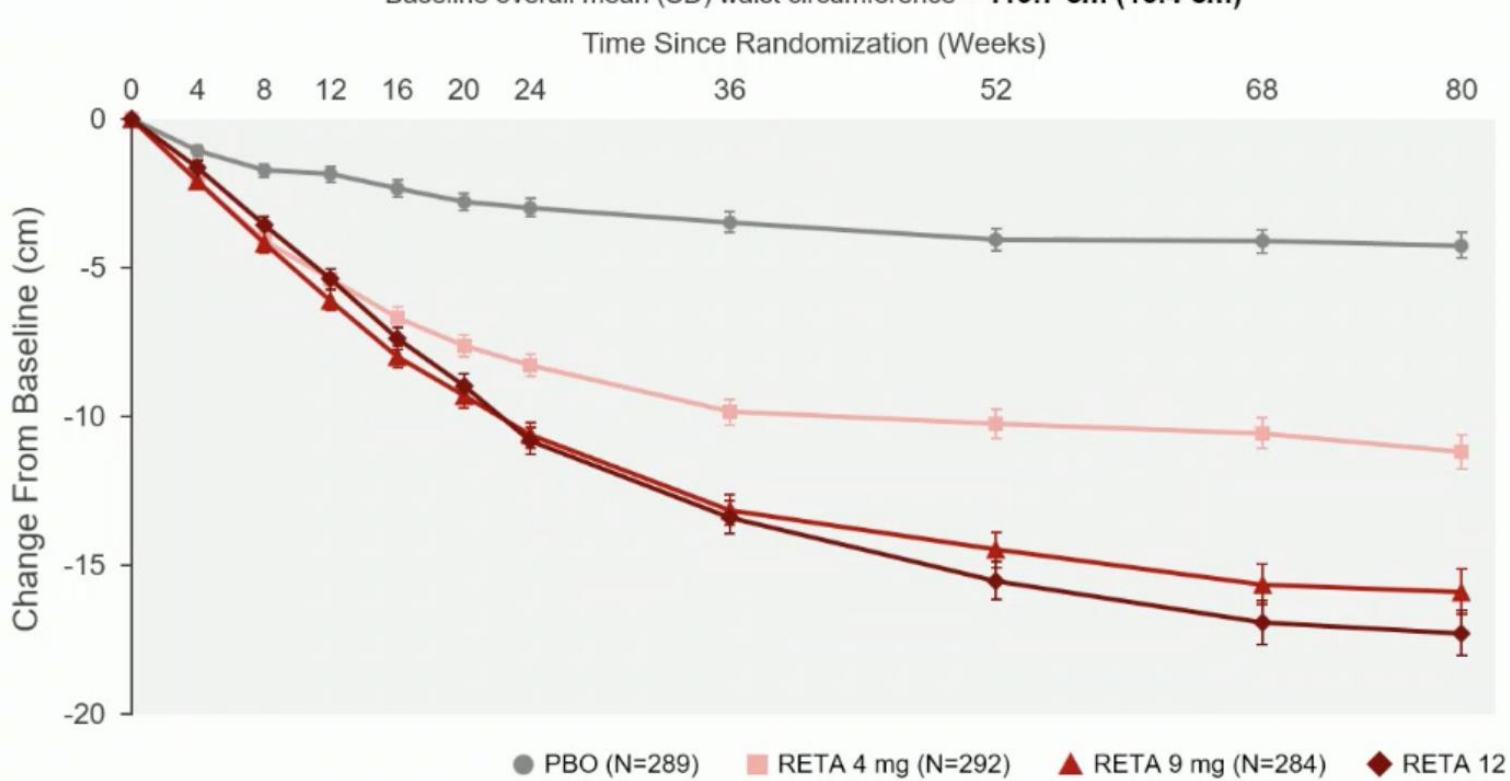
RETA vs. PBO: *p<0.05, **p<0.01, and ***p<0.001. p-values are for MBE risk difference vs. PBO.
Note: Data are shown as MBE (SE) unless otherwise stated. EE analysis was conducted using logistic regression with multiple imputation. Data are from all randomized participants.
BMI=body mass index; EE=efficacy estimand; MBE=model-based estimate; N=number of participants in the population; PBO=placebo; RETA=retatrutide; SE=standard error.

TRIUMPH-2
OBESITY+T2D

Change in Waist Circumference From Baseline to Week 80

Mean Observed Data

Baseline overall mean (SD) waist circumference = **119.7 cm (15.4 cm)**



	Efficacy Estimand	Treatment Regimen Estimand	EE Week 80 Actual Value
PBO (N=289)	-4.0 cm	-4.9 cm	115.7 cm
RETA 4 mg (N=292)	-11.3 cm***	-10.6 cm***	108.3 cm
RETA 9 mg (N=284)	-16.0 cm***	-14.3 cm***	103.7 cm
RETA 12 mg (N=287)	-16.9 cm***	-15.4 cm***	102.8 cm

Mean waist circumference decreased by up to 17 cm with RETA

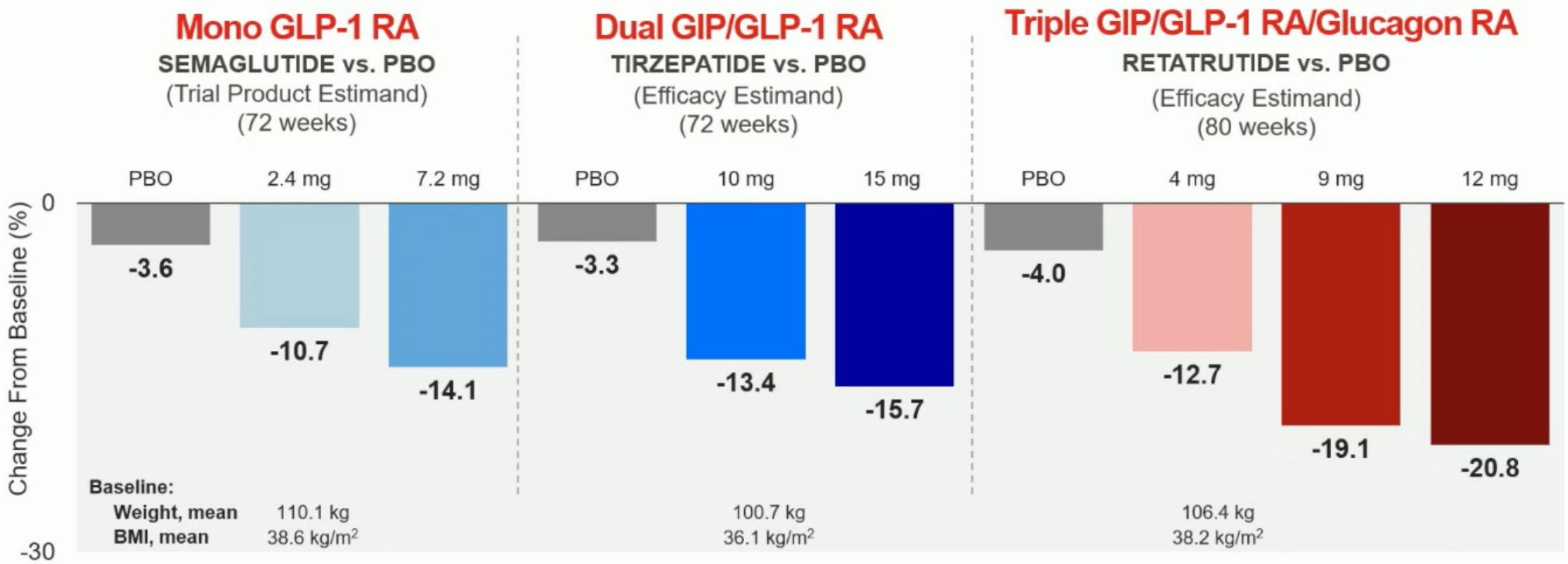
RETA vs. PBO: ***p<0.001. p-values are for MBE change difference vs. PBO.

Notes: Data in time course plot are shown as mean (SE). Data for EE and TRE are MBE (SE) unless otherwise stated. EE analysis was conducted using MMRM. TRE analysis was conducted using ANCOVA. Data are from all randomized participants.

ANCOVA=analysis of covariance; EE=efficacy estimand; MBE=model-based estimate; MMRM=mixed model for repeated measures; N=number of participants in the population; PBO=placebo; RETA=retatrutide; SD=standard deviation; SE=standard error; TRE=treatment regimen estimand.

TRIUMPH-2
OBESITY+T2D

Side-by-Side Indirect Comparison of Percent Change in Body Weight From Baseline vs. Similar Phase 3 Studies



RETA, a triple GIP/GLP-1/Glucagon RA crossed the ceiling of 20% average weight loss in participants with T2D

Note: Drawing conclusions based on the results of different studies is not appropriate.

1. Lingvay I, et al. *Lancet Diabetes Endocrinol*. 2025;13(11):935-948. 2. Garvey WT, et al. *Lancet*. 2023;402:613-626.

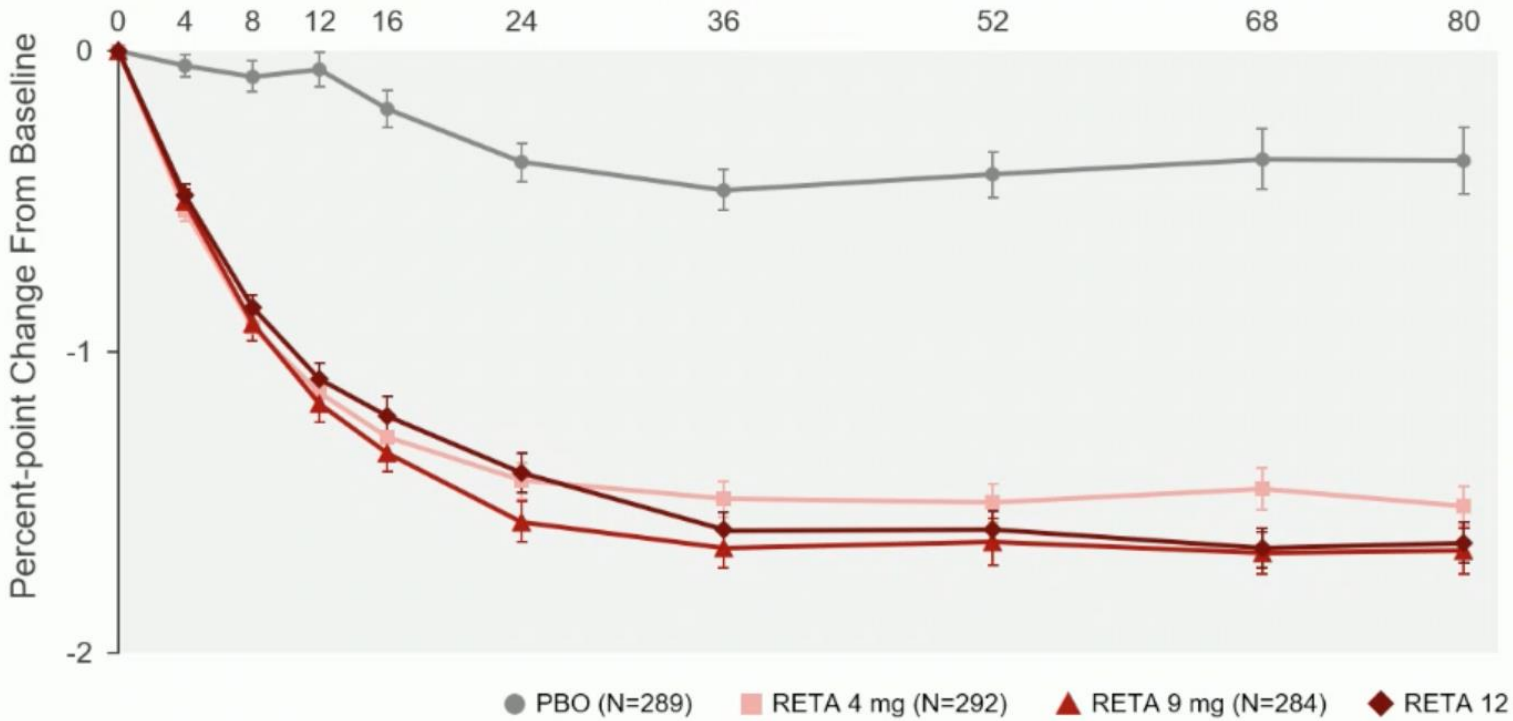
BMI=body mass index; PBO=placebo; RETA=retatrutide;; T2D=type 2 diabetes

TRIUMPH-2
OBESITY+T2D

Change in HbA1c from Baseline to Week 80

Percent-point Change From Baseline

Baseline overall mean (SD) HbA1c = **7.71% (1.07%)**



	Efficacy Estimand	Treatment Regimen Estimand	EE Week 80 Actual Value
PBO (N=289)	-0.19%	-0.45%	7.52%
RETA 4 mg (N=292)	-1.41%***	-1.38%***	6.30%
RETA 9 mg (N=284)	-1.63%***	-1.50%***	6.08%
RETA 12 mg (N=287)	-1.54%***	-1.45%***	6.17%

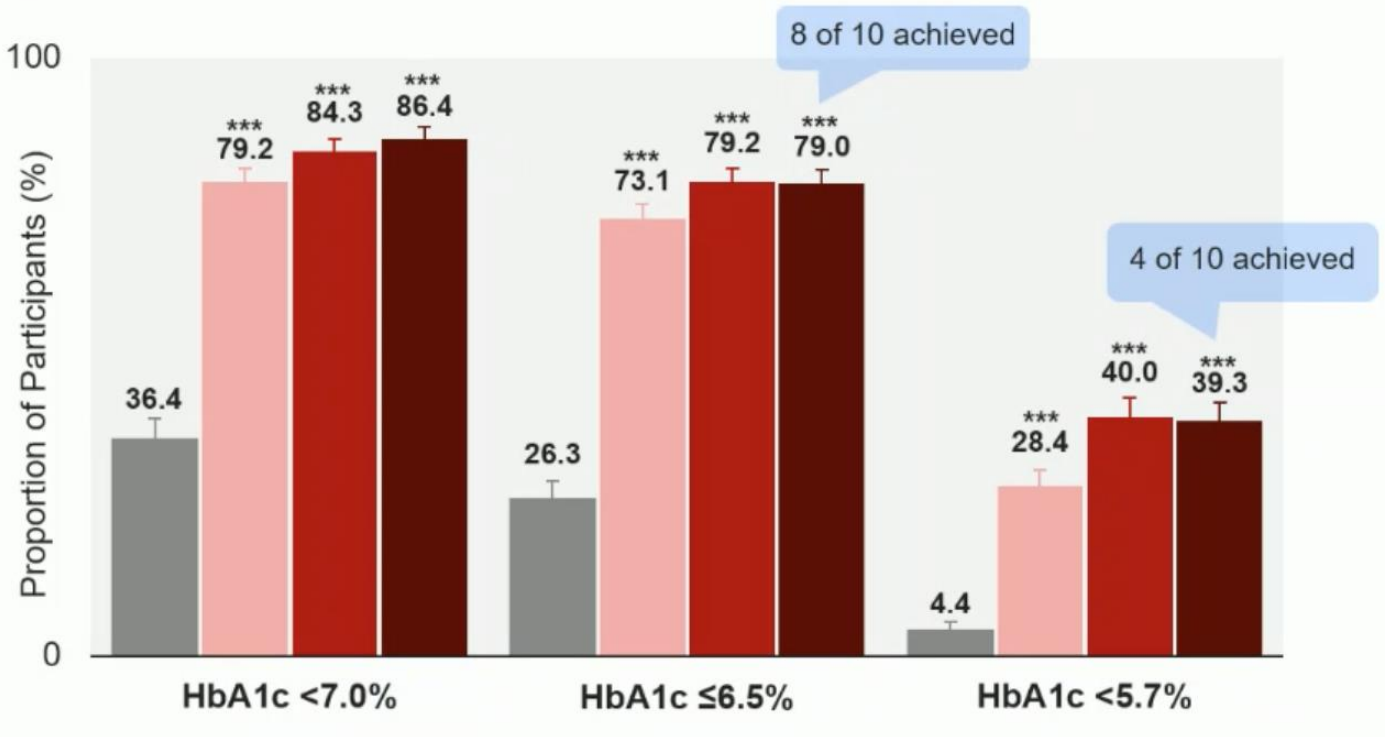
With RETA 12 mg participants reached a mean HbA1c of 6.17% at Week 80
Glycemic control was durable through 80 weeks

RETA vs. PBO: ***p<0.001. p-values are for MBE change difference vs. PBO.
Notes: Data in time course plot are shown as mean (SE). Data for EE and TRE are MBE (SE) unless otherwise stated. EE analysis was conducted using MMRM. TRE analysis was conducted using ANCOVA. Data are from all randomized participants.
ANCOVA=analysis of covariance; EE=efficacy estimand; HbA1c=glycated hemoglobin; MBE=model-based estimate; MMRM=mixed model for repeated measures; N=number of participants in the population; PBO=placebo; RETA=retatrutide; SD=standard deviation; SE=standard error; TRE=treatment regimen estimand.

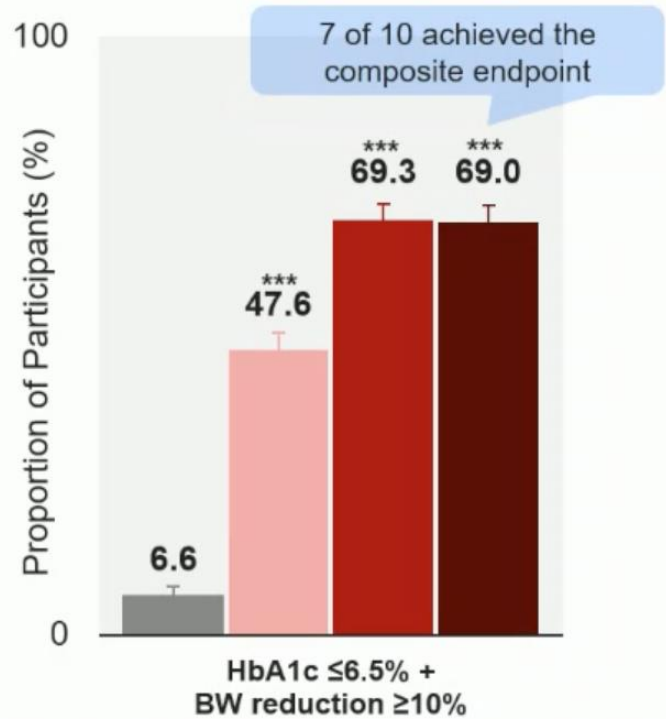
TRIUMPH-2
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Proportion of Participants Achieving HbA1c Targets at Week 80

Efficacy Estimand



Proportion of Participants Achieving HbA1c Targets



Proportion of Participants Achieving a Composite Target for HbA1c and Body Weight Reduction

PBO (N=289) RETA 4 mg (N=292) RETA 9 mg (N=284) RETA 12 mg (N=287)

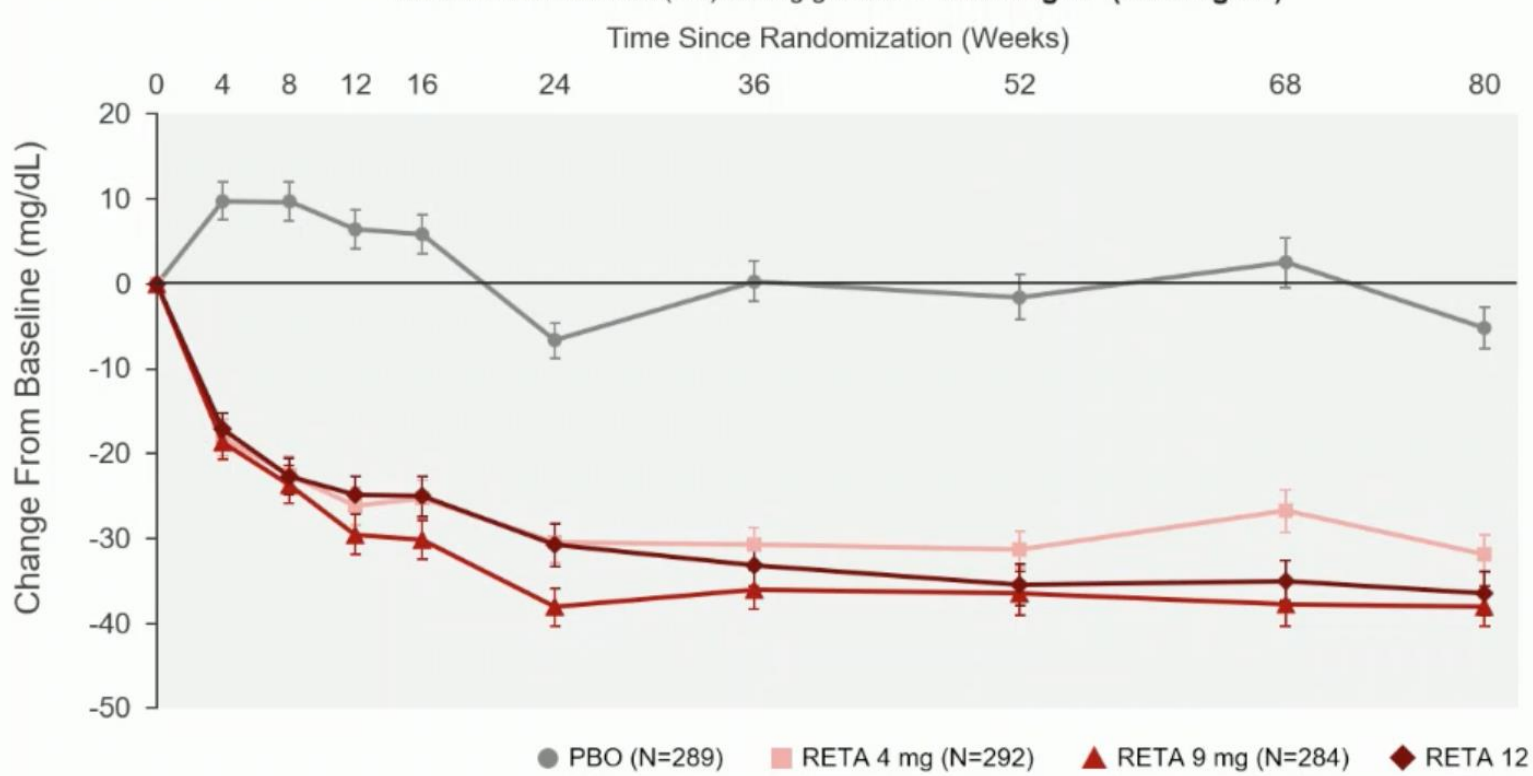
RETA vs. PBO: ***p<0.001. p-values are for MBE risk difference vs. PBO.
Note: Data are shown as MBE (SE) unless otherwise stated. EE analysis was conducted using logistic regression with multiple imputation. Data are from all randomized participants.
BW=body weight; HbA1c=glycated hemoglobin; MBE=model-based estimate; N=number of participants in the population; PBO=placebo; RETA=retatrutide; SE=standard error.

TRIUMPH-2
OBESITY+T2D

Change in Fasting Glucose From Baseline to Week 80

Mean Observed Data

Baseline overall mean (SD) fasting glucose = **137.1 mg/dL (39.5 mg/dL)**



	Efficacy Estimand	Treatment Regimen Estimand	EE Week 80 Actual Value
PBO (N=289)	-4.3 mg/dL	-8.2 mg/dL	132.8 mg/dL
RETA 4 mg (N=292)	-30.9 mg/dL***	-28.8 mg/dL***	106.3 mg/dL
RETA 9 mg (N=284)	-36.8 mg/dL***	-31.6 mg/dL***	100.4 mg/dL
RETA 12 mg (N=287)	-35.7 mg/dL***	-31.4 mg/dL***	101.4 mg/dL

Mean fasting glucose concentrations at Week 80 were ~100 mg/dL (~5.6 mmol/L) for RETA 9 mg and 12 mg

RETA vs. PBO: ***p<0.001. p-values are for MBE change difference vs. PBO.

Notes: Data in time course plot are shown as mean (SE). Data for EE and TRE are MBE (SE) unless otherwise stated. EE analysis was conducted using MMRM. TRE analysis was conducted using ANCOVA. Data are from all randomized participants.

ANCOVA=analysis of covariance; EE=efficacy estimand; MBE=model-based estimate, MMRM=mixed model for repeated measures; N=number of participants in the population, PBO=placebo; RETA=retatrutide; SD=standard deviation, TRE=treatment regimen estimand.

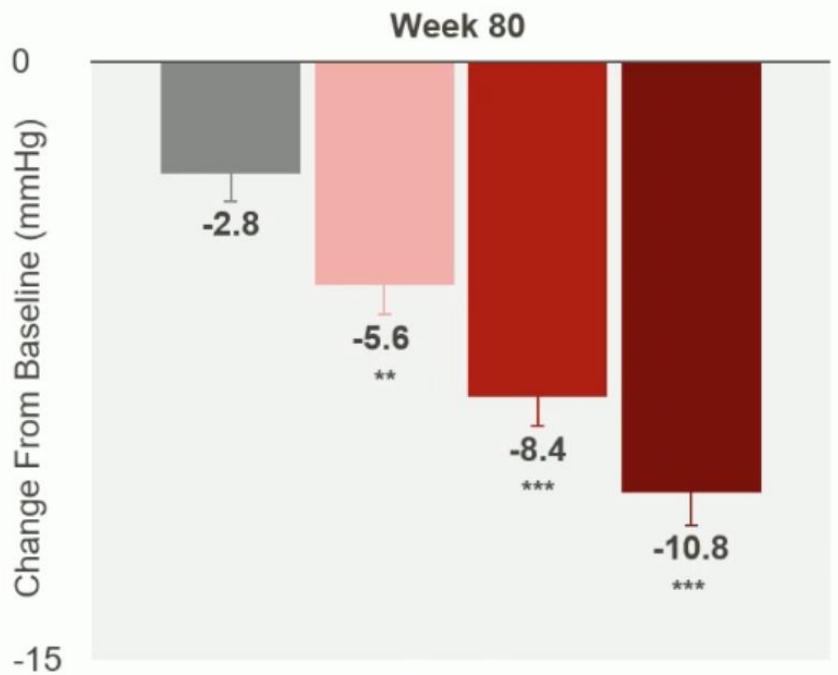
TRIUMPH-2
OBESITY+T2D

Change in Blood Pressure From Baseline to Week 80

Efficacy Estimand

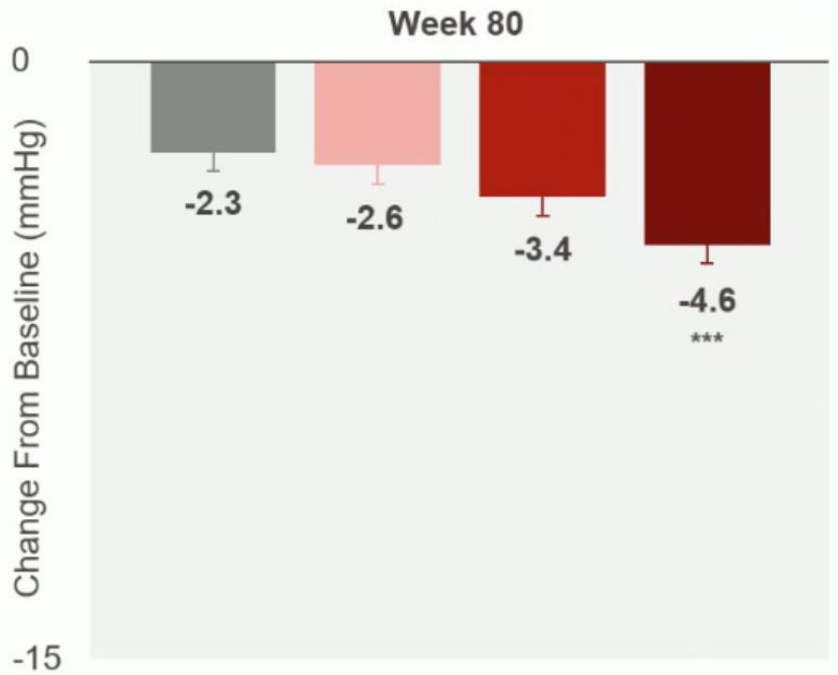
Systolic Blood Pressure

Baseline overall mean (SD) systolic blood pressure = **129.6 (13.7) mmHg**



Diastolic Blood Pressure

Baseline overall mean (SD) diastolic blood pressure = **80.4 (9.0) mmHg**



PBO (N=289) RETA 4 mg (N=292) RETA 9 mg (N=284) RETA 12 mg (N=287)

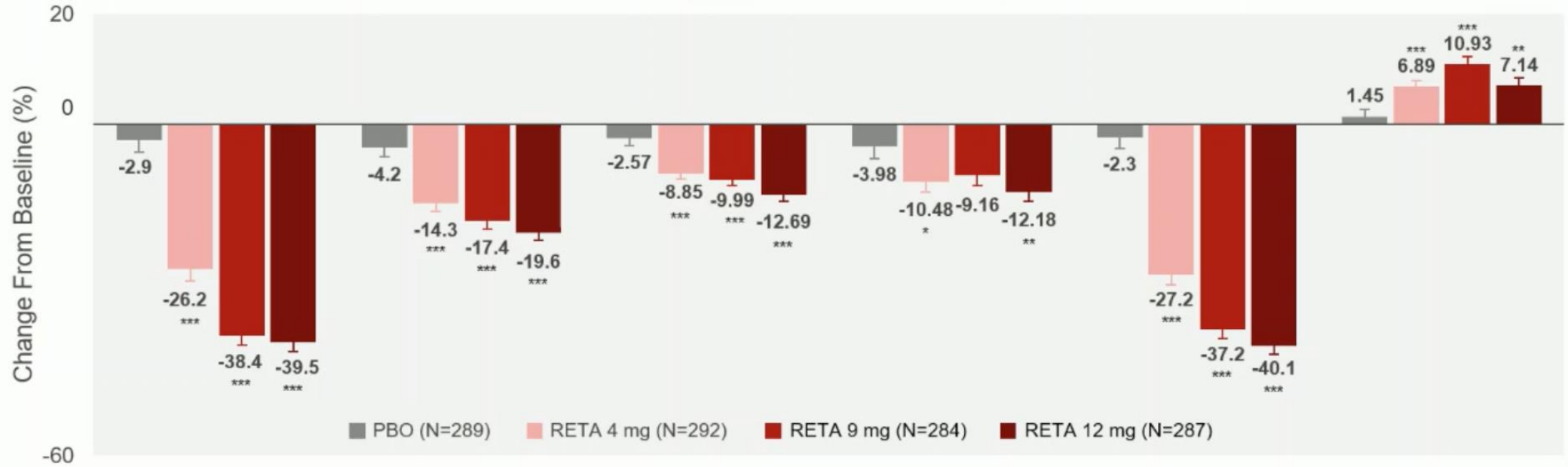
RETA vs. PBO: *p<0.05, **p<0.01, ***p<0.001. p-values are for MBE change difference vs. PBO.
Notes: Data in bar charts are shown as MBE (SE) unless otherwise stated. EE analysis was conducted using MMRM. Data are from all randomized participants.
ANCOVA=analysis of covariance; EE=efficacy estimand; MBE=model-based estimate; MMRM=mixed model for repeated measures; N=number of participants in the population; PBO=placebo; RETA=retatrutide; SD=standard deviation; SE=standard error.

TRIUMPH-2
OBESITY+T2D

Percent Change in Lipid Parameters at Week 80

Efficacy Estimand

	Triglycerides	Non–HDL Cholesterol	Total Cholesterol	LDL Cholesterol	VLDL Cholesterol	HDL Cholesterol
Overall baseline geometric mean (CV [%])	150.4 mg/dL (49.14)	124.1 mg/dL (32.59)	169.2 mg/dL (24.37)	89.9 mg/dL (43.67)	29.3 mg/dL (44.08)	42.0 mg/dL (27.30)



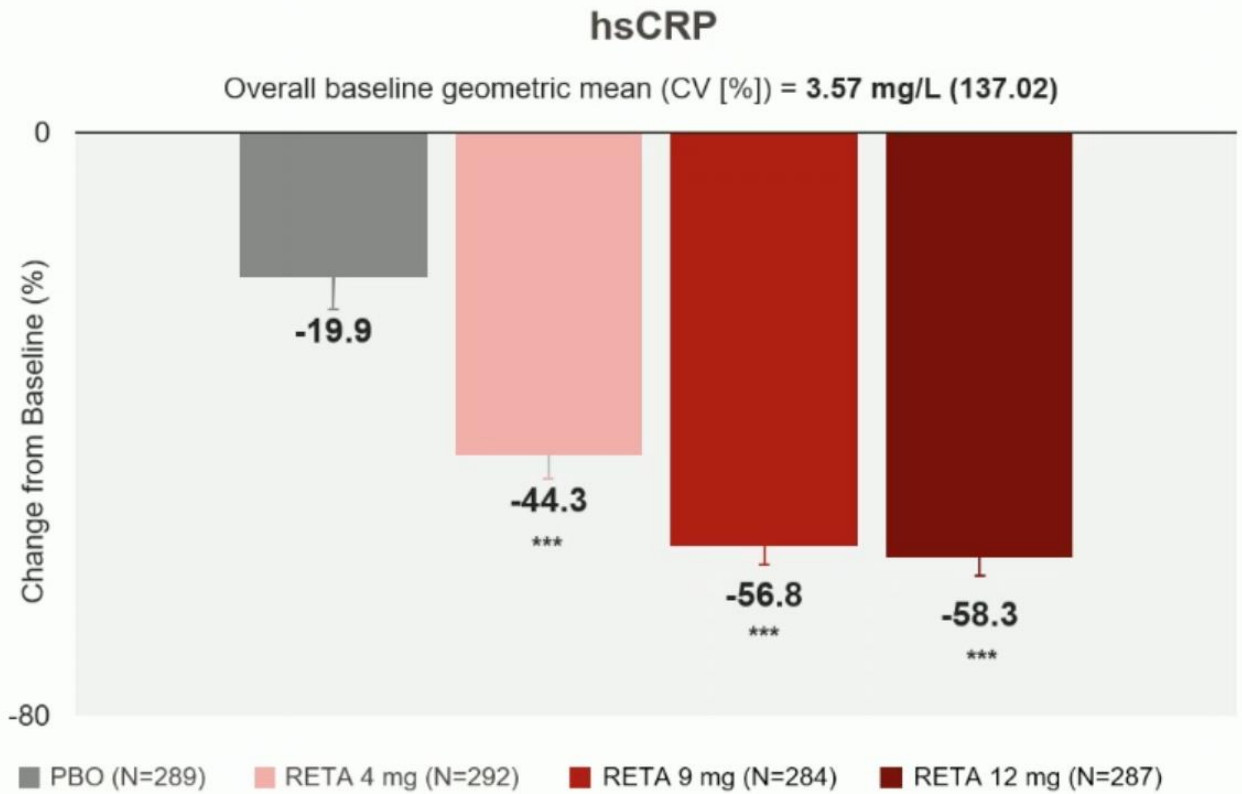
At Week 80, RETA resulted in significant and clinically meaningful reductions in triglycerides and non-HDL cholesterol
LDL-C was reduced up to 12% with RETA

RETA vs. PBO: *p<0.05, **p<0.01, and ***p<0.001. p-values are for MBE percent change difference vs. PBO.
Note: Data are shown as MBE (SE) unless otherwise stated. EE analysis was conducted using MMRM. Data are from all randomized participants.
Only the comparisons between RETA 4mg, 9mg, and/or 12mg vs PBO with respect to the achievement of geometric mean percent change in triglycerides, and non-HDL cholesterol from baseline at week 80 are controlled for the type I error rate.
CV=coefficient of variation; EE=efficacy estimand; HDL=high-density lipoprotein; LDL=low-density lipoprotein; MBE=model-based estimate; MMRM, mixed model for repeated measures; N=number of participants in the population; non-HDL=non–high-density lipoprotein; PBO=placebo, RETA=retatrutide; SD=standard deviation; VLDL=very-low-density lipoprotein.

TRIUMPH-2
OBESITY+T2D

Percent Change in hsCRP at Week 80

Efficacy Estimand



Systemic inflammation, measured by hsCRP, was reduced by over 50% with RETA 9 mg and 12 mg

RETA vs. PBO: *p<0.05, **p<0.01, and ***p<0.001. p-values are for MBE percent change difference vs. PBO.
Note: Data are shown as MBE (SE) unless otherwise stated.. EE analysis was conducted using MMRM. Data are from all randomized participants.
Only the comparisons between RETA 4mg, 9mg, and/or 12mg vs PBO with respect to the achievement of geometric mean percent change in hsCRP from baseline at week 80 are controlled for the type I error rate.
CV=coefficient of variation, EE=efficacy estimand; hsCRP=high-sensitivity C-reactive protein; MBE=model-based estimate; MMRM, mixed model for repeated measures, N=number of participants in the population, PBO=placebo; RETA=retatrutide; SD=standard deviation.

Change in IWQOL-Lite-CT Scores From Baseline to Week 80

Efficacy Estimand



RETA at every dose level[a] resulted in statistically significant and clinically meaningful reported improvements in physical function and psychosocial health

RETA vs. PBO: ***p<0.001. p-values are for MBE change difference vs. PBO.
[a]Individual dose levels were not controlled for multiplicity. IWQOL-Lite-CT Psychosocial Composite Score was not controlled for multiplicity.
Notes: Data are shown as MBE unless otherwise stated. EE analysis was conducted using MMRM. Data are from all randomized participants..
EE=efficacy estimand; IWQOL-Lite-CT=Impact of Weight on Quality of Life–Lite Clinical Trials; MBE=model-based estimate; n=number of participants in the specified category; N=number of participants in the population; PBO=placebo; RETA=retatrutide; T2D=type 2 diabetes.

TRIUMPH-2
OBESITY+T2D

TRIUMPH-2: Summary of Retatrutide Efficacy at Week 80

BODY WEIGHT REDUCTION



−12.7% with 4 mg

−20.8% with 12 mg

Waist circumference decrease: up to 17 cm

WEIGHT REDUCTION THRESHOLDS



≥15%

67% with 12 mg

≥20%

52% with 12 mg

BMI THRESHOLDS



<30 kg/m²

60% with 12 mg

<25 kg/m²

23% with 12 mg

GLYCEMIC CONTROL



HbA1c

- **Up to 79%** reached **HbA1c ≤6.5%**

FSG

- Mean FSG **~100 mg/dL (~5.6 mmol/L)** with 9 mg and 12 mg

LIPIDS



Triglycerides

- Up to **39.5%** reduction

Non-HDL-C

- Up to **19.6%** reduction

LDL-C

- Up to **12.2%** reduction

BLOOD PRESSURE



SBP/DBP

- Up to **10.8 / 4.6 mmHg** reduction

SYSTEMIC INFLAMMATION



hsCRP

- Up to **58.3%** reduction

PHYSICAL FUNCTION



IWQOL-Lite-CT Score

- Up to **22.9** increase

Note: Data are efficacy estimands values; all data are model-based estimates for change from baseline at Week 80 unless otherwise stated. N=289 (PBO), 292 (RETA 4 mg), 284 (RETA 9 mg), 287 (RETA 12 mg).

BMI=body mass index; DBP=diastolic blood pressure; HbA1c=glycated hemoglobin; HDL-C=high-density lipoprotein cholesterol; hsCRP=high-sensitivity C-reactive protein; IWQOL-Lite-CT=Impact of Weight on Quality of Life–Lite Clinical Trials; LDL-C=low-density lipoprotein cholesterol; PBO=placebo; RETA=retatrutide; SBP=systolic blood pressure; TG=triglycerides.

TRIUMPH-2
OBESITY+T2D

TRIUMPH-2: Summary of Retatrutide Efficacy at Week 80

BODY WEIGHT REDUCTION

−12.7% with 4 mg

−20.8% with 12 mg

Waist circumference decrease: up to 17 cm

WEIGHT REDUCTION THRESHOLDS

≥15%

67% with 12 mg

≥20%

52% with 12 mg

BMI THRESHOLDS

<30 kg/m²

60% with 12 mg

<25 kg/m²

23% with 12 mg

GLYCEMIC CONTROL

HbA1c

- **Up to 79%** reached **HbA1c ≤6.5%**

FSG

- Mean FSG **~100 mg/dL (~5.6 mmol/L)** with 9 mg and 12 mg

LIPIDS

Triglycerides

- Up to **39.5%** reduction

Non-HDL-C

- Up to **19.6%** reduction

LDL-C

- Up to **12.2%** reduction

BLOOD PRESSURE

SBP/DBP

- Up to **10.8 / 4.6 mmHg** reduction

SYSTEMIC INFLAMMATION

hsCRP

- Up to **58.3%** reduction

PHYSICAL FUNCTION

IWQOL-Lite-CT Score

- Up to **22.9** increase

RETA demonstrated a robust range of efficacy across doses (4 mg to 12 mg) for weight reduction, glycemic control, and cardiometabolic risk factor improvements in patients with Obesity/Overweight and T2D

Note: Data are efficacy estimands values; all data are model-based estimates for change from baseline at Week 80 unless otherwise stated. N=289 (PBO), 292 (RETA 4 mg), 284 (RETA 9 mg), 287 (RETA 12 mg).
BMI=body mass index; DBP=diastolic blood pressure; HbA1c=glycated hemoglobin; HDL-C=high-density lipoprotein cholesterol; hsCRP=high-sensitivity C-reactive protein; IWQOL-Lite-CT=Impact of Weight on Quality of Life–Lite Clinical Trials; LDL-C=low-density lipoprotein cholesterol; PBO=placebo; RETA=retatrutide; SBP=systolic blood pressure; TG=triglycerides.



UNIVERSITY OF CALGARY

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one child every child

women & children's health research institute

Impact of metformin in gestational diabetes mellitus: Real-world evidence from a population-based cohort study

Presented by: **Sonia Butalia MD, FRCPC, MSc**
Physician-Scientist, Professor of Medicine

Study team: Sonia Butalia, Anamaria Savu, Rose Yeung, Vichy Liyanage, Genevieve Jessiman-Perreault, Padma Kaul

EASD 2026 MILAN

Background & Rationale

Growing off-label use of metformin for managing gestational diabetes mellitus (GDM)

Clinical Guidelines: Many guidelines endorse **insulin** as the recommended first-line therapy for GDM (does not cross the placenta, long-term safety profile, highly effective at lowering glucose)

Patient and Physician Perspectives: Practical advantages for oral tablets with lower treatment burden. Preference for oral medications (compared to daily multiple injections), ease of administration, greater treatment acceptability

Regulatory state: Metformin remains off-label in Canada, and other countries (crosses the placenta, increased complications?, long-term offspring outcomes?)

Clinical concerns

Preterm Birth: Large randomized control trial of GDM demonstrated increased risk of **preterm birth among** pregnancies **exposed to metformin**, compared to insulin (no difference in composite outcome).

Offspring growth: Questions regarding potential birth weight alterations – lower birth weight, small for gestational age, or is there a reduction in macrosomia or large for gestational age babies.

Evidence gap: There is need to better understand the real-world impact of metformin in GDM.

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Study Objective & Methods

Objective: To assess the association of metformin and pregnancy and neonatal outcomes in individuals with gestational diabetes mellitus.



Large Population | Validated Algorithm



Linked Administrative Databases (2013 to 2024)



Exposures – Metformin, insulin, or both

Maternal and Neonatal Outcomes

- Gestational age at delivery, preterm delivery rates, C-section delivery, and labor induction rates
- Neonatal hypoglycemia, birth weight outcomes (SGA, LGA, macrosomia), APGAR scores, respiratory distress syndrome, jaundice, and NICU admissions

Analyses

- Multivariate logistic regression assessed the association between metformin alone vs. insulin alone and pregnancy or neonatal outcomes adjusted for several factors.
- Sensitivity analyses: 2023 – 2024, >95% had BMI

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Results



- 17,248 pregnancies with pharmacologically treated gestational diabetes mellitus
- Maternal age 33.1 ± 4.7 years

Table 1. Maternal characteristics* by management type for 2013 - 2024

Variable	Metformin only	Insulin only	Combined	p-value
Total pregnancies, number	1738	14785	725	
Age at delivery (y), mean (SD)	33.1 (5.1)	33.1 (4.7)	33.3 (4.7)	0.62
Body Mass Index, kg/m^2	28.9 (6.2)	30.1 (6.8)	31.7 (7.3)	<0.01
Body mass index, missing**	1010 (58.1)	7380 (49.9)	354 (48.8)	<0.01
Parity, 0	633 (36.4)	5223 (35.3)	249 (34.3)	0.46
1	597 (34.3)	5401 (36.5)	269 (37.1)	
2+	508 (29.2)	4161 (28.1)	207 (28.6)	
Rural residence (%)	372 (21.4)	1540 (10.4)	114 (15.7)	<0.01
Renal and/or cardiovascular disease	53 (3.0)	496 (3.4)	25 (3.4)	0.78
Pre-existing hypertension	226 (13.0)	1932 (13.1)	105 (14.5)	0.54
Gestational hypertension	112 (6.4)	930 (6.3)	51 (7.0)	0.71
Pre-eclampsia, eclampsia	89 (5.1)	663 (4.5)	37 (5.1)	0.38
Gestational age at delivery (week), mean (SD)	38.0 (1.3)	37.9 (1.3)	37.7 (1.3)	<0.01

*Abbreviated version; **BMI available for 95.4% of pregnancies for 2023 & 2024

Metformin prescriptions increased 7.4-fold from 2013 to 2024

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Table 2a. MATERNAL OUTCOMES (N=17,248, 2013-2024)

Variable	Metformin only	Insulin only	Combined	p-value	
Preterm birth	159 (9.1)	1429 (9.7)	72 (9.9)	0.76	✖
34-36 weeks	136 (7.8)	1215 (8.2)	60 (8.3)	0.95	
28-33 weeks*	*	214 (1.4)	*		
Induced delivery	958 (55.1)	8488 (57.4)	404 (55.7)	0.14	
C-section	678 (39.0)	6501 (44.0)	346 (47.7)	<0.01	⬅
Elective	319 (18.4)	3234 (21.9)	172 (23.7)	<0.01	
Urgent	359 (20.7)	3267 (22.1)	174 (24.0)	0.16	
Stillborn	< 10	23 (0.2)	< 10	0.08	✖

*suppressed due to low counts

Table 2b. NEONATAL OUTCOMES (N=17,248, 2013-2024)

Variable	Metformin only	Insulin only	Combined	p-value	
Birth weight (g), Mean (SD)	3256.8 (515.8)	3273.6 (534.3)	3289.0 (540.4)	0.32	✖
SGA	158 (9.1)	1250 (8.5)	51 (7.0)	0.25	✖
LGA	201 (11.6)	2033 (13.8)	119 (16.4)	<0.01	⬅
Birth weight ≥ 4000g	116 (6.7)	1185 (8.0)	65 (9.0)	0.09	
APGAR at 5 minutes, Mean (SD)	8.8 (0.8)	8.8 (0.8)	8.8 (0.8)	0.55	
Admission at NICU	189 (10.9)	183 (12.4)	90 (12.4)	0.19	
Neonatal hypoglycemia	196 (11.3)	1913(12.9)	108 (14.9)	0.03	⬅
Respiratory distress syndrome	19 (1.1)	248 (1.7)	11 (1.5)	0.19	
Jaundice	132 (7.6)	1280 (8.7)	47 (6.5)	0.05	
Birth injury	36 (2.1)	265 (1.8)	21 (2.9)	0.09	

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Table 3. Maternal and Neonatal Outcomes – Adjusted Associations Between Treatment for GDM
a) Main Analysis* (2013-2024) b) Sensitivity Analysis** (2023 – 2024; 95.4% BMI captured, n= 3,623)

	a) 2013-2024 (Main Analysis)			b) 2023 – 2024 (Sensitivity Analysis)		
Outcome	**Adj. OR***	**95% CI**	**p-value**	**Adj. OR****	**95% CI**	**p-value**
Preterm Birth	0.93	(0.78, 1.11)	0.44 ✖	0.68	(0.47,0.99)	0.04
C-section	0.81	(0.74, 0.90)	<0.01 ⬅	0.80	(0.65, 0.99)	0.04
SGA	1.09	(0.91, 1.30)	0.33 ✖	0.91	(0.65, 1.27)	0.59
LGA	0.76	(0.65, 0.89)	<0.01 ⬅	0.89	(0.58, 1.37)	0.60
Birth wt. ≥ 4 kg	0.75	(0.61, 0.92)	<0.01 ⬅	0.92	(0.58, 1.46)	0.73
Neonatal hypo.	0.81	(0.69, 0.95)	0.01 ⬅	0.69	(0.51, 0.94)	0.02
RDS	0.63	(0.39, 1.0)	0.05	0.58	(0.25, 1.33)	0.20
Jaundice	0.85	(0.70, 1.02)	0.08	0.90	(0.60, 1.35)	0.60
Birth injury	1.19	(0.84, 1.70)	0.32	-	-	-

SGA: small for gestational age, LGA: large for gestational age, RDS: respiratory distress syndrome
Adjusted for *age, urban/rural residence, marital status, parity, markers of SES, pre-existing hypertension, pre-eclampsia/eclampsia, pre-existing or gest. HTN, cardiovascular & renal disease ** All factors and BMI

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Table 3. Maternal and Neonatal Outcomes – Adjusted Associations Between Treatment for GDM
a) Main Analysis* (2013-2024) b) Sensitivity Analysis** (2023 – 2024) (95.4% BMI captured, n= 3,623)

	a) Main Analysis (2013-2024)			b) Sensitivity Analysis (2023 – 2024)		
Outcome	**Adj. OR***	**95% CI**	**p-value**	**Adj. OR****	**95% CI**	**p-value**
Preterm Birth	0.93	(0.78, 1.11)	0.44 ✗	0.68	(0.47,0.99)	0.04 ←
C-section	0.81	(0.74, 0.90)	<0.01 ←	0.80	(0.65, 0.99)	0.04 ←
SGA	1.09	(0.91, 1.30)	0.33 ✗	0.91	(0.65, 1.27)	0.59 ✗
LGA	0.76	(0.65, 0.89)	<0.01 ←	0.89	(0.58, 1.37)	0.60 ✗
Birth wt. ≥ 4 kg	0.75	(0.61, 0.92)	<0.01 ←	0.92	(0.58, 1.46)	0.73 ✗
Neonatal hypo.	0.81	(0.69, 0.95)	0.01 ←	0.69	(0.51, 0.94)	0.02 ←
RDS	0.63	(0.39, 1.0)	0.05	0.58	(0.25, 1.33)	0.20
Jaundice	0.85	(0.70, 1.02)	0.08	0.90	(0.60, 1.35)	0.60
Birth injury	1.19	(0.84, 1.70)	0.32	-	-	-

SGA: small for gestational age, LGA: large for gestational age, RDS: respiratory distress syndrome
Adjusted for *age, urban/rural residence, marital status, parity, markers of SES, pre-existing hypertension, pre-eclampsia/eclampsia, pre-existing or gest. HTN, cardiovascular & renal disease ** All factors and BMI

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Summary of Findings

- Large, contemporary population-based study of 17,248 pregnancies with GDM requiring glucose-lowering therapy, metformin use was associated with favorable maternal and neonatal outcomes compared with insulin alone.
  - After adjustment for potential confounders, metformin alone was associated with:

  ↓ risk of C-section, LGA, and neonatal hypoglycaemia compared with insulin alone, without ↑ risk of preterm birth, or SGA

- Sensitivity analysis that included BMI (>95%), metformin was associated with:
  - ↓ risk of C-section, neonatal hypoglycemia, ↓ preterm birth
  - BMI possibly was a negative confounder, attenuating the association in the main analyses
    - Obesity ↑'s preterm birth (preeclampsia, HTN) and associated with treatment selection (metformin may ↓ preeclampsia)
    - Adjustment for BMI reduced negative confounding, revealing lower preterm birth

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Clinical Implications and Conclusion



Growing off-label use of metformin because it offers practical advantages, including ease of administration, lower treatment burden, and potentially greater treatment acceptability.



Our study provides important information for clinicians and pregnant individuals on the important pregnancy and neonatal outcomes.

- Lowered risk of important outcomes (LGA, neonatal hypoglycaemia, C-section), without an increased risk of pre-term labour.
- Preterm birth may be one of the reasons clinicians have reservations about using metformin more routinely in practice.



Further study into this area is needed as well as into what other patient and/or provider factors influenced therapy modality, and the long-term maternal and offspring impact of metformin use, given the implications on patient counselling.

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Impact of Metformin in Gestational Diabetes Mellitus (GDM): Real-world Evidence From A Population-based Cohort Study

Sonia Butalia (MD, FRCPC, MSc)[1], Anamaria Savu (PhD)[2], Rose Yeung (MD, FRCPC, MPH)[2], Vichy Liyanage (PhD)[2], Genevieve Jessiman-Perreault (PhD)[3], Padma Kaul (PhD)[2]

[1]Medicine and Community Health Sciences, University of Calgary, Calgary, AB, Canada, [2]University of Alberta, Edmonton, AB, Canada, [3]Health Shared Services, Provincial Research Data Services, Edmonton, AB, Canada.

Background & Rationale

Growing off-label use of metformin for managing GDM

Clinical Guidelines: Many guidelines endorse insulin as the recommended first-line therapy for GDM (does not cross the placenta, long-term safety profile, highly effective at lowering glucose).

Patient and Physician Perspectives: Practical advantages for oral tablets with lower treatment burden. Preference for oral medications (compared to daily multiple injections), ease of administration, greater treatment acceptability.

Regulatory state: Metformin remains off-label in Canada, and other countries (crosses the placenta, increased complications?, long-term offspring outcomes?).

Study Objective & Methods

To assess the association of metformin use and pregnancy and neonatal outcomes in individuals with GDM.



Maternal and Neonatal Outcomes

- Gestational age at delivery, preterm delivery rates, C-section delivery, and labor induction rates
- Neonatal hypoglycemia, birth weight outcomes (SGA, LGA, macrosomia), APGAR scores, respiratory distress syndrome, jaundice, and NICU admissions

Analyses

- Multivariate logistic regression assessed the association between metformin alone vs. insulin alone and pregnancy or neonatal outcomes adjusted for several factors
- Sensitivity analyses: 2023 – 2025, >95% had BMI

Results

Cohort and Prescribing Trends

- 17,248 pregnancies with pharmacologically-treated GDM in Alberta, Canada
- Maternal age 33.1 ± 4.7 years



Metformin prescriptions for GDM increased 7.4-fold from 2013 to 2024

Table 1. Maternal characteristics* by GDM management type for 2013 - 2024

Variable	Metformin only	Insulin only	Combined	p-value
Total pregnancies, number	1738	14785	725	
Age at delivery (y), mean (SD)	33.1 (5.1)	33.1 (4.7)	33.3 (4.7)	0.62
Body Mass Index, kg/m^2	28.9 (6.2)	30.1 (6.8)	31.7 (7.3)	<0.01
Body mass index, missing**	1010 (58.1)	7380 (49.9)	354 (48.8)	<0.01
Parity, 0	633 (36.4)	5223 (35.3)	249 (34.3)	0.46
1	597 (34.3)	5401 (36.5)	269 (37.1)	
2+	508 (29.2)	4161 (28.1)	207 (28.6)	
Rural residence (%)	372 (21.4)	1540 (10.4)	114 (15.7)	<0.01
Renal and/or cardiovascular disease	53 (3.0)	496 (3.4)	25 (3.4)	0.78
Pre-existing hypertension	228 (13.0)	1932 (13.1)	105 (14.5)	0.54
Gestational hypertension	112 (6.4)	930 (6.3)	51 (7.0)	0.71
Pre-eclampsia, eclampsia	89 (5.1)	663 (4.5)	37 (5.1)	0.38
Gestational age at delivery (week), mean (SD)	38.0 (1.3)	37.9 (1.3)	37.7 (1.3)	<0.01

*Abbreviated version; **BMI available for 95.4% of pregnancies for 2023 & 2024

Table 2a. Maternal Outcomes (N=17,248, 2013-2024)

Variable	Metformin only	Insulin only	Combined	p-value
Preterm birth	159 (9.1)	1429 (9.7)	72 (9.9)	0.76
34-36 weeks	136 (7.8)	1215 (8.2)	60 (8.3)	0.95
28-33 weeks*	*	214 (1.4)	*	
Induced delivery	956 (55.1)	8488 (57.4)	404 (55.7)	0.14
C-section	678 (39.0)	6501 (44.0)	346 (47.7)	<0.01
Elective	319 (18.4)	3234 (21.9)	172 (23.7)	<0.01
Urgent	359 (20.7)	3267 (22.1)	174 (24.0)	0.16
Stillborn	< 10	23 (0.2)	< 10	0.08

*suppressed due to low counts

Table 2b. Neonatal Outcomes (N=17,248, 2013-2024)

Variable	Metformin only	Insulin only	Combined	p-value
Birth weight (g), Mean (SD)	3256.8 (515.8)	3273.6 (534.3)	3289.0 (540.4)	0.32
SGA	158 (9.1)	1250 (8.5)	51 (7.0)	0.25
LGA	201 (11.6)	2033 (13.8)	119 (16.4)	<0.01
Birth weight ≥ 4000g	116 (6.7)	1185 (8.0)	65 (9.0)	0.09
APGAR at 5 minutes, Mean (SD)	8.8 (0.8)	8.8 (0.9)	8.8 (0.8)	0.55
Admission at NICU	189 (10.9)	183 (12.4)	90 (12.4)	0.19
Neonatal hypoglycemia	196 (11.3)	1913(12.9)	108 (14.9)	0.03
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Jaundice	132 (7.6)	1280 (8.7)	47 (6.5)	0.05
Birth injury	36 (2.1)	265 (1.8)	21 (2.9)	0.09

Table 3. Maternal and Neonatal Outcomes – Adjusted Associations Between Treatment for GDM
a) Main Analysis (2013-2024) b) Sensitivity Analysis (2023-2024, 95.4% BMI captured, n= 3,623)

Outcome	a) Main Analysis (2013-2024)			b) Sensitivity Analysis 2023 – 2025		
	Adjusted OR*	95% CI	p-value	Adjusted OR**	95% CI	p-value
Preterm Birth	0.93	(0.78, 1.11)	0.44	0.68	(0.47,0.99)	0.04
C-section	0.81	(0.74, 0.90)	<0.01	0.80	(0.66, 0.99)	0.04
SGA	1.09	(0.91, 1.30)	0.33	0.91	(0.66, 1.27)	0.59
LGA	0.76	(0.65, 0.89)	<0.01	0.89	(0.58, 1.37)	0.60
Birth weight ≥ 4 kg	0.75	(0.61, 0.92)	<0.01	0.92	(0.58, 1.46)	0.73
Neonatal hypoglycemia	0.81	(0.69, 0.95)	0.01	0.69	(0.51, 0.94)	0.02
RDS	0.83	(0.39, 1.0)	0.05	0.58	(0.25, 1.33)	0.20
Jaundice	0.85	(0.70, 1.02)	0.08	0.90	(0.60, 1.35)	0.60
Birth injury	1.19	(0.84, 1.70)	0.32	-	-	-

SGA: small for gestational age, LGA: large for gestational age, RDS: respiratory distress syndrome
Adjusted for *age, urban/rural residence, marital status, parity, markers of SES, pre-existing hypertension, pre-eclampsia/eclampsia, pre-existing or gest. HTN, cardiovascular & renal disease. ** All factors and BMI

Summary of Findings



Clinical Implications and Conclusion

Growing off-label use of metformin because it offers practical advantages, including ease of administration, lower treatment burden, and potentially greater atment acceptability.

Our study provides important information for clinicians and pregnant individuals on the important pregnancy and neonatal outcomes.

- Lowered risk of important outcomes (LGA, neonatal hypoglycemia, C-section), without an increased risk of pre-term labour.
- Preterm birth may be one of the reasons clinicians have reservations about using metformin more routinely in practice.

Further study into this area is needed as well as into what other patient and/or provider factors influenced therapy modality, and the long-term maternal and offspring impact of metformin use, given the implications on patient counselling.

EASD 2026 MILAN

MET-KIDS

Longitudinal follow up study of mother-offspring dyads from the Emerge randomized control trial of metformin in pregnancies complicated by gestational diabetes.

Christine Newman, Roberta Scairati, Alberto Alvarez-Iglesias, Andrew Smyth, Paula M. O'Shea, Declan Devane, Paddy Gillespie, Aoife M Egan, Martin O'Donnell, Mary Fitzgerald, David Aguilar Macias, Mairead Crowley, Robert McEvoy, Fidelma P Dunne

Follow-up of mother-offspring dyads from the EMERGE randomised controlled trial

EASD| September 2026

Ollscoil na Gaillimhe
University of Galway

Why this follow-up matters

Metformin crosses the placenta, so long-term offspring safety remains clinically important.

Clinical context

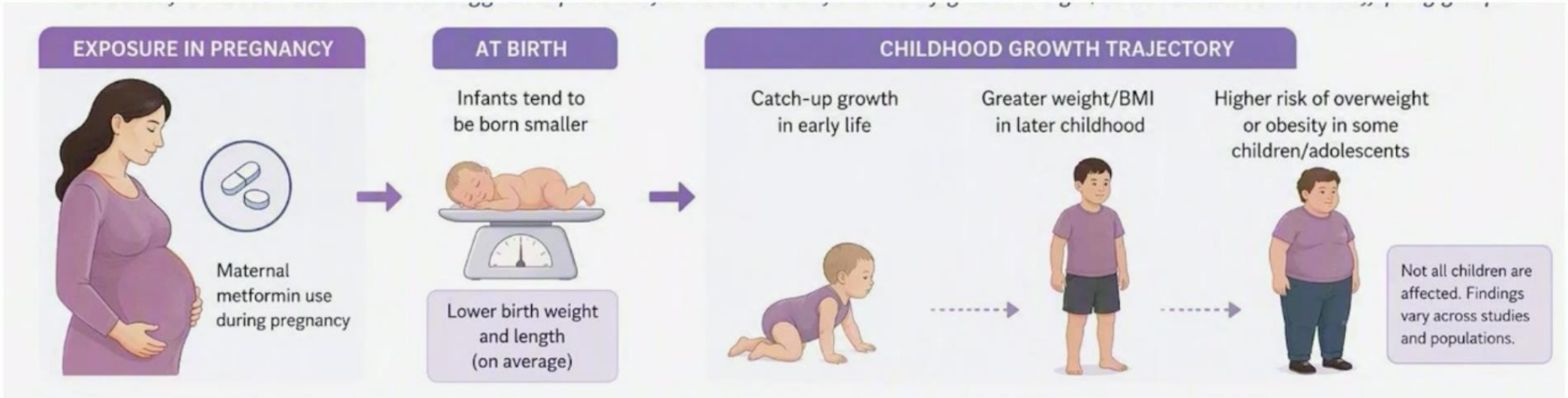
- Metformin is increasingly used for gestational diabetes.
- **Some** previous follow-up studies raised concern about higher offspring adiposity.
- Randomised follow-up provide strong evidence base.

Primary question

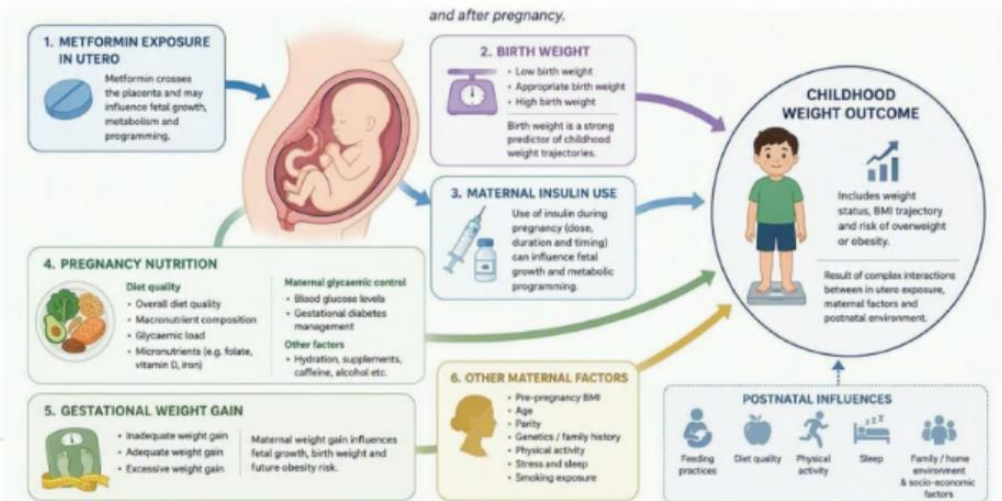
At 3 to 6 years of age, do children randomised in utero to early metformin differ from placebo in growth or adiposity?

Growth | BMI z score | Skinfold thickness

Why follow up matters



Concern regarding in-utero metformin exposure centres around changes in birth weight (including SGA infants) and a subsequent trend towards obesity in childhood – however multiple factors should be considered



Study design

Longitudinal follow-up of the original EMERGE randomised allocation.



510 pregnancies

Metformin up to 2.5 g or placebo

Treatment from ≤28+6 weeks

Follow-up at 3–6 years

270 dyads attended 52.4%

Offspring outcomes: height, weight, BMI and age/sex-standardised BMI percentile, BMI category, triceps/subscapular/suprailiac skinfolds, total skinfolds and blood pressure.
Neurocognitive outcomes also assessed
Maternal outcomes: height, weight, BMI, lipid and glucose tolerance, BP, QoL, renal and liver function

Baseline neonatal outcomes from EMERGE trial

Ollscoil na Gaillimhe
University of Galway

Descriptive measures were closely aligned between treatment groups.

Outcome	Overall	Attenders	Non-attenders	p
Crown-heel-length (cm)	52.0 (49.5, 53.0)	52.0 (49.0, 53.8)	51.5 (50.0, 53.0)	0.589
Birth weight (g)	3,480 (3,200, 3,750)	3,500 (3,150, 3,750)	3,460 (3,200, 3,750)	0.886
Birth weight percentile (%)	60 (34, 78)	59 (34, 78)	60 (34, 78)	0.876
Gestational age at delivery (weeks)	39.30 (38.60, 40.00)	39.30 (38.60, 40.00)	39.30 (38.50, 40.10)	0.897
Preterm birth (%)	37 (7.9%)	22 (8.2%)	15 (7.5%)	0.779
Small for gestational age (%)	21 (4.5%)	13 (4.9%)	8 (4.0%)	0.652
Large for gestational age (%)	50 (11%)	30 (11%)	20 (10.0%)	0.666
Neonatal ICU admission (%)	68 (14%)	39 (14%)	29 (15%)	0.986
Neonatal hypoglycaemia (%)	62 (13%)	30 (11%)	32 (16%)	0.121
Respiratory distress (%)	38 (8.1%)	24 (8.9%)	14 (7.0%)	0.448

No unadjusted comparison showed evidence of a between-group difference.

Children's outcomes at a median 4.8 years

Outcome	Placebo (n=148)	Metformin (n=121)	Difference	95% CI	P value
Age (years)	4.81 (3.51, 5.89)	4.74 (3.76, 5.93)	-0.03	-0.35, 0.28	0.837
Female	58 (39%)	70 (57%)	18%	31%, 5.7%	**0.004**
Weight (kg)	18.8 (16.4, 22.6)	19.2 (16.7, 22.2)	0.40	-0.73, 1.5	0.486
Height (cm)	107 (97, 115)	107 (99, 115)	0.05	-2.4, 2.5	0.967
BMI percentile	88 (57–98)	87 (66–96)	1.6	-5.3, 8.4	0.650
BMI (kg/m^2)	17.2 (15.7–18.6)	17.1 (16.0–18.2)	0.18	-0.33, 0.70	0.487
Obesity (%)	37%	31%	6.2%	-5.9%, 18%	0.353
Overweight (%)	17%	23%	−6.1%	-17%, 4.3%	0.271
BMI z score	1.1 (1.2)	1.0 (1.3)	0.09	-0.22, 0.39	0.568

NIH definitions
Overweight defined >85th percentile
Obesity defined >95th percentile

[1]n (%); Median (Q1, Q3)
[2]Pearson's Chi-squared test; Wilcoxon rank sum test

Children's outcomes at a median 4.8 years

Outcome	Placebo (n=148)	Metformin (n=121)	Difference	95% CI	P value
Triceps skinfold (cm)	10.00 (8.00, 12.00)	10.00 (8.00, 12.00)	0.22	-0.52, 0.95	0.561
Subscapular skinfold (cm)	6.00 (5.00, 8.00)	6.00 (5.00, 8.00)	-0.16	-0.83, 0.51	0.637
Suprailiac skinfold (cm)	10.0 (8.0, 12.5)	10.0 (7.0, 13.0)	0.20	-0.69, 1.1	0.659
Sum of skinfolds (cm)	27 (23, 31)	26 (22, 32)	0.29	-1.4, 2.0	0.739
Systolic blood pressure (mmHg)	100 (9)	100 (8)	0.17	-2.1, 2.4	0.884
Diastolic blood pressure (mmHg)	60 (10)	58 (10)	1.7	-0.98, 4.3	0.214

[1]n (%); Median (Q1, Q3)
[2]Pearson's Chi-squared test; Wilcoxon rank sum test

Estimated effect in offspring anthropometric outcomes at follow-up

Weight at follow-up visit		
Model 1	-0.401 (-1.566 to 0.764)	0.499
Model 2	-0.364 (-1.23 to 0.501)	0.408
Model 3	-0.008 (-0.869 to 0.853)	0.986
Height at follow-up visit		
Model 1	-0.051 (-2.485 to 2.384)	0.967
Model 2	0.023 (-1.287 to 1.333)	0.972
Model 3	0.27 (-1.09 to 1.629)	0.696
BMI at follow-up visit		
Model 1	-0.182 (-0.701 to 0.337)	0.490
Model 2	-0.212 (-0.741 to 0.316)	0.430
Model 3	-0.043 (-0.576 to 0.489)	0.873
BMI category at follow-up visit		
Model 1	0.89 (0.57 to 1.4)	0.613
Model 2	0.92 (0.58 to 1.46)	0.719
Model 3	1.07 (0.66 to 1.75)	0.775

Values are estimated mean differences with 95% confidence intervals from linear regression models or odds ratios from ordinal logistic regression models.

Model 1 was unadjusted.

Model 2 adjusted for offspring age at follow-up and sex.

Model 3 additionally adjusted for maternal insulin initiation during index pregnancy, birth weight, and breastfeeding following index pregnancy for weight, BMI, and BMI-category outcomes, while the height model was additionally adjusted for maternal insulin initiation during index pregnancy, crown–heel length at birth, and breastfeeding following index pregnancy.

Conclusions and next steps

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University of Galway

1 Reassuring comparison

No evidence that early antenatal metformin altered weight, height, BMI category or skinfold adiposity at approximately 4 years.

2 Interpret cautiously

Follow-up was 52.4%; effect estimates were small but imprecise, and sex distribution differed between groups.

3 Continue follow-up

Longer-term assessment through later childhood is needed, including cardiometabolic, developmental and behavioural outcomes.

Sex-specific differences in the effects of diabetic kidney disease medications

Hiddo L Heerspink
Professor Clinical Trials and Personalized Medicine
Dept Clinical Pharmacy and Pharmacology
University Medical Center Groningen
The Netherlands

GRONINGEN KOLFF CENTER

UMCG

Sex-specific differences in DKD management exist at multiple levels



- Differences in screening, monitoring, referral and drug prescription



- Differences in drug efficacy



- Differences in drug safety



- Differences in drug monitoring and dose adjustments

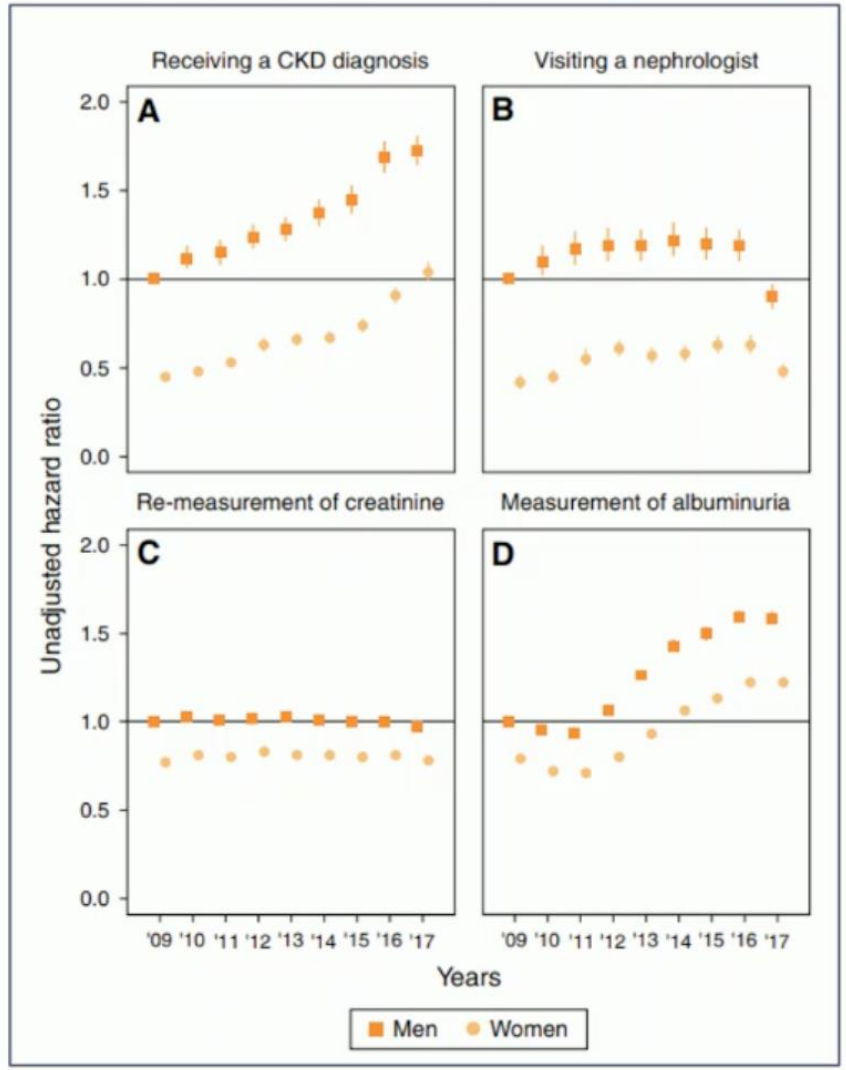


- Differences in drug adherence

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Females are less likely to receive the same degree of screening, monitoring, and referral to a nephrologist compared to males



Healthcare based study in Sweden of 227847 adults (55% women) with eGFR<60 ml/min and followed from 2009 - 2017

Swartling et.al. J AM Soc Neprol 2022:33:1903-1914

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Differences in drug efficacy and safety can be attributed to Pharmacokinetic and Pharmacodynamic differences

Pharmacokinetic differences:

- Drug absorption
  - Higher gastic pH
- Body composition
  - Fatt vs Lean mass
  - Circulating volume
- Metabolic enzyme activity
  - Higher Cyp3A4 activity
  - Lower Cyp2D6 activity
- Drug clearance
  - Lower GFR
  - Altered active secretion



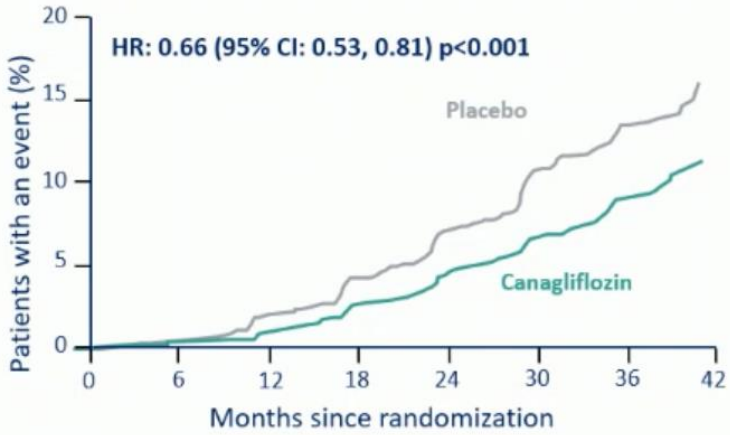
Pharmacodynamic differences:

- Receptor disposition
- Receptor down-stream signalling
- Epigenetic regulation
- Role of sex hormones

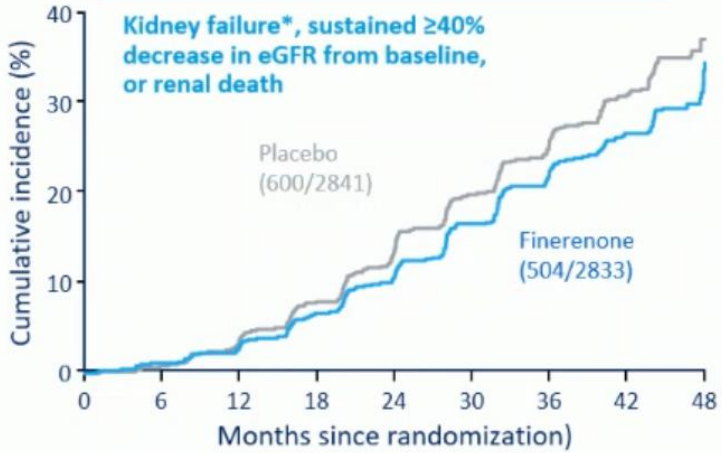
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New treatments have revolutionized the management of DKD

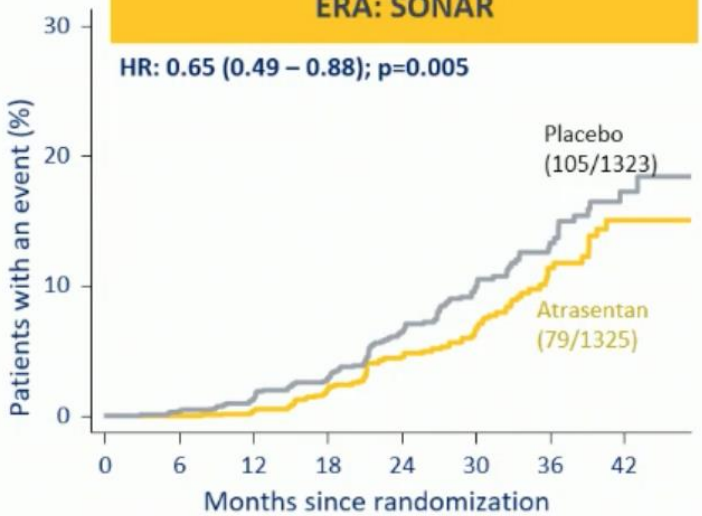
SGLT2 inhibition: CREDENCE[1a]



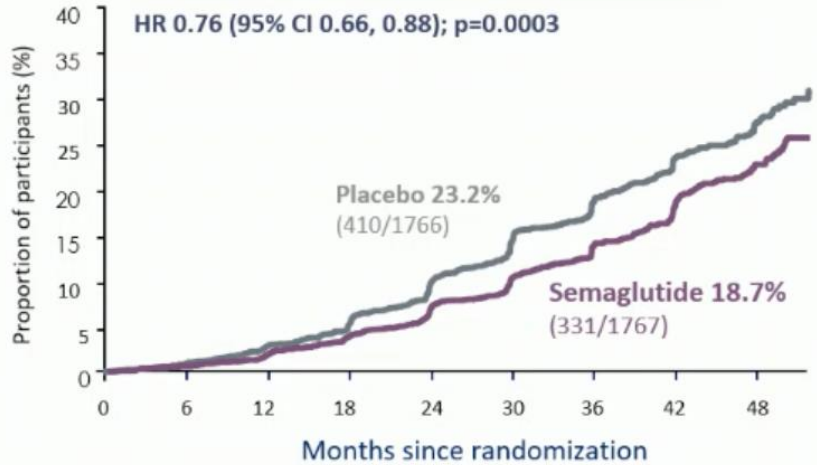
ns-MRA: FIDELIO-DKD



ERA: SONAR



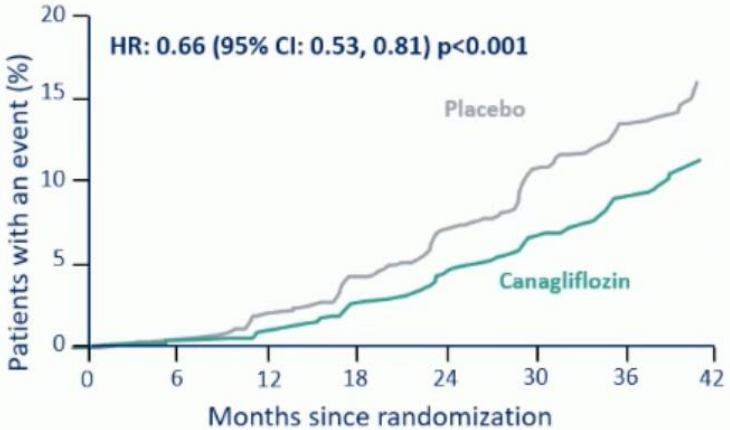
GLP-1 RA: FLOW



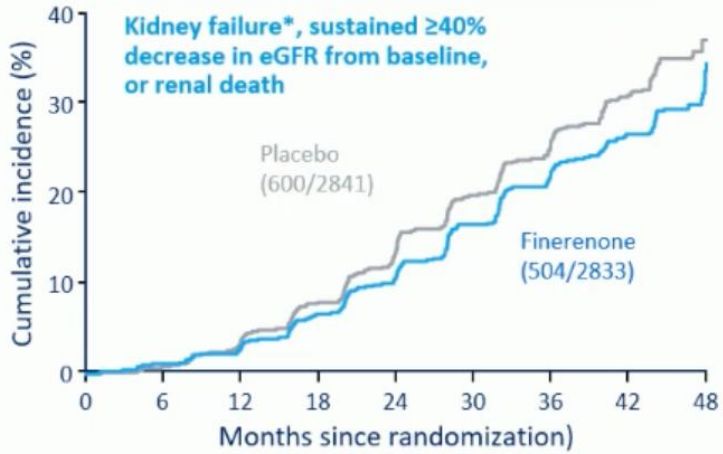
Perkovic et.al. New Engl J Med 2019;380(24):2295-2306: Bakris et.al. New Engl J Med 2020: 383(23):2219-2229: Heerspink et.al. Lancet 2019: 393(10184):1937-1947: Perkovic et.al. New Engl J Med 2024: 391(2):109-121

New treatments have revolutionized the management of DKD

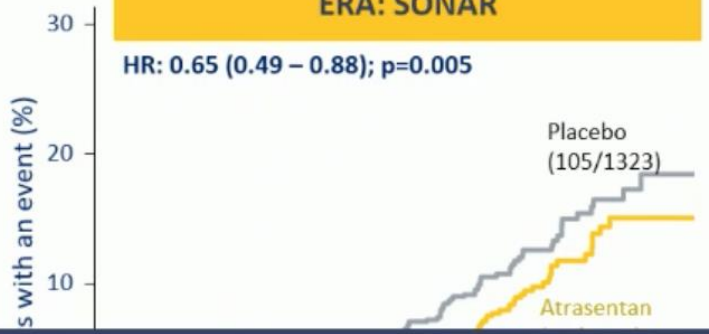
SGLT2 inhibition: CREDENCE[1a]



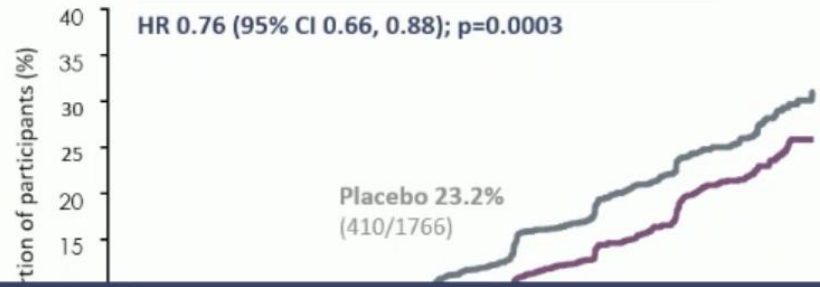
ns-MRA: FIDELIO-DKD



ERA: SONAR



GLP-1 RA: FLOW



KDIGO recommends SGLT2 inhibitors, Finerenone and Semaglutide in diabetic CKD (Class 1A)

Perkovic et.al. New Engl J Med 2019;380(24):2295-2306: Bakris et.al. New Engl J Med 2020: 383(23):2219-2229:
Heerspink et.al. Lancet 2019: 393(10184):1937-1947: Perkovic et.al. New Engl J Med 2024: 391(2):109-121

Females with CKD are less likely to receive RASi and SGLT2i compared to males

	Unadjusted		Model 1*		Model 2*	
Therapy receipt, No. (%)	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
RAS inhibitors	**0.80** (0.70-0.92)	0.001	**0.74** (0.65-0.86)	<0.001	**0.73** (0.63-0.86)	<0.001
Diuretics	1.02 (0.89-1.16)	0.8	0.95 (0.82-1.10)	0.5	**1.00** (0.85-1.17)	0.9

*Model 1 was adjusted for age (continuous variable), race (categorical variable), BMI (continuous variable). Model 2 was adjusted for age, race, BMI, presence of CVD and diabetes (categorical variables CKD etiology and prognosis risk

Global Kidney Patient Trials Network analysis among 4348 paitents with CKD (41% female)
Patient recruited in Australia, Argentina, Canada, Italy, Japan, Spain, and the United States

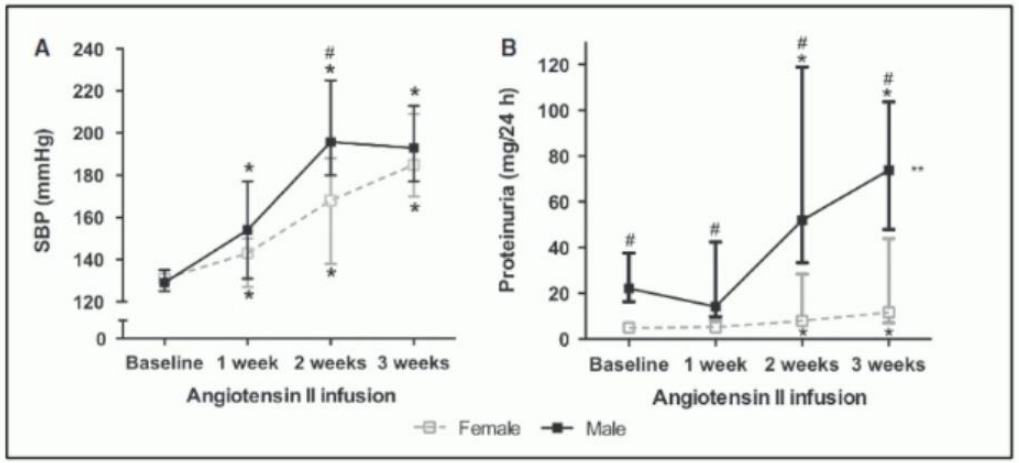
Du et.al. Submitted 2026

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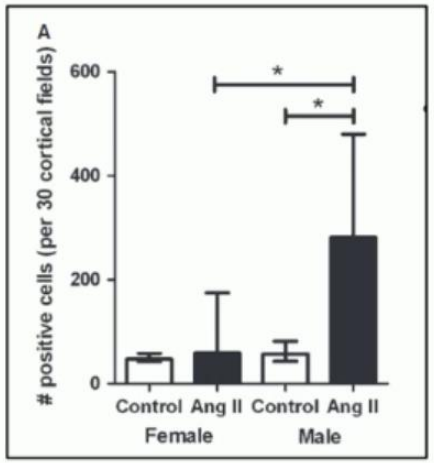
Females are less sensitive to RAAS compared to males

Animal Study

Faster blood pressure increase and more proteinuria in male vs female rats upon Ang II infusion

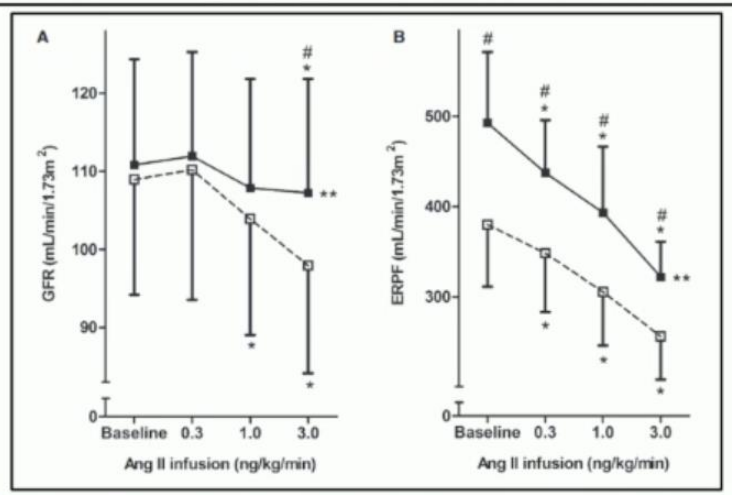


Inflammation in Males upon Ang II infusion

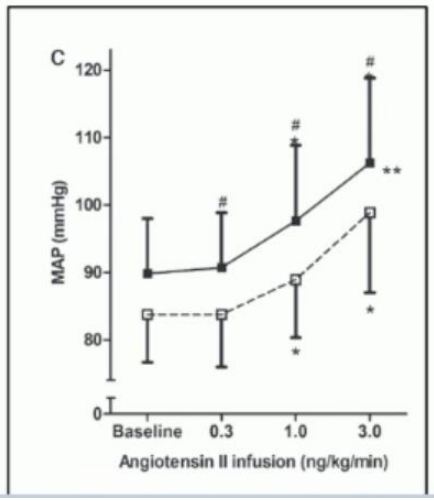


Healthy Volunteers Study

Renal plasma flow declines more in male vs female



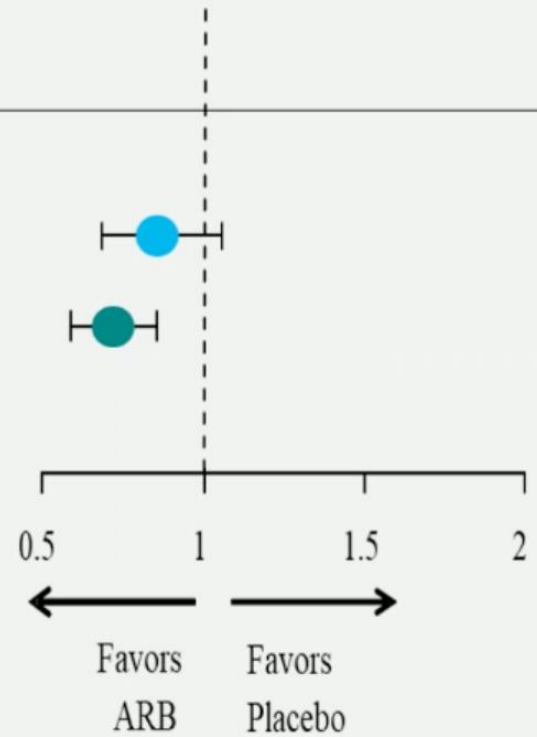
MAP increases more in male vs female



Toering et.al. Physiol Rep. 2015 Jul;3(7):e12434

ARBs are kidney protective in DKD in males and females

	Placebo Events (%)	Treatment Events (%)	Hazard ratio 95% CI
Composite kidney			
Women (n=923)*	165 (38.0)	167 (34.1)	0.86 (0.69-1.06)
Men (n=1737)	256 (28.5)	184 (21.9)	0.72 (0.59-0.86)



Analysis of 2661 (35% Female) patients with Diabetic Kidney Disease participating in the RENAAL and IDNT trials

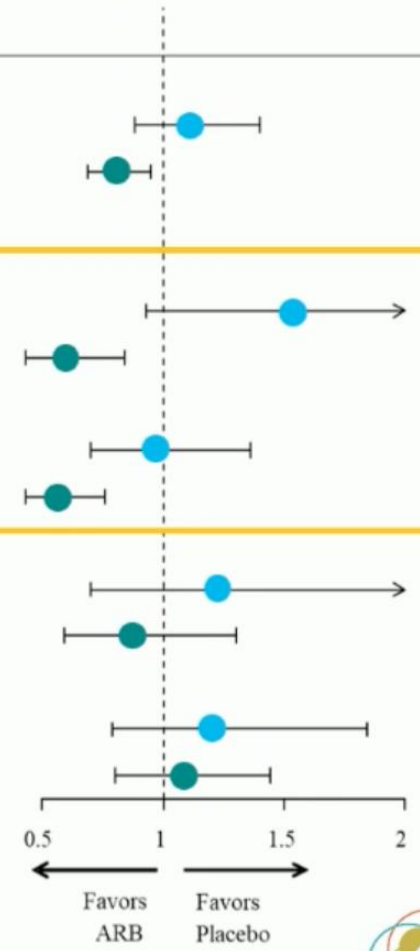
De Vries et. al. Diabetologia 2025

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ARBs are cardioprotective in males but not in females with DKD

	Placebo Events (%)	Treatment Events (%)	Hazard ratio 95% CI
Composite cardiovascular			
Women (n=924)	130 (30.0)	160 (32.6)	1.11 (0.88-1.40)
Men (n=1737)	323 (36.0)	259 (30.8)	0.81 (0.69-0.95)
Myocardial infarction			
Women (n=924)	24 (5.5)	41 (8.4)	1.53 (0.93-2.54)
Men (n=1737)	90 (10.0)	53 (6.3)	0.60 (0.43-0.84)
Heart failure			
Women (n=924)	68 (15.7)	75 (15.3)	0.98 (0.70-1.36)
Men (n=1737)	130 (14.5)	74 (8.8)	0.57 (0.43-0.76)
Stroke			
Women (n=924)	22 (5.1)	30 (6.1)	1.22 (0.70-2.12)
Men (n=1737)	54 (6.0)	45 (5.4)	0.87 (0.59-1.30)
Cardiovascular death			
Women (n=924)	38 (8.8)	51 (10.4)	1.21 (0.79-1.84)
Men (n=1737)	87 (9.7)	91 (10.8)	1.08 (0.80-1.44)

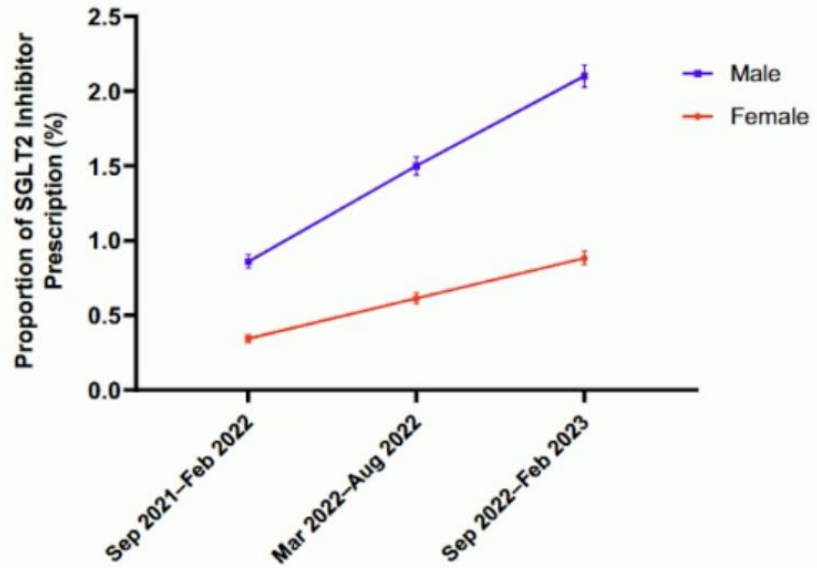


- Female
- Male

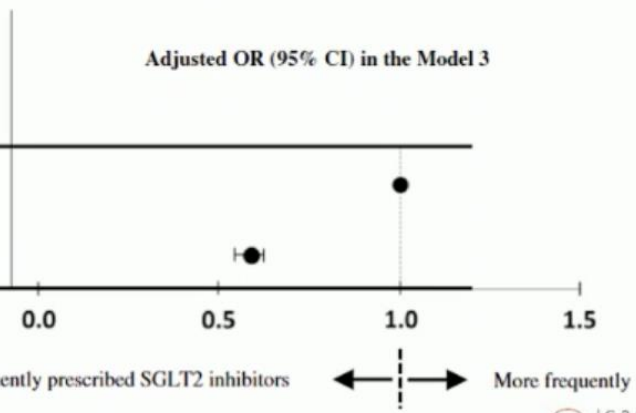
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Sex disparities in SGLT2 inhibitor prescription in Japan



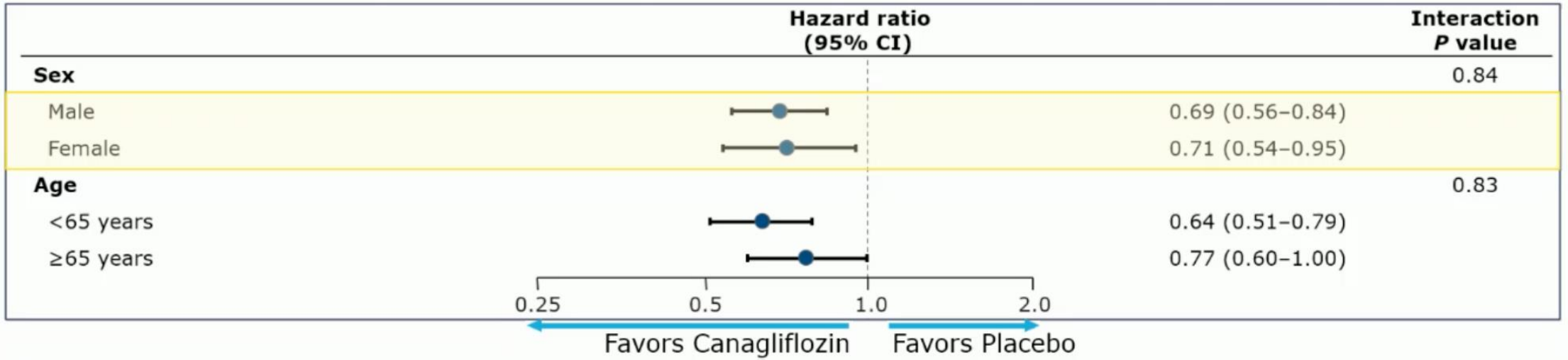
Association between Gender and SGLT2 Inhibitor Prescription	Number of Individuals	Number of Prescriptions	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Males	167,855	3,689	1 (reference)	1 (reference)	1 (reference)
Females	190,279	1,833	0.43 (0.41–0.46)	0.42 (0.40–0.45)	0.58 (0.55–0.62)



Azegami et.al. Diabetes Obesity Metabolism 2025:27:6294-6303

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CREDENCE: Canagliflozin confers kidney protection in males and females



Perkovic et.al. N Engl J Med. 2019 Jun 13;380(24):2295-2306

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CREDENCE: Adverse events with Canagliflozin in DKD

All adverse events						
Female	632/761	623/731	975.3	1143.2	0.89 (0.80 to 1.00)	0.70
Male	1152/1439	1237/1466	851.9	1060.2	0.86 (0.80 to 0.93)	
Serious adverse events						
Female	246/761	243/731	163.9	173.2	0.94 (0.78 to 1.12)	0.34
Male	491/1439	563/1466	175.5	207.9	0.84 (0.75 to 0.95)	
Urinary tract infection						
Female	170/761	130/731	110.6	89.7	**1.23 (0.98 to 1.54)**	**0.035**
Male	75/1439	91/1466	23.2	28.7	0.82 (0.6 to 1.11)	
Mycotic genital infections						
Female	22/761	10/731	12.9	6.2	2.11 (1.00 to 4.45)	**0.038**
Male	28/1439	3/1466	8.5	0.9	**9.30 (2.83 to 30.60)**	

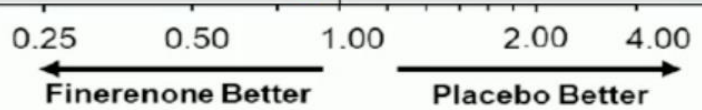
Perkovic et.al. N Engl J Med. 2019 Jun 13;380(24):2295-2306

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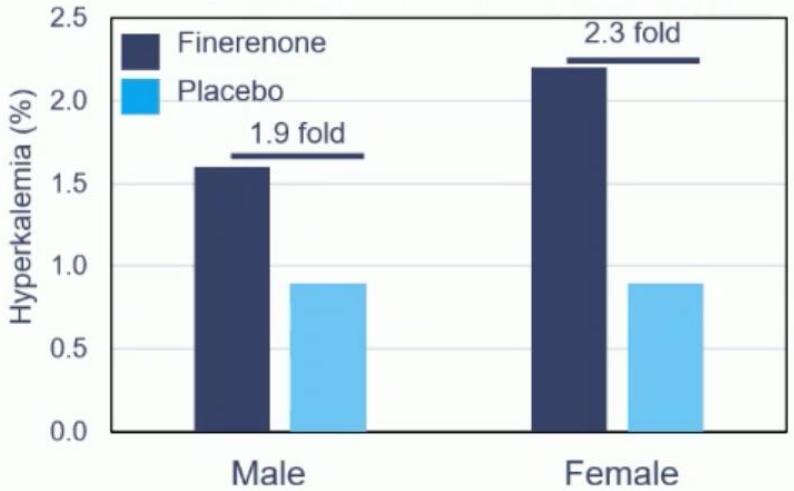
Finerenone efficacy and safety in males and females

Finerenone efficacy in reducing CKD progression (40% GFR decline / Kidney Failure / Renal Death)

Subgroup	Finerenone	Placebo	Finerenone	Placebo	Hazard Ratio (95% CI)
	no. of patients with event /total no.		*No. of patients with events per 100 patient years*		
All patients	**504/2833**	**600/2841**	**7.59**	**9.08**	**0.82 (0.73–0.93)**
Age at run-in visit					
<65 years	267/1205	302/1174	9.70	11.29	0.85 (0.72–1.01)
≥65 years	237/1628	298/1667	6.09	7.58	0.79 (0.67–0.94)
Sex					
Male	351/1953	432/2030	7.60	9.14	0.81 (0.70–0.93)
Female	153/880	168/811	7.57	8.93	0.87 (0.70–1.09)



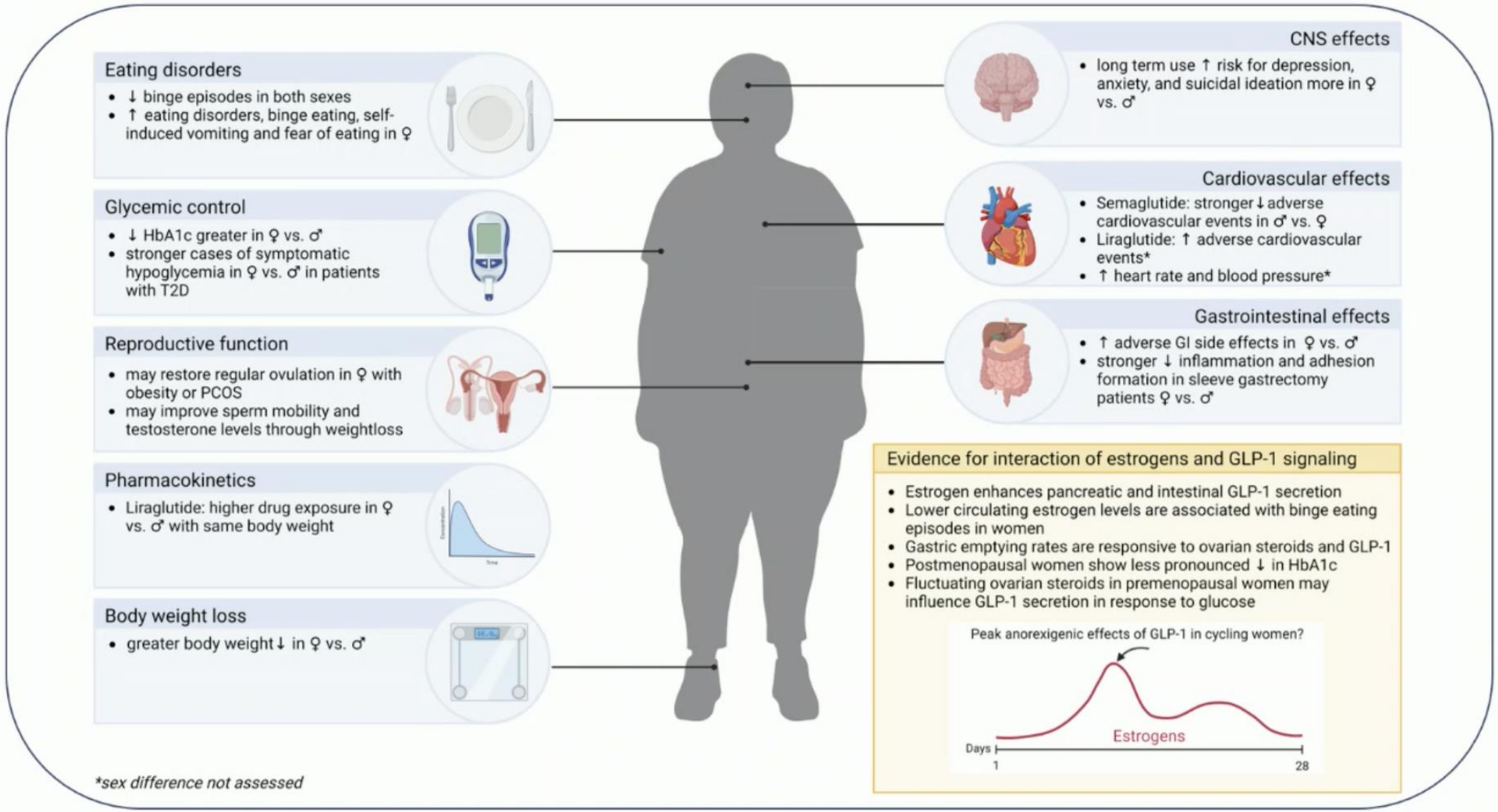
Hyperkalemia incidence (%)



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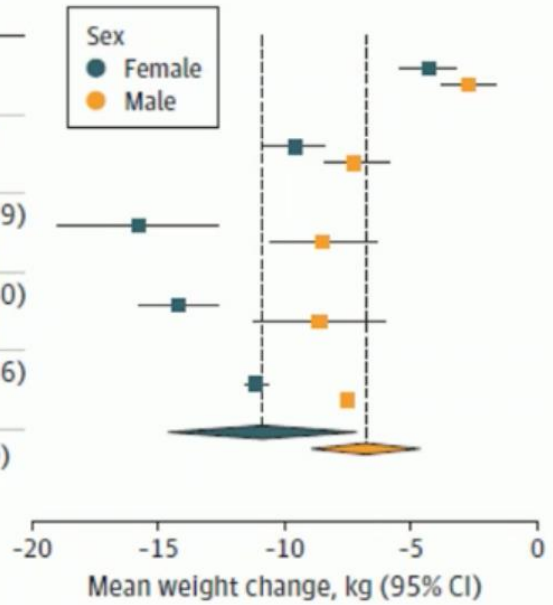
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Sex specific effects of GLP-1 analogs and their potential interaction with estrogens



A Larger Reduction in Body Weight in Female Compared to Male during GLP1 RA treatment

Sex	Patients, No.	Mean weight change, kg (95% CI)
Baur et al,[20] 2023	138	-4.30 (−5.40 to −3.20)
	92	-2.70 (−3.80 to −1.60)
Butler et al,[24] 2024	525	-9.60 (−10.90 to −8.40)
	527	-7.20 (−8.40 to −5.90)
Kadowaki et al,[34] 2022	148	-15.79 (−18.98 to −12.59)
	253	-8.47 (−10.59 to −6.34)
Knop et al,[37] 2023	445	-14.20 (−15.80 to −12.60)
	167	-8.60 (−11.20 to −6.00)
Ryan et al,[11] 2024	4878	-11.11 (−11.56 to −10.66)
	12733	-7.50 (−7.78 to −7.23)
QM test: $P = .08$	6134	-10.88 (−14.76 to −7.00)
	13772	-6.78 (−8.95 to −4.61)



More weight loss among women than men:

- GLP-1 RA interacts with estrogen
- Altered Pharmacokinetics
  - Lower median body weight (higher exposure?)

Meta-analysis of 48 RCTs
Weight loss assessed by sex in 6 RCTs
(N=20006; 6134 females)

Alexander et.al. JAMA Intern Med. 2026;186(5):567-577

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GLP-1 RA Gastro-intestinal side effects in Males and Females

Characteristics, *n* (%)	All GLP-1 RAs (*n* = 16,568)	Exenatide (*n* = 4401; 26.6)	Liraglutide (*n* = 4126; 24.9)	Dulaglutide (*n* = 4075; 24.6)	Semaglutide (*n* = 3966; 23.9)
Gender					
Female	**10,270 (62.0)**	2797 (63.6)	2788 (67.6)	2306 (566)	2379 (60.0)
Male	**6152 (37.1)**	1591 (36.2)	1325 (32.1)	1684 (41.3)	1552 (39.1)
Not specified	**146 (0.9)**	13 (0.3)	13 (0.3)	85 (2.1)	35 (0.9)

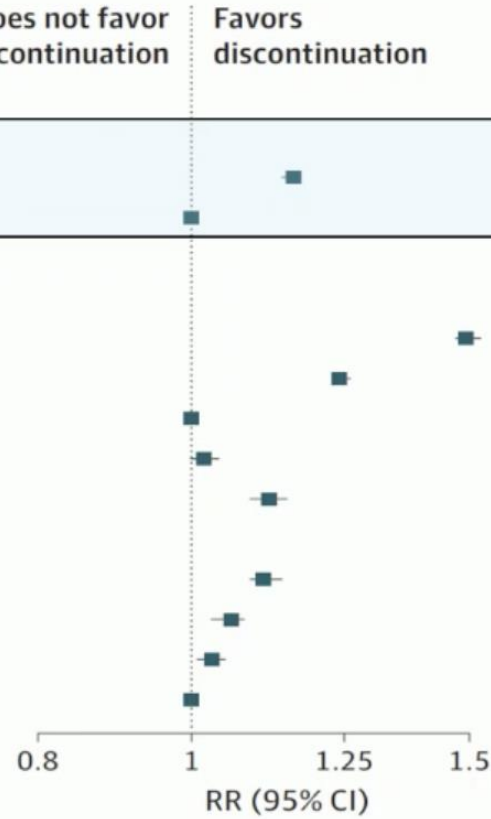
- Analysis of the US FDA Adverse Event Reporting System from 2007 – 2023
- Spontaneous reported adverse events from clinical practice
- Gastro-intestinal events (total 16422 events) during GLP-1 RA treatment are shown

Osei et.a Diagnosticsl 2024 Dec 16;14(24):2829

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GLP-1 RA discontinuation in men and women
Females less likely to discontinue GLP-1 RA compared to Males

Factors	Total, No. (%)	Discontinuers, No. (%)	Age- and sex-adjusted RR (95% CI)
Sociodemographic factors			
Sex			
Men	49 271 (31.2)	26 477 (53.7)	1.16 (1.14-1.17)
Women	108 551 (68.8)	51 006 (47.0)	1 [Reference]
Age			
Median (IQR)	49 (39-58)	NA	NA
18-29	15 442 (9.8)	10 005 (64.8)	1.49 (1.47-1.52)
30-44	44 818 (28.4)	24 304 (54.2)	1.24 (1.23-1.26)
45-59	68 302 (43.3)	29 804 (43.6)	1 [Reference]
60-69	21 873 (13.9)	9754 (44.6)	1.02 (1.00-1.04)
≥70	7387 (4.7)	3616 (49.0)	1.12 (1.09-1.15)
Average disposable annual income, DKK[a]			
≤240 000	14 340 (9.1)	7589 (52.9)	1.11 (1.09-1.14)
240 001-260 000	61 995 (39.4)	30 589 (49.3)	1.06 (1.03-1.08)
260 001-300 000	67 956 (43.2)	32 991 (48.5)	1.03 (1.01-1.05)
>300 000	13 017 (8.3)	6006 (46.1)	1 [Reference]



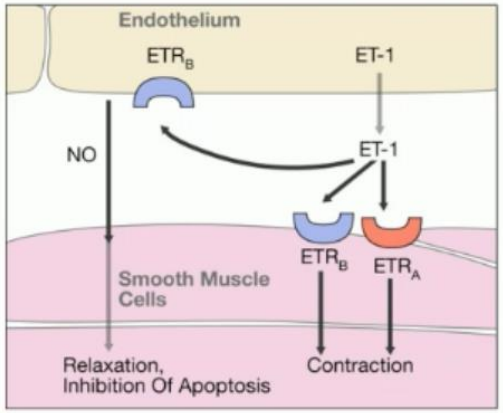
Analysis of Danish data among 157 822 first-time initiators of semaglutide between December 1, 2022, and November 1, 2024 comprising 108 551 women (69%) and 49 271 men (31%); 77483 (49%) patients discontinued within 12 months after initiation
Mailhac et.al Jama Network Open 2026;9(8):e2631371

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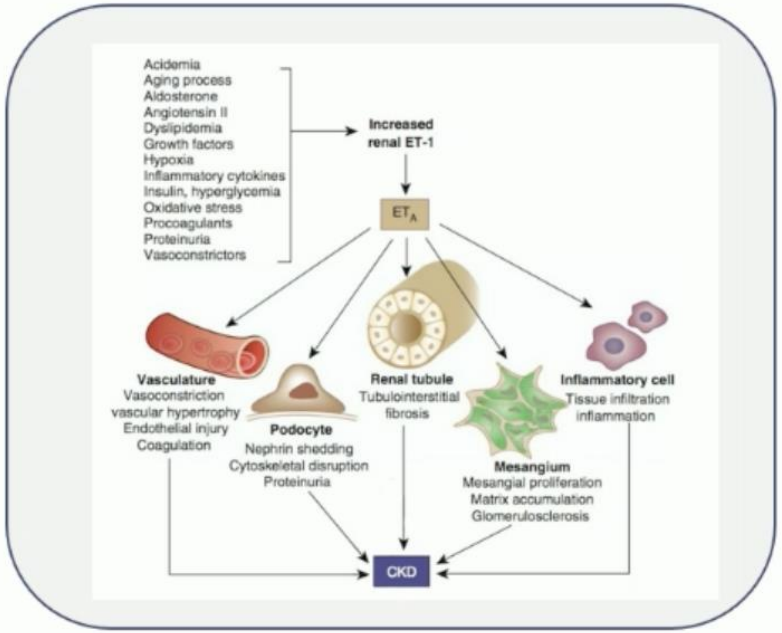
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Endothelin-1 is a Key Mediator in the Pathophysiology of DKD

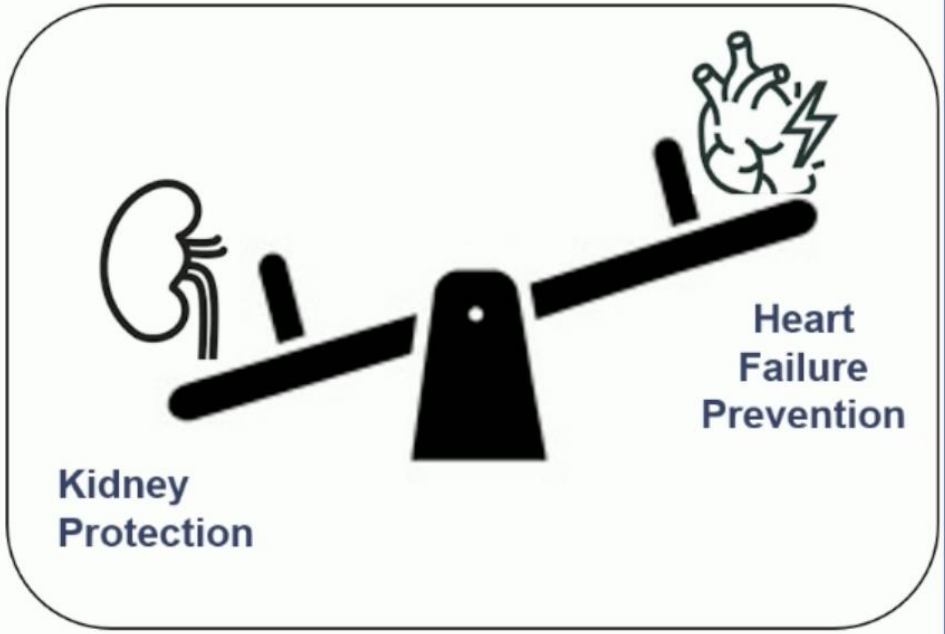
ET-1 and ET Receptors



ET-1 causes progresssion of DKD



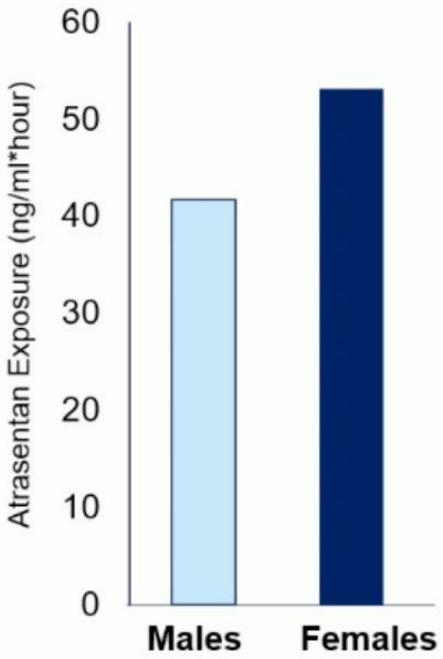
Balancing Efficay and Safety with ERA



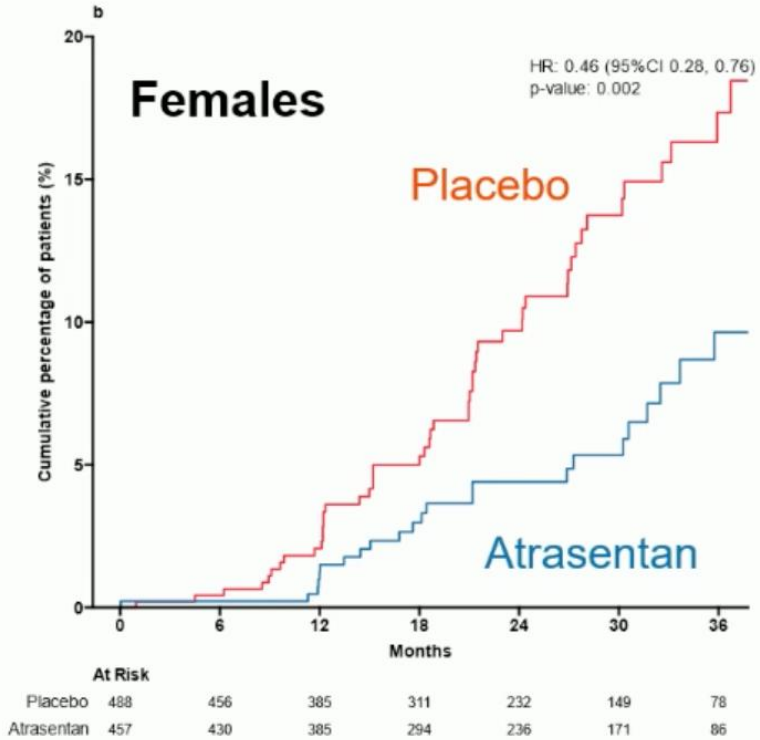
Kohan et.al. Kidney Int 2014

SONAR: Sex Differences in Efficacy Response

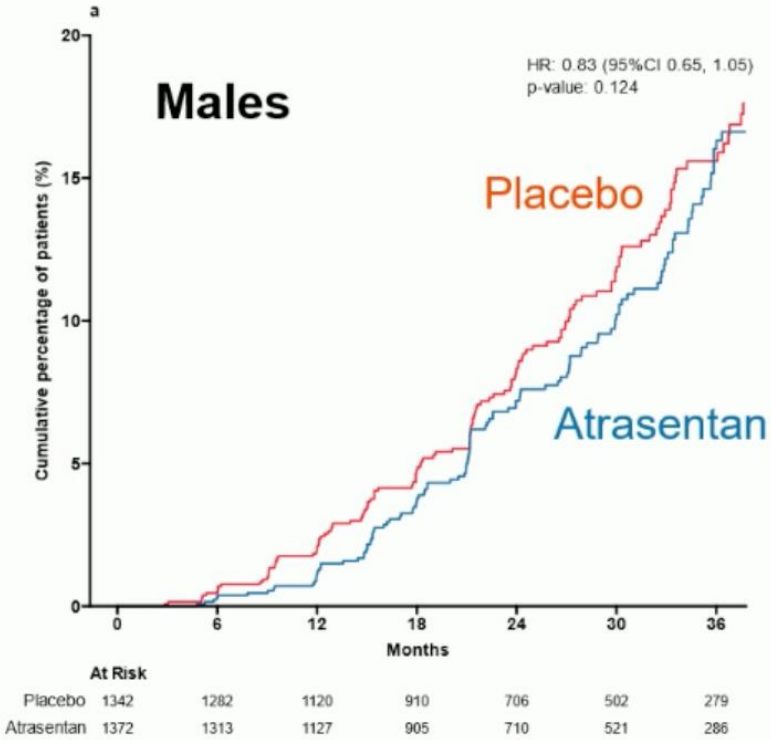
Exposure



Kidney Protection



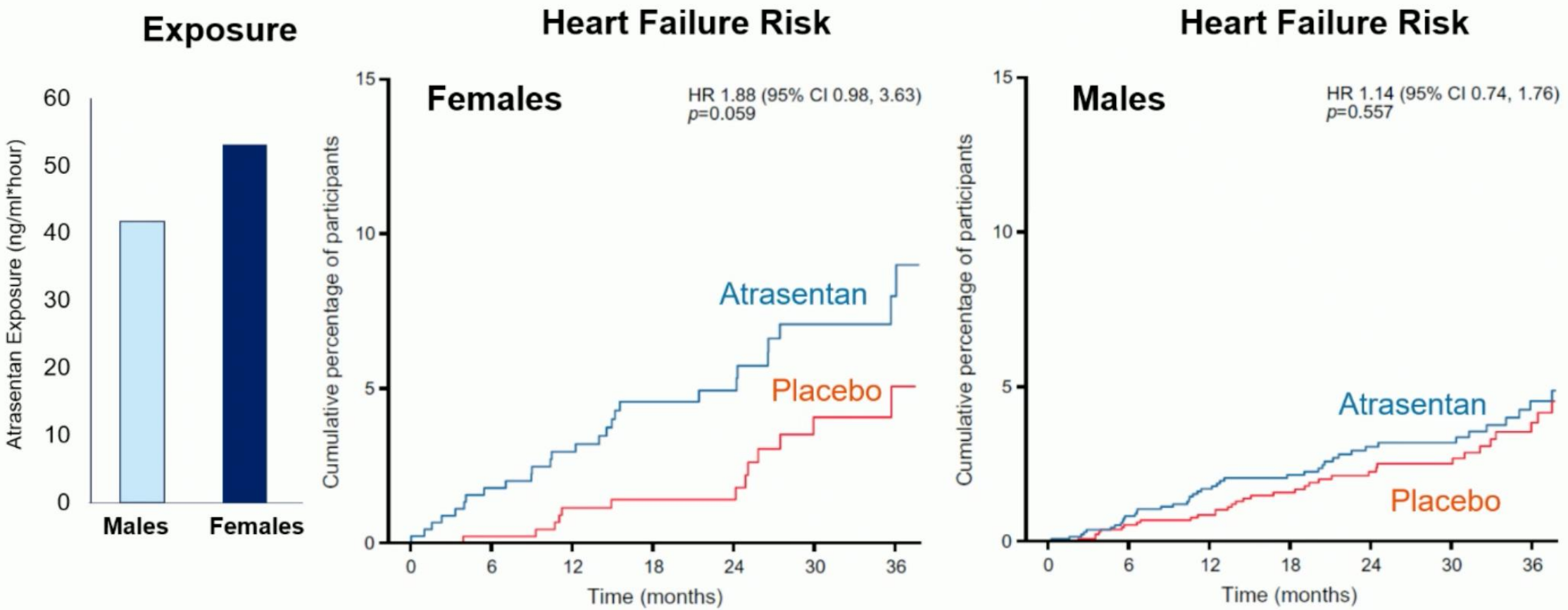
Kidney Protection



Smeijer Diabetologia. 2025 Mar;68(3):516-525

GRONINGEN KOLFF CENTER umcg

SONAR: Sex Differences in Safety Response



Smeijer Diabetologia. 2025 Mar;68(3):516-525

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DKD 2026 Guideline and Sex Differences

- The term “sex” appeared 8 times in the guideline (gender did not appear; Guideline 183 pages)
- Two statements about sex:
  - Monitoring of HbA1c is effective in both sexes
  - SGLT2 inhibitor efficacy consistent in males and females
  - GLP-1 RA efficacy consistent in male and females
- No statements about safety of any of the medications by sex
- No sex specific recommendations

KDIGO 2026 GUIDELINE

A Novel Unimolecular Peptide Tetra-agonist (PTT-A) Targeting GLP-1, GIP, Amylin And Calcitonin Receptors Produces Superior Efficacy and Quality of Weight Loss than Tirzepatide and CagriSema in Obese Rats

Soumitra S. Ghosh[1], Beatriz Herrero, Pilar Valdecantos[2], Patricia Rada[2],
Ángela M. Valverde[2], **Cristina M. Rondinone**[1]

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EASD 62th Scientific Sessions
September 28 - October 2 , 2026

Pep2Tango Therapeutics

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Goal For Obesity Medicines: Better Quality of Weight Loss

Superior Weight Loss Through Fat Mass Loss while Preserving Muscle Mass and Improving Tolerability



No Sarcopenia



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Our Goal For Obesity Medicines

BENEFITS OF MUSCLE MASS PRESERVATION

- Contributes to calorie burn at rest (associated with Basal Metabolic Rate), leading to more energy expenditure at rest
- Potential benefits to bone health
- Potential benefits to insulin sensitivity and prevention of type 2 diabetes
- Provides protein reserves when immune system is activated, leading to potential benefits in recovering from illness
- Contributes to sustainable weight loss
- Contributes to improved overall health of elderly population



IMPACT OF MUSCLE MASS LOSS

- ↓ Decreased resting energy expenditure
- ↓ Decreased insulin sensitivity
- ↓ Decreased strength and physical abilities
- ↑ Increased risk of falls and fractures
- ↑ Increased tiredness and muscular pain
- ↑ Increased risk of hospitalization

Source: Christoffersen et al, "Beyond appetite regulation: targeting energy expenditure, fat oxidation, and lean mass preservation for sustainable weight loss", Obesity, 2021. Minniti et al, International Journal of Molecular Sciences, 2022. Signe Torekov, University of Copenhagen, 2021.

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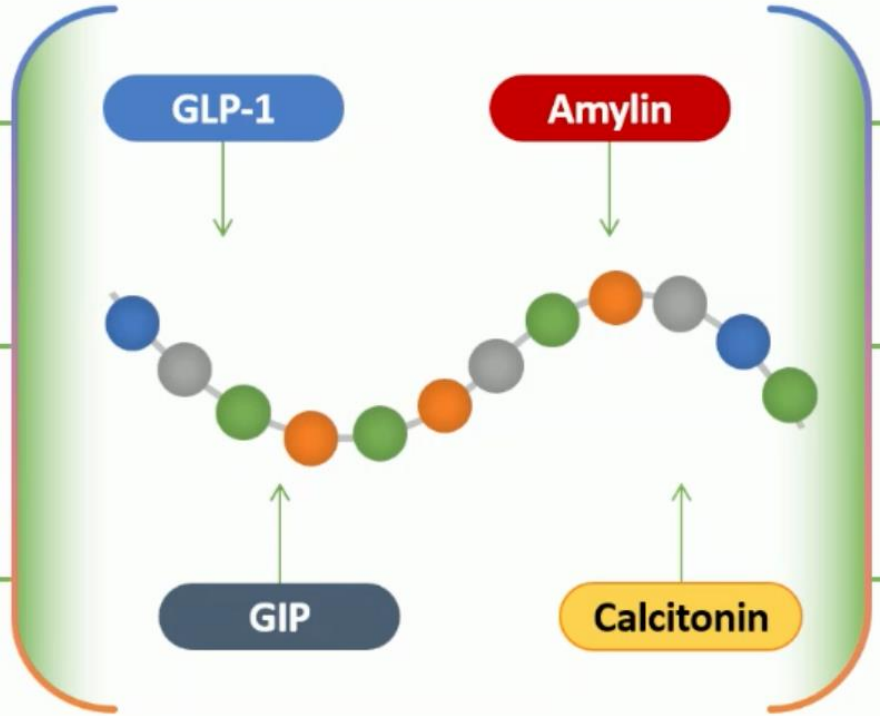
Design of Novel Tetra-Agonist for Obesity & Related Disorders

A GLP-1-GIP-Amylin-Calcitonin receptor agonist with key points of differentiation

Category leading highest **quality weight loss**, primarily from **fat mass** reduction

Preservation of muscle mass

Improve overall metabolic health, including blood lipid profile, diabetes, CV, renal & liver



Improve adherence with excellent tolerability (GI)

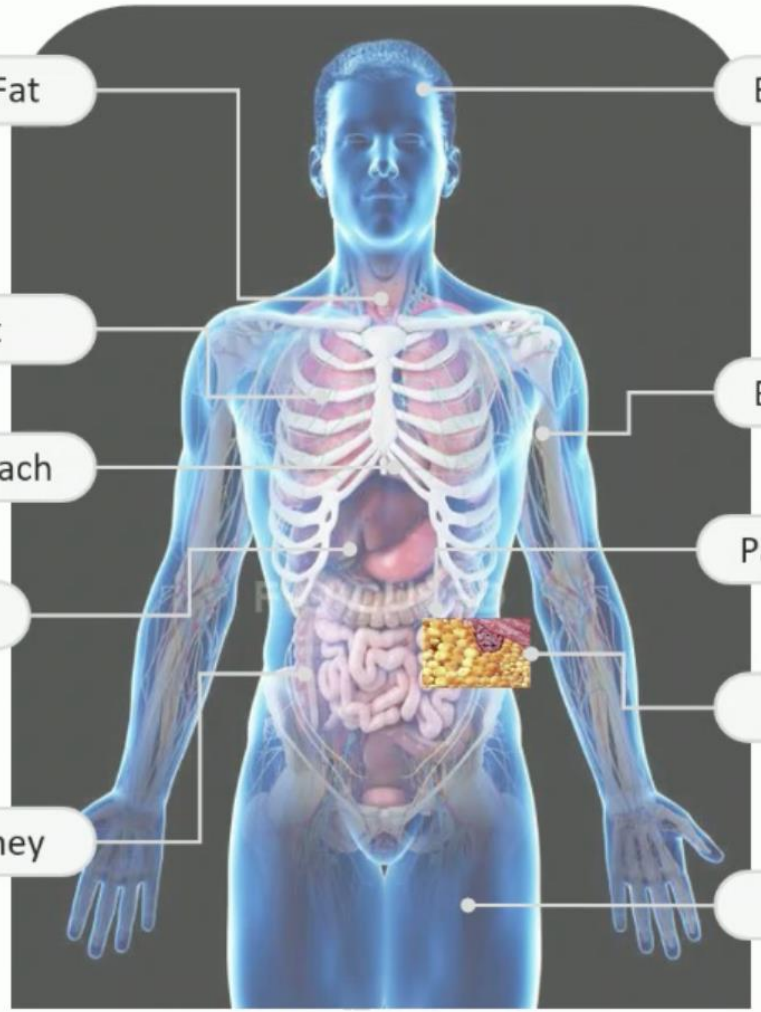
Once-weekly/monthly injectable dosing for induction and maintenance

Designed for ease of development, and **manufacturability**

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Targeting Multiple Pharmacologies in One Molecule

KEY:
- ▲ GLP-1
- ▲ GIP
- ▲ Amylin
- ▲ Calcitonin



Brown Fat
- BAT activity ↑
- EE

Heart
- Cardioprotection ↑
- Cardiac function ↑

Stomach
- Gastric emptying ↓↓

Liver
- Insulin sensitivity ↑
- Glucose production ↓
- Fatty liver / inflammation ↓

Kidney
- Natriuresis ↑↑↑
- Diuresis
- Ca Reabsorption ↓

Brain
- Satiety (meal size) ↑↑
- Food intake ↓↓↓
- Leptin sensitivity ↑↑
- Neuroprotection ↑↑
- Emesis ↓↑
- Anxiolytic/antidepressant Antipsychotic ↑↑
- Addiction ↓↓

Bone
- Bone formation ↑
- Bone resorption ↓↓↓

Pancreas
- GSIS ↑↑
- Glucagon secretion ↓↓

Fat
- BW, fat mass ↓↓
- Lipolysis ↑↑
- LPL activity (lowering TG) ↑

Muscle
- Insulin sensitivity ↑
- Glucose uptake ↑
- Preservation of muscle mass ↓↑

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Phase II clinical trial testing BCG immunotherapy for type 1 diabetes with juvenile onset: Five-year analysis of safety, HbA_{1c}, time in range and insulin use

Presented by Denise L. Faustman, MD, PhD
Mass General Brigham/Harvard Medical School
Boston, Mass., USA

WHY BCG?

What Is Bacillus Calmette-Guérin (BCG)?

Avirulent *Mycobacterium bovis* developed as a vaccination for tuberculosis prevention; Used for >100 years, with WHO declaring it safest vaccine in history

- **Global randomized clinical trial data supports BCG immunotherapy for efficacy in diverse diseases**
  - Multiple sclerosis, type 1 diabetes (T1D), infectious disease, allergy, bladder cancer, Alzheimer's disease
- Vast basic science data on immune training shows:
  - **Acute** (innate trained immunity) histone changes, monocytes only (*PlosOne* 2021; *NPJ Vaccines* 2018)
    - Acute tumor necrosis factor (TNF) induction kills cytotoxic T lymphocytes (CTLs), induces regulatory T cells (Tregs)
  - **Chronic** epigenetic methylation on genes directly on signaling pathways
    - Glycolysis changes, stable Treg induction
- **Phase IA** and **Phase IB** clinical trials of BCG immunotherapy in adults with longstanding T1D showed induction of Tregs, transient death of autoreactive T cells and durable, 8-year long improvements in HbA1c
  - HbA1c improvements were from restoration of lymphoid glucose metabolism (↑ **aerobic glycolysis**) (*NPJ Vaccines* 2018)
  - Induction of Tregs to decrease inflammation (*Sci Rep* 2021)
  - Pancreatic insulin did not contribute to glucose control
- Two additional **open-label** clinical trials of BCG in adults with T1D showed similar reductions in HbA1c (*iScience* 2021, *Sci Rep* 2024)
- Over **660 subjects with T1D** have been enrolled in past or current trials

Phase II, double-blind, randomized controlled trial of BCG in adults with longstanding juvenile-onset T1D

(ClinicalTrials.gov ID: NCT02081326)

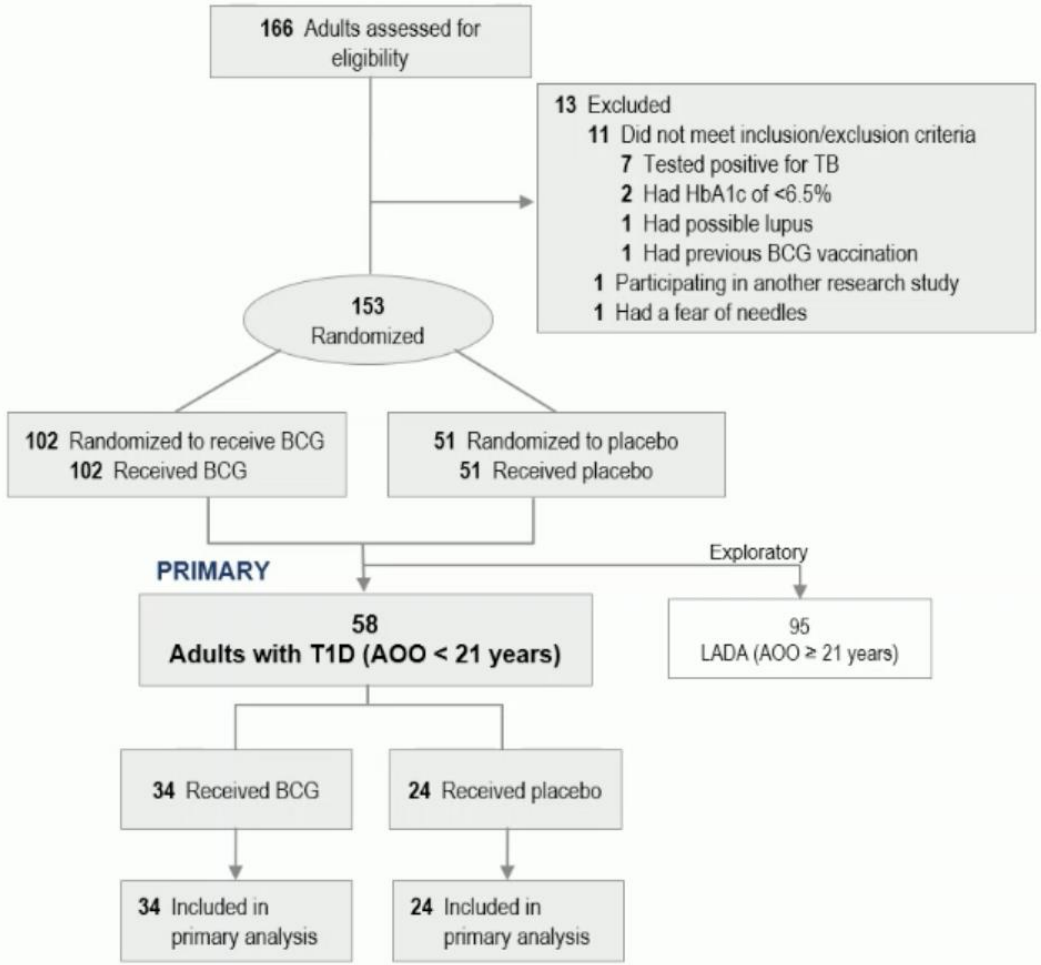
Primary Endpoint:
HbA1c reduction

Secondary Endpoints:
Insulin use, time with normoglycemia, stimulated C-peptide secretion

First data analysis at Year 5, followed by 5 additional years of data collection

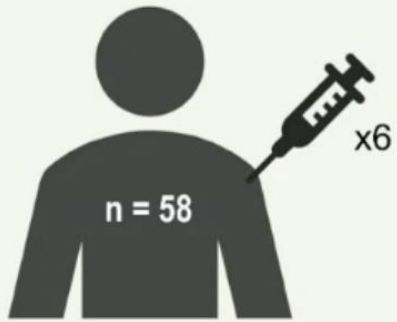
PHASE II BCG TRIAL: ADULTS WITH JUVENILE-ONSET T1D

Consort Outline



POPULATION

Adults with juvenile-onset T1D treated with Tokyo BCG (*n*=34) or placebo (*n*=24)



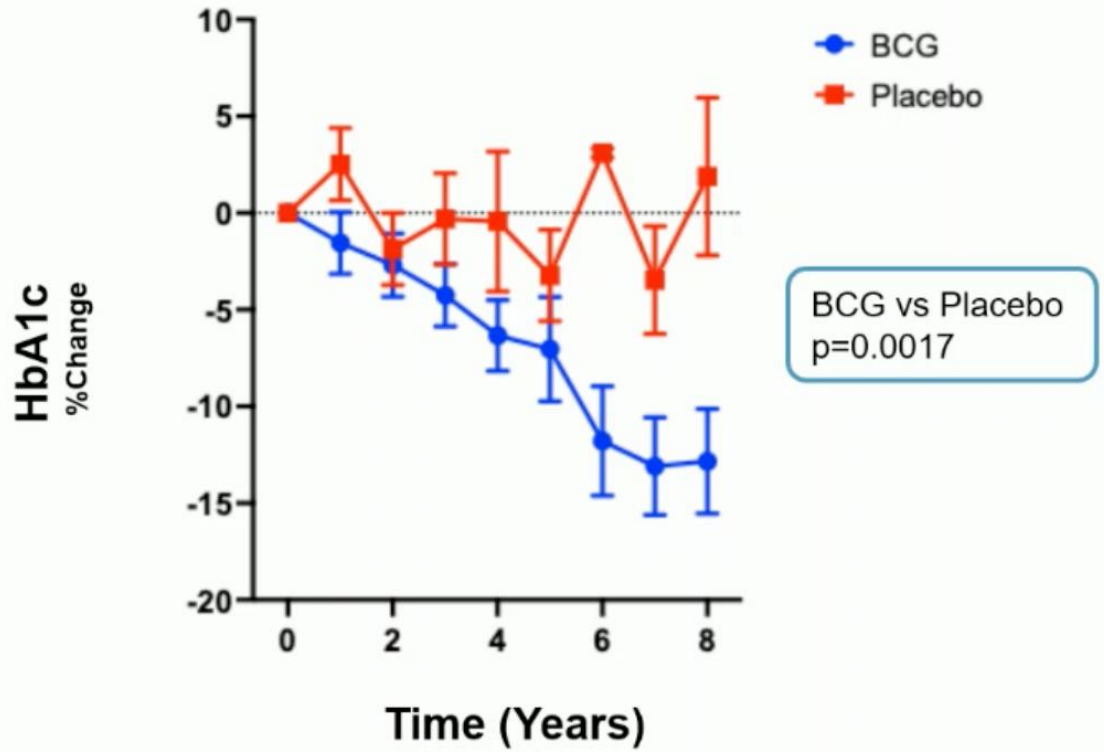
Mean age: 28 years

Mean AOO: 14 years

Little or no C-peptide present with 10+ years of disease

PHASE II BCG TRIAL: PRIMARY OUTCOME MEASURE

Effect of multi-dose BCG immunotherapy on HbA1c



Multi-dose BCG immunotherapy lowers HbA1c – slowly and with long-term durability – in adults with longstanding juvenile-onset T1D.

PHASE II BCG TRIAL: PRIMARY OUTCOME MEASURE

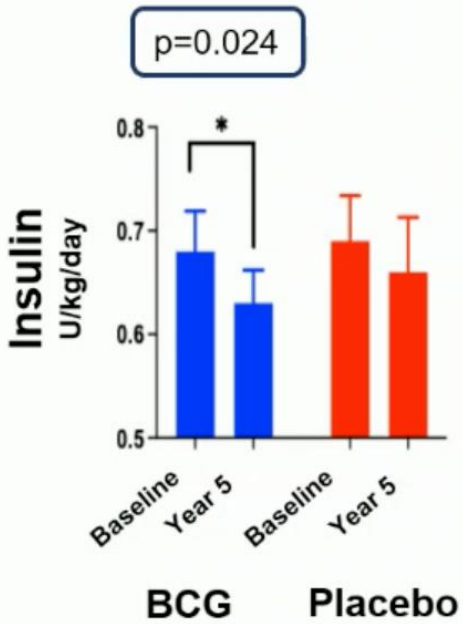
Primary Outcome (HbA1c) achieves high statistical significance, durability

	Timepoint	BCG (n=33)	Placebo (n=24)	Statistics
HbA1c % Change from Baseline	Year 0-5	-7.04 ± 2.695	-3.23 ± 2.361	*BCG* 0.006[a] *Placebo* 0.079[a]
	Year 0-8	-12.84 ± 2.705	1.89 ± 4.074	*BCG* 0.0002[a] *Placebo* 0.635[a] *BCG vs Placebo* 0.002[b]
HbA1c Raw	Baseline Year 5	7.85 ± 0.165 7.30 ± 0.224	7.32 ± 0.149 7.06 ± 0.200	*Year 5* *BCG* 0.006[a] *Placebo* 0.079[a]
	Baseline Year 8	7.85 ± 0.165 6.72 ± 0.161	7.32 ± 0.149 6.70 ± 0.058	*Year 8* *BCG* 0.0002[a] *Placebo* 0.635[a] *BCG vs Placebo* 0.002[b]

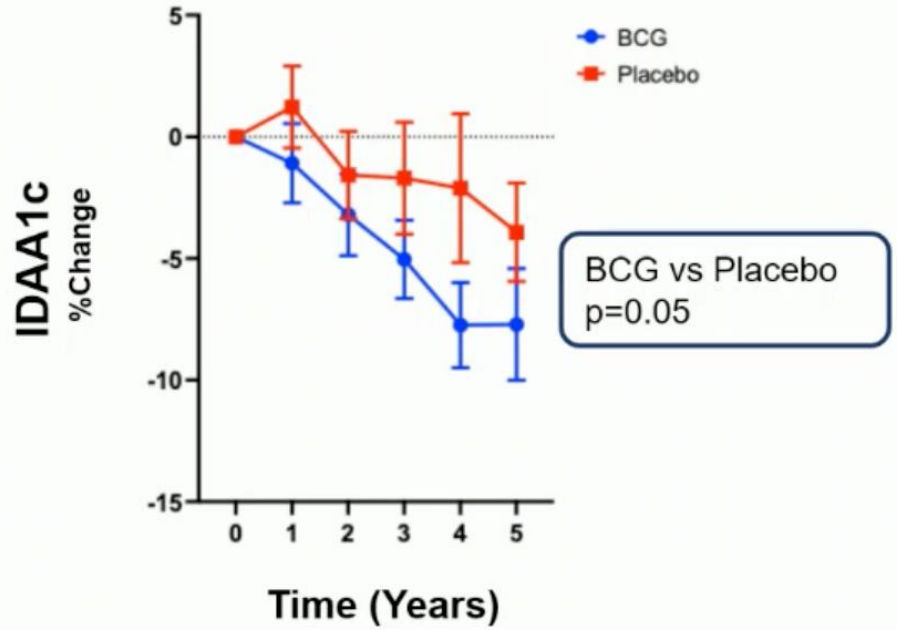
All values are Mean ± SEM
[a] Wilcoxon Sign Rank test One-tailed Y5 or Y8 vs baseline
[b] Mixed Model Repeated Measures

PHASE II BCG TRIAL: SECONDARY OUTCOME MEASURES

Insulin Use



Insulin Dose Adjusted A1c



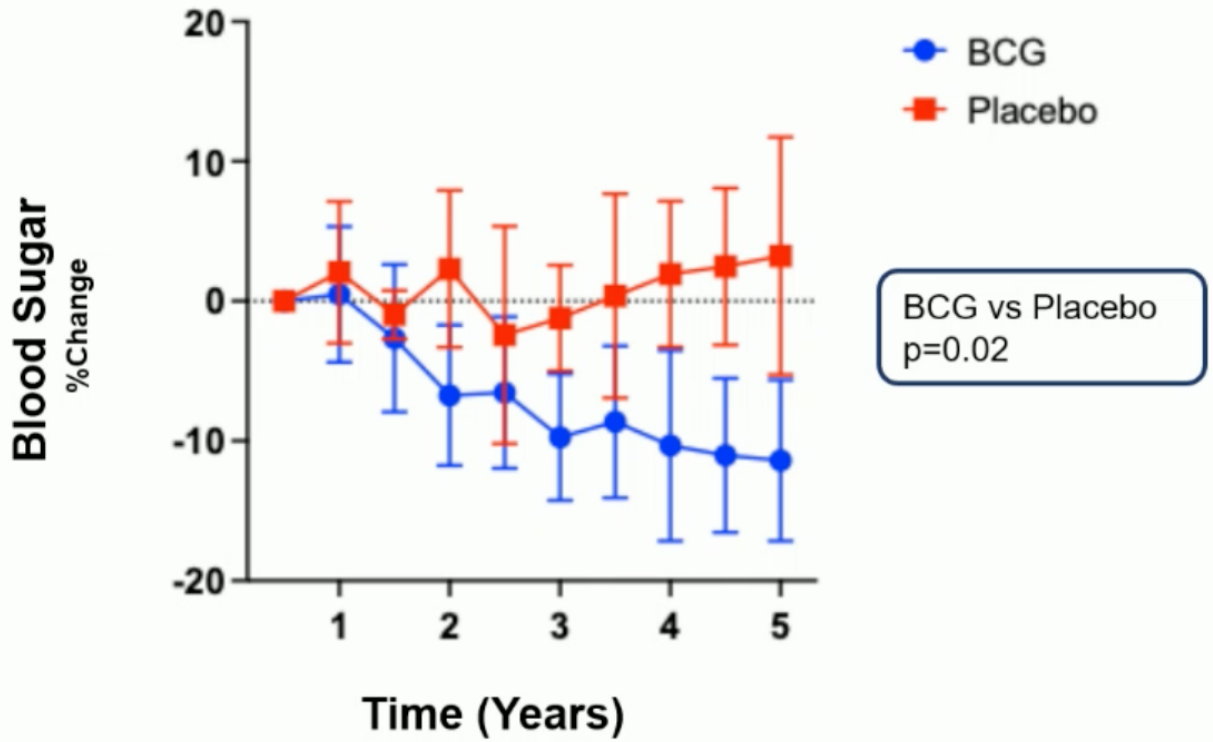
IDAA1c = A1c(%) + [4 x insulin dose (U/kg/24h)]

Multi-dose BCG therapy in longstanding T1D lowers HbA1c with a decrease in insulin use.

Long-term lowering of HbA1c is not due to more insulin or decreasing weight.

PHASE II BCG TRIAL: SECONDARY OUTCOME MEASURES

CGM Data: Blood Glucose

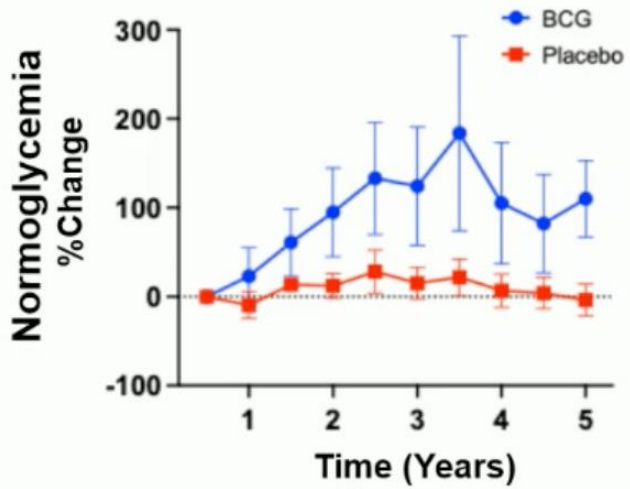


CGM data confirms HbA1c data: Multidose BCG lowers blood sugars over 5 years of monitoring.

PHASE II BCG TRIAL: SECONDARY OUTCOME MEASURES

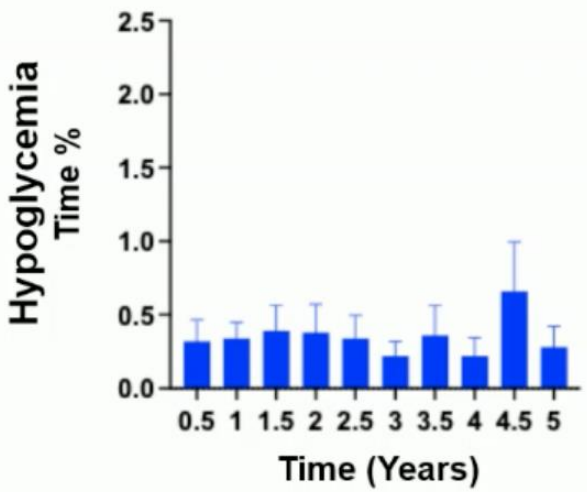
CGM Data: Monitoring for normoglycemia, hypoglycemia, decreasing blood sugars

Blood sugar 70-99 mg/dL

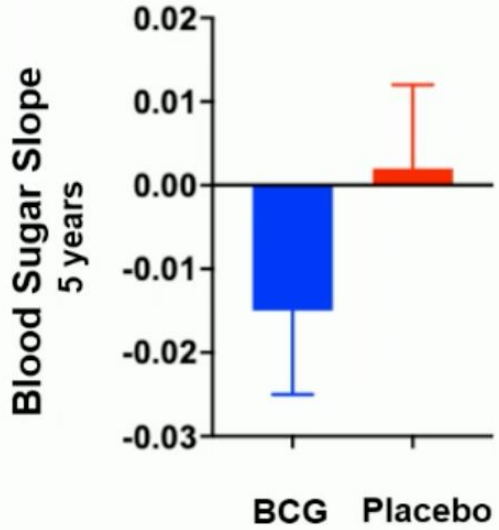


BCG vs Placebo
p=0.0391

Blood sugar <45 mg/dL



p=NS



BCG vs Placebo
p=0.036

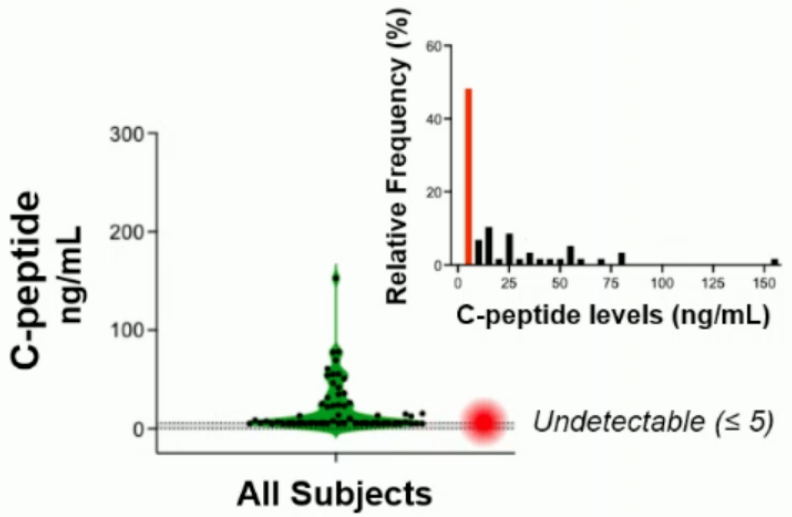
CGM data confirms increased return to normoglycemia, no increase in hypoglycemia.

Blood sugar slopes at 5 years confirm blood sugars drop in only the BCG-treated group.

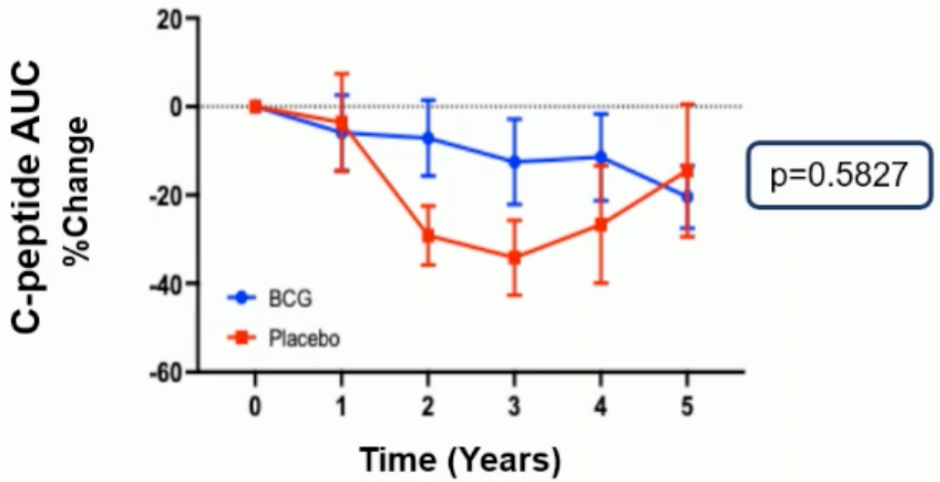
PHASE II BCG TRIAL: SECONDARY OUTCOME MEASURES

Insulin secretion from the pancreas

Baseline C-peptide



Yearly glucagon stimulated C-peptide testing



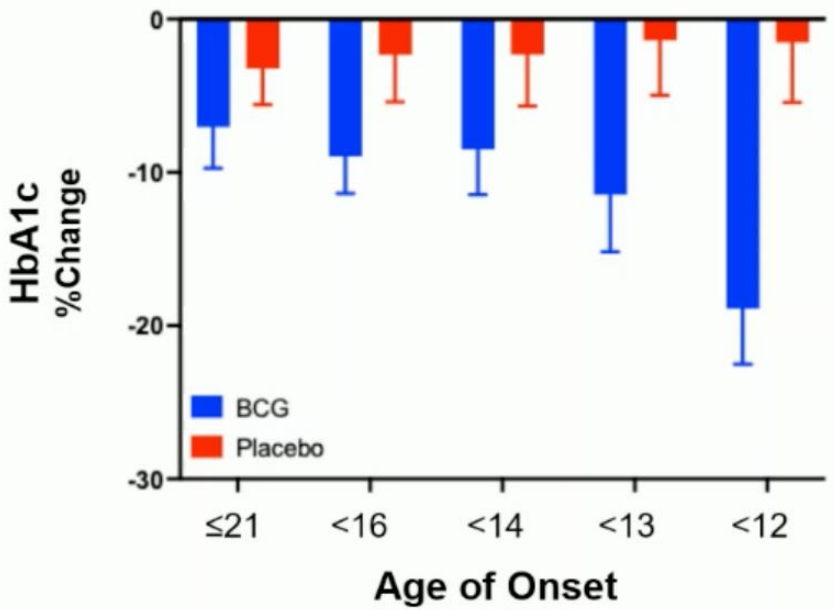
Conclusion: Individuals with longstanding T1D have minimal to undetectable C-peptide at enrollment.

With BCG treatment, there is no pancreas recovery.

The return to normoglycemia with BCG is independent of the pancreas.

PHASE II BCG TRIAL: IMPACT OF AGE OF ONSET

In adults with longstanding T1D, what factor magnifies BCG's efficacy in lowering HbA1c?



HbA1c % Change from Baseline BCG vs Placebo at Year 5			
Age of Onset	#BCG	#Placebo	Mixed Model Repeated Measures (one-tailed) P-value
≤21	31	22	0.089
<16	24	13	0.030
<14	16	11	0.071
<13	10	10	0.031
<12	5	8	0.009

As observed in *in vitro* glycolysis assays: Age of onset determines the magnitude of the defects as well as the magnitude of the HbA1c correction.

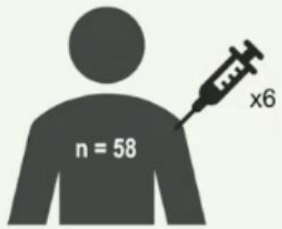
PHASE II BCG TRIAL: SAFETY

- No serious unexpected drug-related adverse effects (AE) were recorded in the BCG group
- While the AE rate per subject in the BCG group (6.26 events/subject) was somewhat lower as compared to the placebo group (7.54 events/subject), this difference was not significant (p=0.124)

SUMMARY & CONCLUSIONS

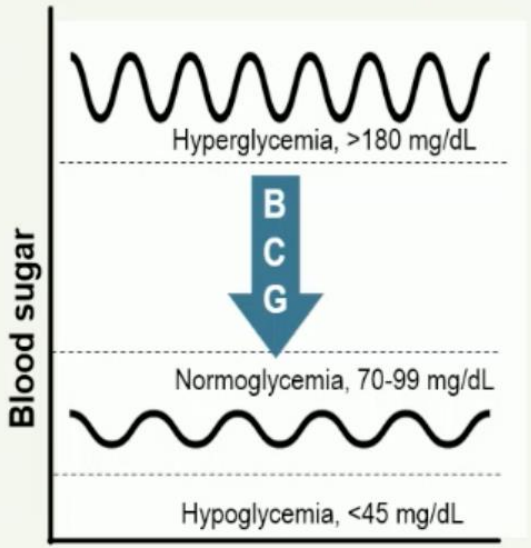
POPULATION

Adults with juvenile-onset T1D treated with Tokyo BCG (*n*=34) or placebo (*n*=24)



Mean age: 28 years
Mean AOO: 14 years
Little to no C-peptide present with 10+ years of disease

FINDINGS

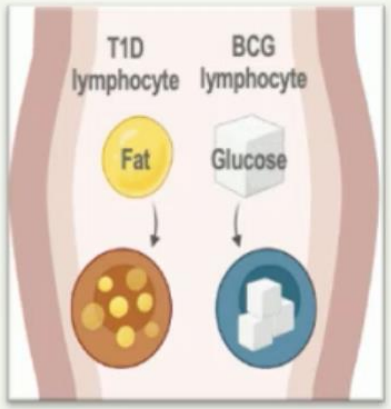




HbA1c and insulin use both decrease after BCG treatment

INTERPRETATION

BCG alters white blood cell metabolism in T1D patients → Increased blood glucose uptake in the white blood cells



- With 5-8 years of follow-up, multi-dose BCG is safe in subjects with longstanding T1D
- Multi-dose BCG **lowered HbA1c**, **reduced insulin use**, **improved time with true normoglycemia** and showed **no increase in hypoglycemic events** in adults with juvenile-onset T1D and longstanding disease
- BCG's therapeutic effect on blood sugar control is **independent of pancreas function** and likely a durable correction of an underlying aerobic lymphoid metabolic defect
  - **BCG restored aerobic glycolysis** in the lymphoid system for improved tight glucose control



Thank you!

QUESTIONS?

DFAUSTMAN@mgh.harvard.edu

THE LANCET
Obstetrics, Gynaecology, & Women's Health

UNIVERSITY OF LEICESTER

Lancet series on GLP-1RAs and women's health.

Preconception, pregnancy & postnatal use: systematic review and international consensus statement.

PROF CLAIRE L. MEEK

LEICESTER DIABETES RESEARCH CENTRE AND LEICESTER NIHR BIOMEDICAL RESEARCH CENTRE

DIABETES UK
KNOW DIABETES. FIGHT DIABETES.

EASD

bmfms British Maternal & Fetal Medicine Society



Claire Meek

Incretin therapies in diabetes: preconcep pregnancy and post

The context: GLP-1RAs are among the most successful pharmaceutical agents ever developed

- Total global market >$70 billion

- UK: 11% of adult women
- US: 22% of adult women
- Europe: less access, 2-5% use in adults.

- 80% of private prescriptions in women.
- Typical user 30-55 years old.
- Reproductive safety data is scarce.



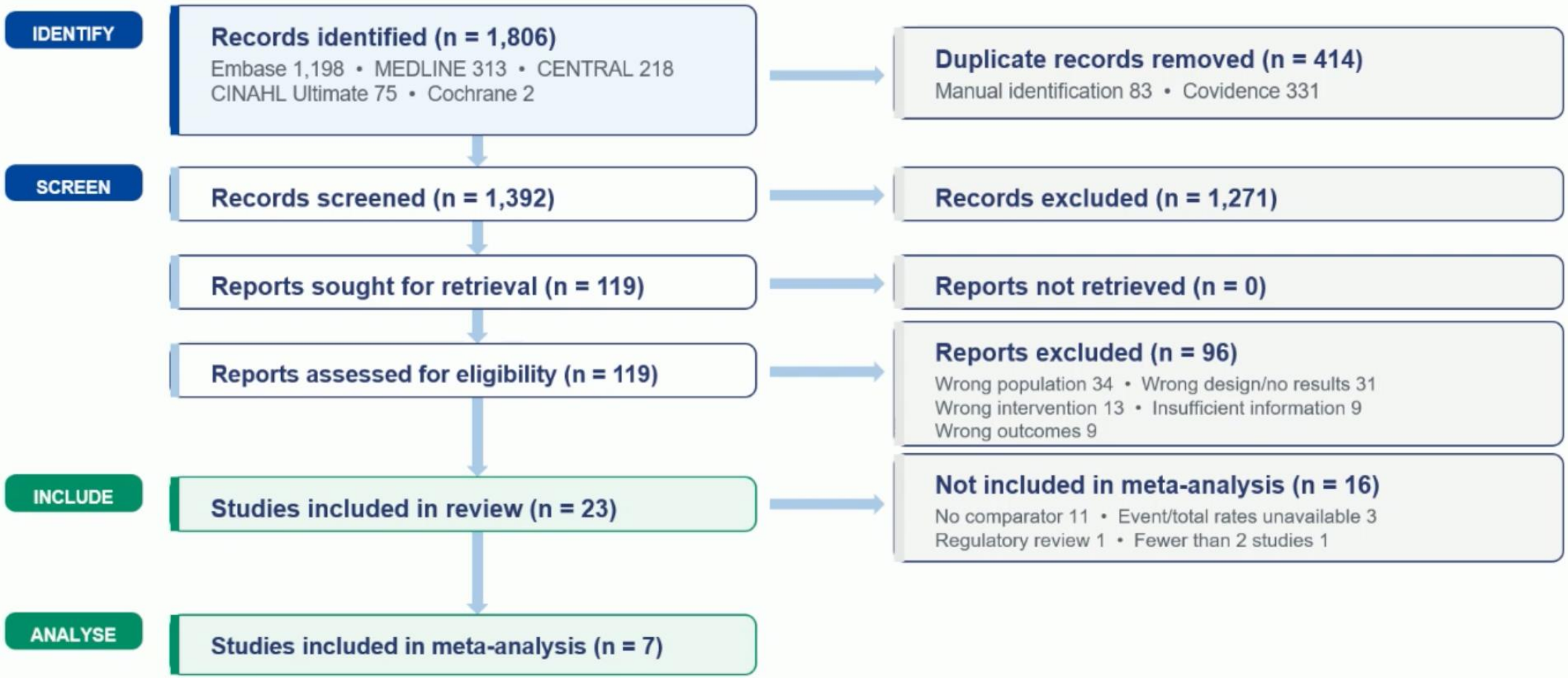
Aim



To systematically review the literature and develop consensus recommendations for the safe and effective use of GLP-1RAs in women of reproductive age with diabetes (T1D, T2D and previous GDM) before, during and after pregnancy.

Novelty: Focus on diabetes, not obesity alone.

Study selection



EASD

Study characteristics: 23 studies, 9 in metanalysis

Study Design

- 9/23 Case reports / series
- 9/23 Retrospective cohorts
- 1/23 Multicentre prospective registry
- 1/23 Analysis of FDA / EMA data
- 1/23 Post GDM study
- 2/23 Pharmacokinetic lactation studies



- GRADE of evidence very low
- Very few prospective studies

Population

- 12/23 T2D
- 3/23 Mixed T1D and T2D
- 7/23 Mixed T2D and obesity
- 1/23 Recent GDM



- 13/23 Did not report race /ethnicity
- Usually no suitable reference group

Exposure

Timing of Exposure

- 20/23 Preconception / early pregnancy
  - E.g. LMP +/- 8 weeks
  - Any exposure to 8, 12, 13, 15, 23 wks
  - Any prescription 3, 6, 12 , 24 months pre-pregnancy



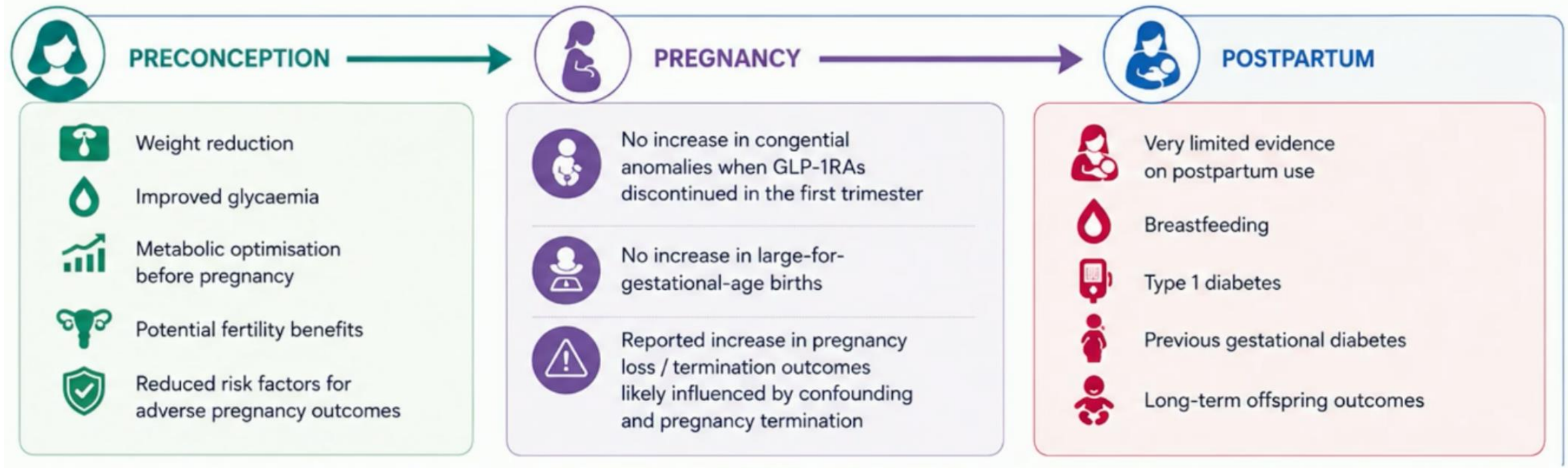
- 1/23 Post GDM study
- 2/23 Pharmacokinetic lactation studies

Medication

- Semaglutide
- Tirzepatide
- Liraglutide
- Dulaglutide



- “Any GLP-1 related agent”

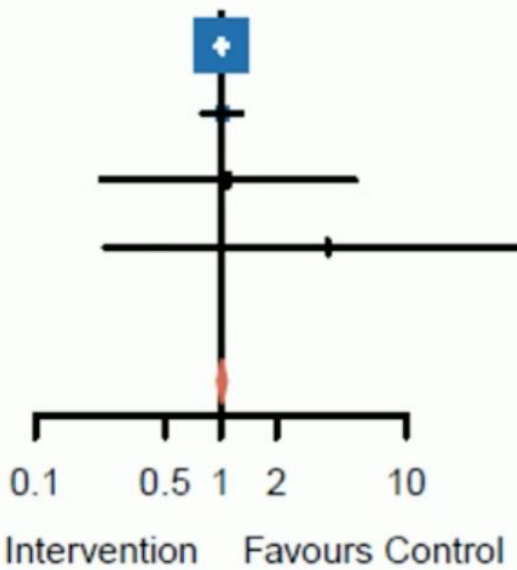

PRECONCEPTION
Weight reduction
Improved glycaemia
Metabolic optimisation before pregnancy
Potential fertility benefits
Reduced risk factors for adverse pregnancy outcomes
PREGNANCY
No increase in congential anomalies when GLP-1RAs discontinued in the first trimester
No increase in large-for-gestational-age births
Reported increase in pregnancy loss / termination outcomes likely influenced by confounding and pregnancy termination
POSTPARTUM
Very limited evidence on postpartum use
Breastfeeding
Type 1 diabetes
Previous gestational diabetes
Long-term offspring outcomes

EASD

Congenital Anomalies

Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%−CI	Weight
Lewin, 2025	1361	40929	4301	131279	1.01	[0.96; 1.08]	93.8%
Cesta, 2024	75	938	400	5078	1.02	[0.80; 1.29]	6.0%
Dao, 2024	3	117	3	128	1.09	[0.23; 5.31]	0.1%
Chou, 2025	1	160	1	606	3.79	[0.24; 60.22]	0.0%
Random effects model	**1440**	**42144**	**4705**	**137091**	**1.02**	**[0.96; 1.08]**	**100.0%**

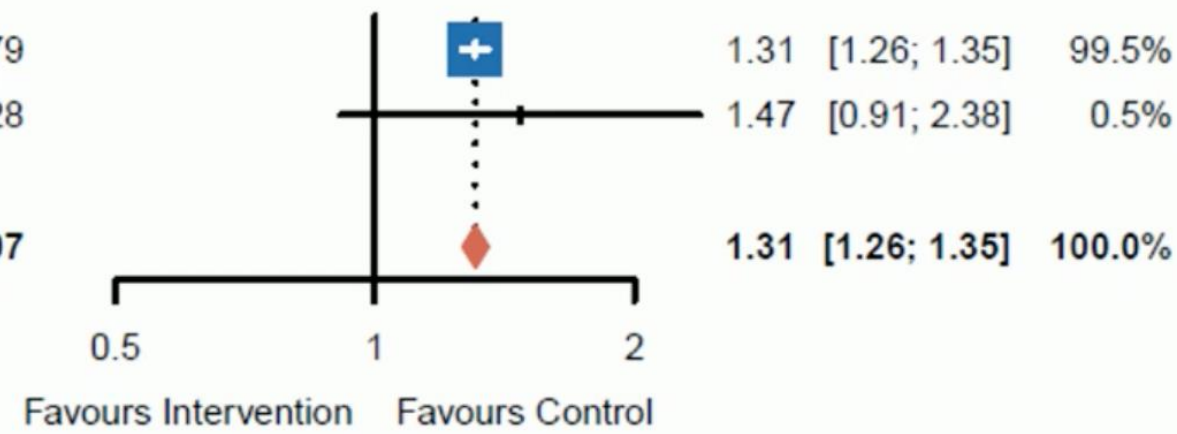
Heterogeneity: $I^2 = 0.0\%$, $\tau^2 = 0$, $p = 0.8306$



Pregnancy Termination or Miscarriage

Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%−CI	Weight
Lewin, 2025	4000	40929	9812	131279	1.31	[1.26; 1.35]	99.5%
Dao, 2024	31	117	23	128	1.47	[0.91; 2.38]	0.5%
Random effects model	**4031**	**41046**	**9835**	**131407**	**1.31**	**[1.26; 1.35]**	**100.0%**

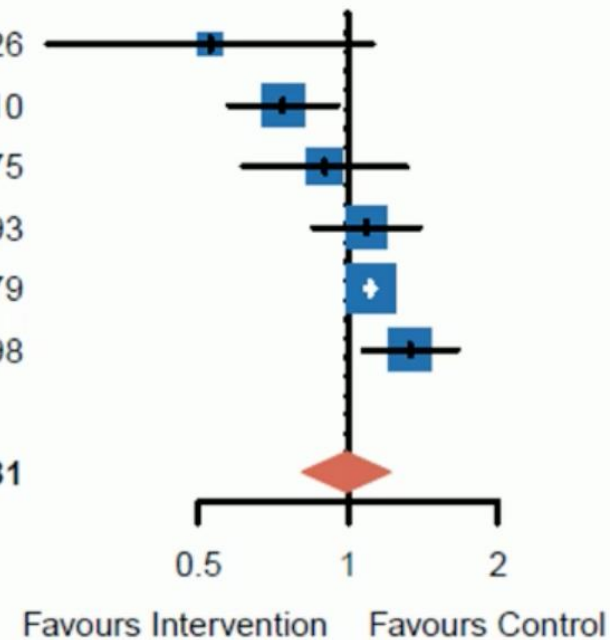
Heterogeneity: $I^2 = 0.0\%$, $\tau^2 = 0$, $p = 0.6228$



Preterm Birth

Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%−CI	Weight
Dao, 2024	9	113	19	126	0.53	[0.25; 1.12]	5.6%
Imbroane, 2025	102	3290	139	3310	0.74	[0.57; 0.95]	18.1%
Pondugula, 2025	29	103	55	175	0.90	[0.61; 1.31]	13.4%
Chou, 2025	53	153	189	593	1.09	[0.85; 1.39]	18.3%
Lewin, 2025	9442	40929	27358	131279	1.11	[1.08; 1.13]	25.1%
Maya, 2025	99	566	223	1698	1.33	[1.07; 1.65]	19.5%
Random effects model	**9734**	**45154**	**27983**	**137181**	**0.99**	**[0.81; 1.21]**	**100.0%**

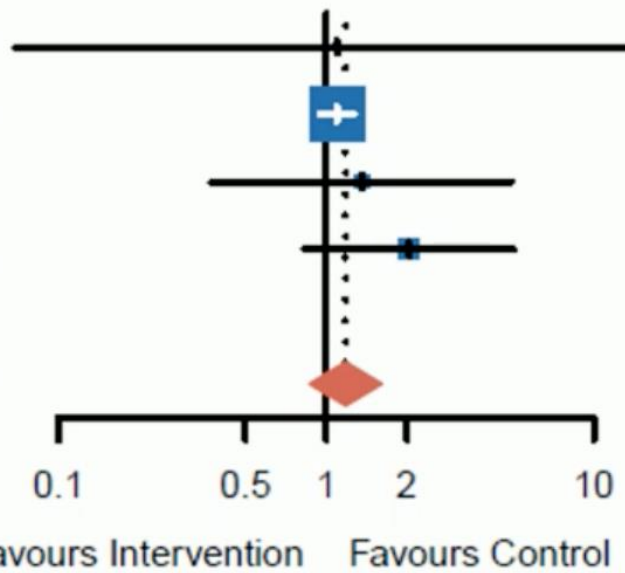
Heterogeneity: I^2 = 71.8%, τ^2 = 0.0425, p = 0.0033



Stillbirth

Study	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio (95% CI)	RR	95%−CI	Weight
Dao, 2024	1	117	1	128		1.09	[0.07; 17.29]	1.2%
Lewin, 2025	244	40929	715	131279		1.09	[0.95; 1.27]	83.0%
Pondugula, 2025	4	103	5	175		1.36	[0.37; 4.95]	5.4%
Chou, 2025	7	160	13	606		2.04	[0.83; 5.03]	10.4%
Random effects model	**256**	**41309**	**734**	**132188**		**1.18**	**[0.87; 1.61]**	**100.0%**

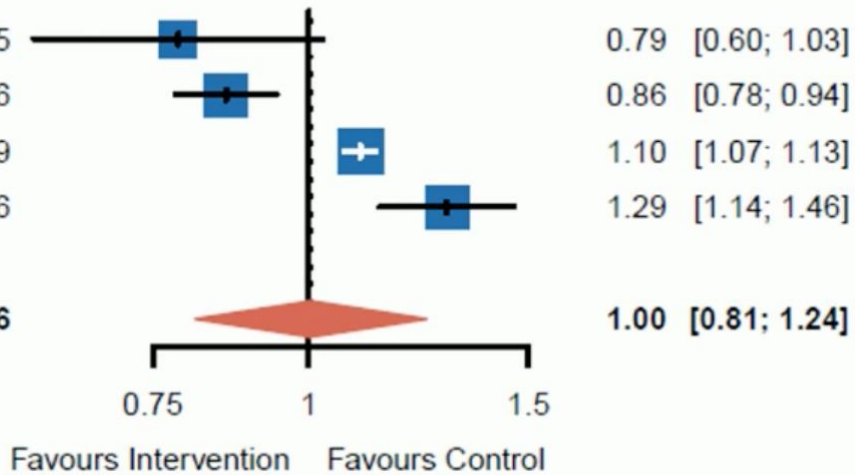
Heterogeneity: $I^2 = 0.0\%$, $\tau^2 = 0.0242$, $p = 0.5990$



Hypertensive Disorders

Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%−CI
Pondugula, 2025	43	103	93	175	0.79	[0.60; 1.03]
Imbroane, 2025	647	3345	752	3336	0.86	[0.78; 0.94]
Lewin, 2025	5360	40929	15633	131279	1.10	[1.07; 1.13]
Maya, 2025	200	432	465	1296	1.29	[1.14; 1.46]
Random effects model	**6250**	**44809**	**16943**	**136086**	**1.00**	**[0.81; 1.24]**

Heterogeneity: I^2 = 92.1%, τ^2 = 0.0422, p < 0.0001

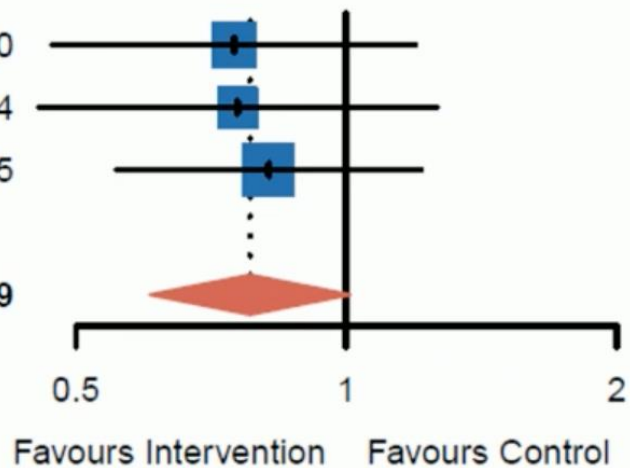


EASD

Large–for–Gestational Age

Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%–CI	Weight
Maya, 2025	18	100	72	300	0.75	[0.47; 1.19]	30.8%
Dao, 2024	20	113	29	124	0.76	[0.45; 1.26]	25.5%
Pondugula, 2025	27	103	56	175	0.82	[0.55; 1.21]	43.7%
Random effects model	**65**	**316**	**157**	**599**	**0.78**	**[0.60; 1.01]**	**100.0%**

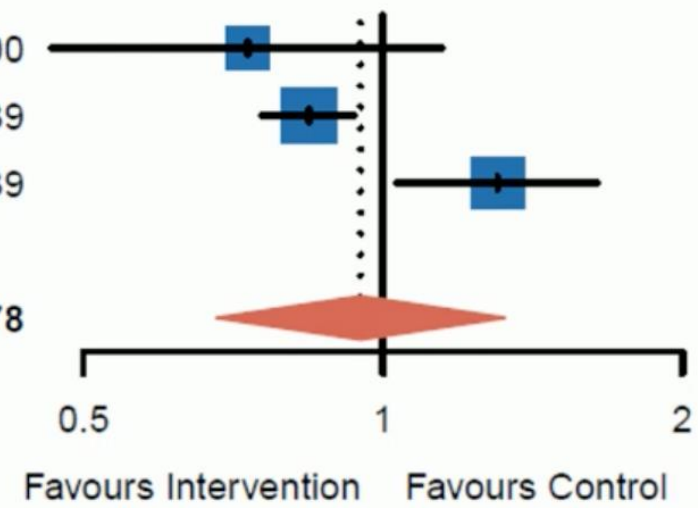
Heterogeneity: $I^2 = 0.0\%$, $\tau^2 = 0$, $p = 0.9505$



Gestational Diabetes

Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%−CI	Weight
Pondugula, 2025	23	140	45	200	0.73	[0.46; 1.15]	23.8%
Imbroane, 2025	513	3331	611	3339	0.84	[0.76; 0.94]	40.8%
Maya, 2025	83	413	191	1239	1.30	[1.03; 1.64]	35.3%
Random effects model	**619**	**3884**	**847**	**4778**	**0.95**	**[0.68; 1.33]**	**100.0%**

Heterogeneity: I^2 = 83.5%, τ^2 = 0.0680, p = 0.0024



What's new?

Type 2 diabetes

- First acknowledgement that GLP-1RAs are beneficial preconception
- New targets
- Strategies for stopping pre-pregnancy are needed
- Contraception strongly recommended
- If early pregnancy exposure – stop immediately.

Type 1 diabetes

- Very little evidence
- First acknowledgement that GLP-1RAs may be beneficial preconception
- Advice on safe prescribing

Gestational diabetes

- Very little evidence
- First acknowledgement that GLP-1RAs may be beneficial preconception
- Recommended 12 months' use

Postnatally

- Breastfeeding recommended
- Insufficient data on safety to support any use of GLP-1RAs during lactation.
- The repercussions of GLP-1RA use and related weight loss on the nutritional value of breastmilk is unknown.

Conclusions

THE LANCET
Obstetrics, Gynaecology, & Women's Health

- We present the first international consensus on GLP-1RA use in women with diabetes before, during and after pregnancy, aiming to guide clinical care in areas of uncertainty

- We call for:

Greater investment in women's health research

Regulatory change that enables evidence generation while maintaining safety.

Mandatory reporting of sex disaggregated & reproductive safety data

Orforglipron and the ACHIEVE Programme

Molecular Profile and Clinical Overview

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

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Background

GLP-1 RAs used in type 2 diabetes for glycemic control, weight loss, and reducing cardiorenal risk[1].

Most GLP-1 RAs require **subcutaneous injection**[2].

Oral administration with an **absorption enhancer** has low bioavailability and **restrictions** around food and water consumption[3,4].

An **oral non-peptide GLP-1 RA** would provide an additional treatment option to meet individual preferences or needs.

1. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes 2026; Diabetes Care 2026. 2. Yu M, et al. Adv Drug Deliv Rev 2018. 3: Solis-Herrera C et al. Clin Diabetes. 2024 4: Lewis AL et al. Drug Delivery and Translational Science. 2021

Orforglipron: a non-peptide, oral GLP-1 receptor agonist

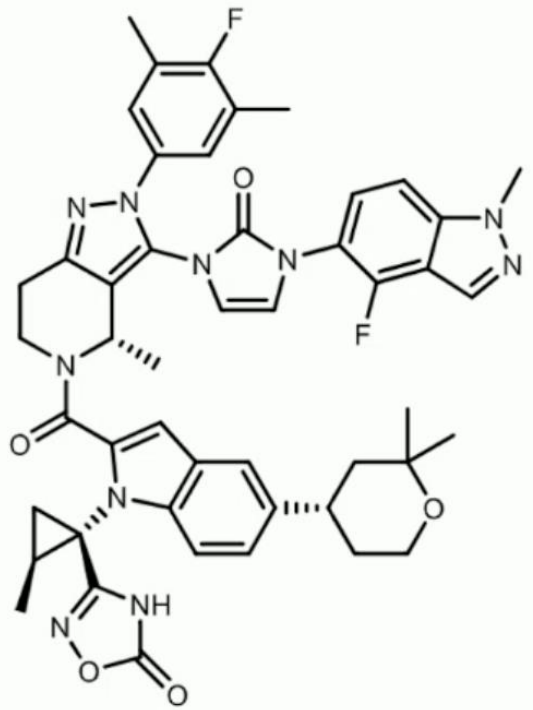
- Non-peptide, small molecule [1,2]
- Chemically synthesized [1,3]
- High affinity binding to GLP-1 receptor [4]

- Once-daily dosing [1,3,5,6]
- Terminal half life 29-49 hours [3,6]

- Oral administration [1,3,5,6]
- No food or water restriction [1,5,6]
- High bioavailability 79.1% [7]

- Promotes glucose-dependent insulin secretion [1]
- Supports body weight reduction [3,6]

Chemical structure of orforglipron [7]



1. Kawai T, et al. Proc Natl Acad Sci USA. 2020; 2. Kansakar U, et al. Int J Mol Sci. 2026; 3. Pratt E, et al. Diabetes Obes Metab. 2023; 4. Sloop K, et al. Sci Transl Med. 2024; 5. Ma X, et al. Diabetes. 2024; 6. Frias JP, et al. Lancet. 2023; 7. Morse BL, et al. Clin Pharm in Drug Dev. 2025

Orforglipron: target disease states

Orforglipron is approved for the treatment of **overweight and obesity** and **type 2 diabetes** in some countries, and under investigation for other cardiometabolic diseases.

Orforglipron

Phase 3 global clinical trials programme

- **Type 2 Diabetes**
  ACHIEVE programme [1-5]
- **Obesity and overweight**
  ATTAIN programme [6-8]
- **Obstructive sleep apnoea**
  ATTAIN-OSA [9]
- **Osteoarthritis**
  ATTAIN-OA PAIN [10]
- **Peripheral artery disease**
  ATTAIN-PAD [11]
- **CVOT**
  ATTAIN-Outcomes [12]
- **Hypertension**
  ATTAIN-Hypertension [13]
- **Stress Urinary Incontinence**
  RESTRAIN-SUI [14]
- **Paediatric/Adolescent**
  ACHIEVE-PEDS [15]; ATTAIN-ADOLESCENTS [16]

1. https://clinicaltrials.gov/study/NCT05971940; 2. https://clinicaltrials.gov/study/NCT06192108; 3. https://clinicaltrials.gov/study/NCT06045221; 4. https://clinicaltrials.gov/study/NCT05803421; 5. https://clinicaltrials.gov/study/NCT06109311; 6. https://clinicaltrials.gov/study/NCT05869903; 7. https://clinicaltrials.gov/study/NCT05872620; 8. https://clinicaltrials.gov/study/NCT06584916; 9.https://clinicaltrials.gov/study/NCT06649045; 10. https://clinicaltrials.gov/study/NCT07153471; 11. https://clinicaltrials.gov/study/NCT07223593; 12.https://clinicaltrials.gov/study/NCT07241390; 13. https://clinicaltrials.gov/study/NCT06948422; 14. https://clinicaltrials.gov/study/NCT07202884; 15. https://clinicaltrials.gov/study/NCT07668336; 16. https://clinicaltrials.gov/study/NCT06672939;

Orforglipron in Type 2 Diabetes: The ACHIEVE Phase 3 Programme

		Comparator	Adults With T2D	40 weeks	52 weeks	104* weeks
ACHIEVE-1[1] **N=559**	Monotherapy	**Placebo**	Inadequate glycaemic control with **diet and exercise alone**			
ACHIEVE-2[2] **N=962**	Combination with metformin	**Dapagliflozin**	Inadequate glycaemic control with **metformin**			
ACHIEVE-3[3] **N=1698**	Combination with metformin	**Oral semaglutide**	Inadequate glycaemic control with **metformin**			
ACHIEVE-4[4] **N=2749**	Combination with multiple therapies *CV Safety (MACE-4)*	**Insulin glargine**	Participants with obesity or overweight at increased CV risk and on stable treatment of **1 to 3 oral antihyperglycemic medications**			
ACHIEVE-5[5] **N=546**	Combination with insulin glargine	**Placebo**	Inadequate glycaemic control with **insulin glargine, with or without metformin and/or SGLT-2 inhibitor**			

1. Rosenstock J. et al. The New England Journal of Medicine. 2025; 2.Welch M. et al. The Lancet. 2026; 3. Rosenstock J. et al. The Lancet. 2026.
4. https://clinicaltrials.gov/study/NCT05803421 (Accessed July 22, 2026); 5. Giorgino F. et al. JAMA. 2026

*ACHIEVE-4 was an endpoint-driven trial. Minimum duration of treatment was 52 weeks, and at least 500 orforglipron-treated participants had treatment ≥104 weeks.

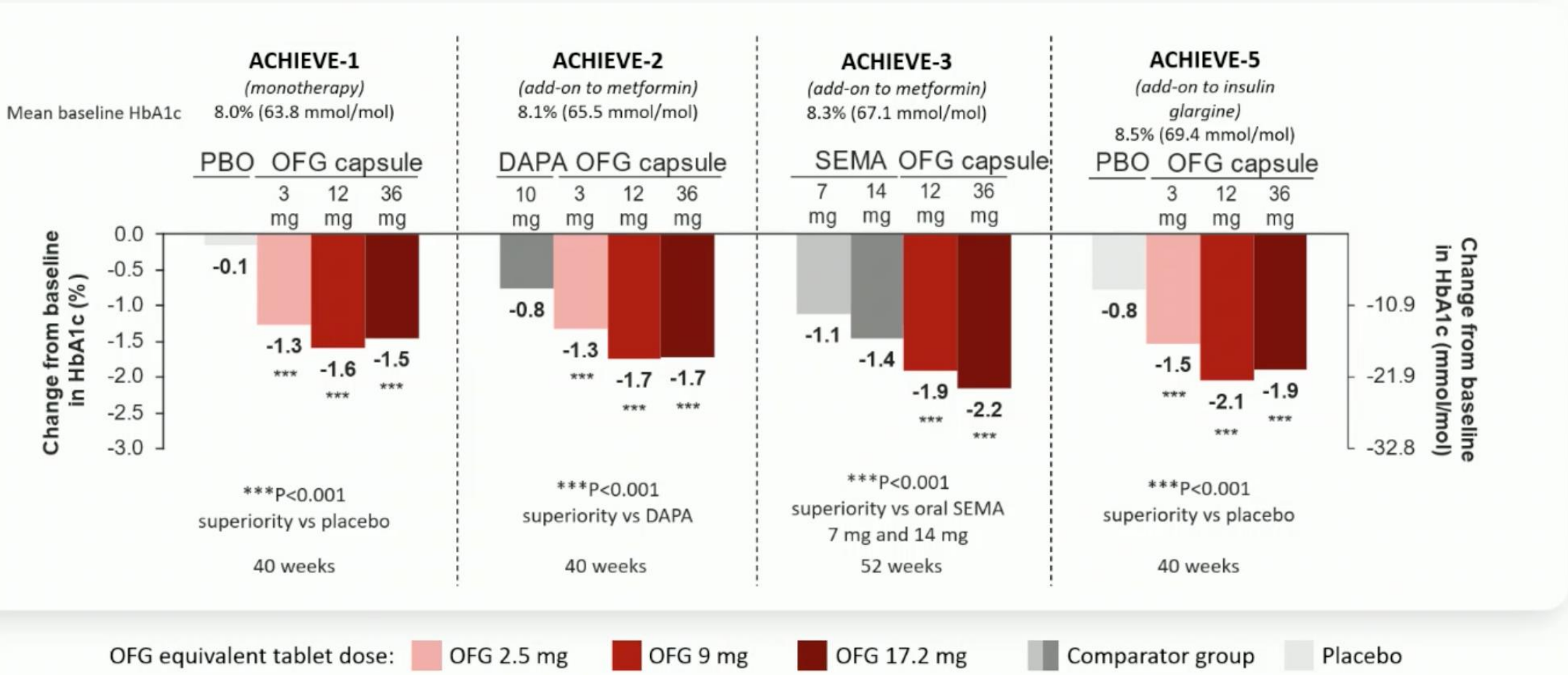
Orforglipron: Capsule vs. Tablet dosage equivalence

Capsule Formulation *Investigational use*	**1 mg**	**3 mg**	**6 mg**	**12 mg**	**24 mg**	**36 mg**
Tablet Formulation *Equivalent form*	**0.8 mg**	**2.5 mg**	**5.5 mg**	**9.0 mg**	**14.5 mg**	**17.2 mg**

- The ACHIEVE trials used the investigational capsule doses of orforglipron.
- In some regions where orforglipron is approved, the available formulation is a tablet using exposure-equivalent doses of orforglipron.
- At matching doses, tablets and capsules deliver comparable systemic exposure, despite the different milligram amounts.[1]

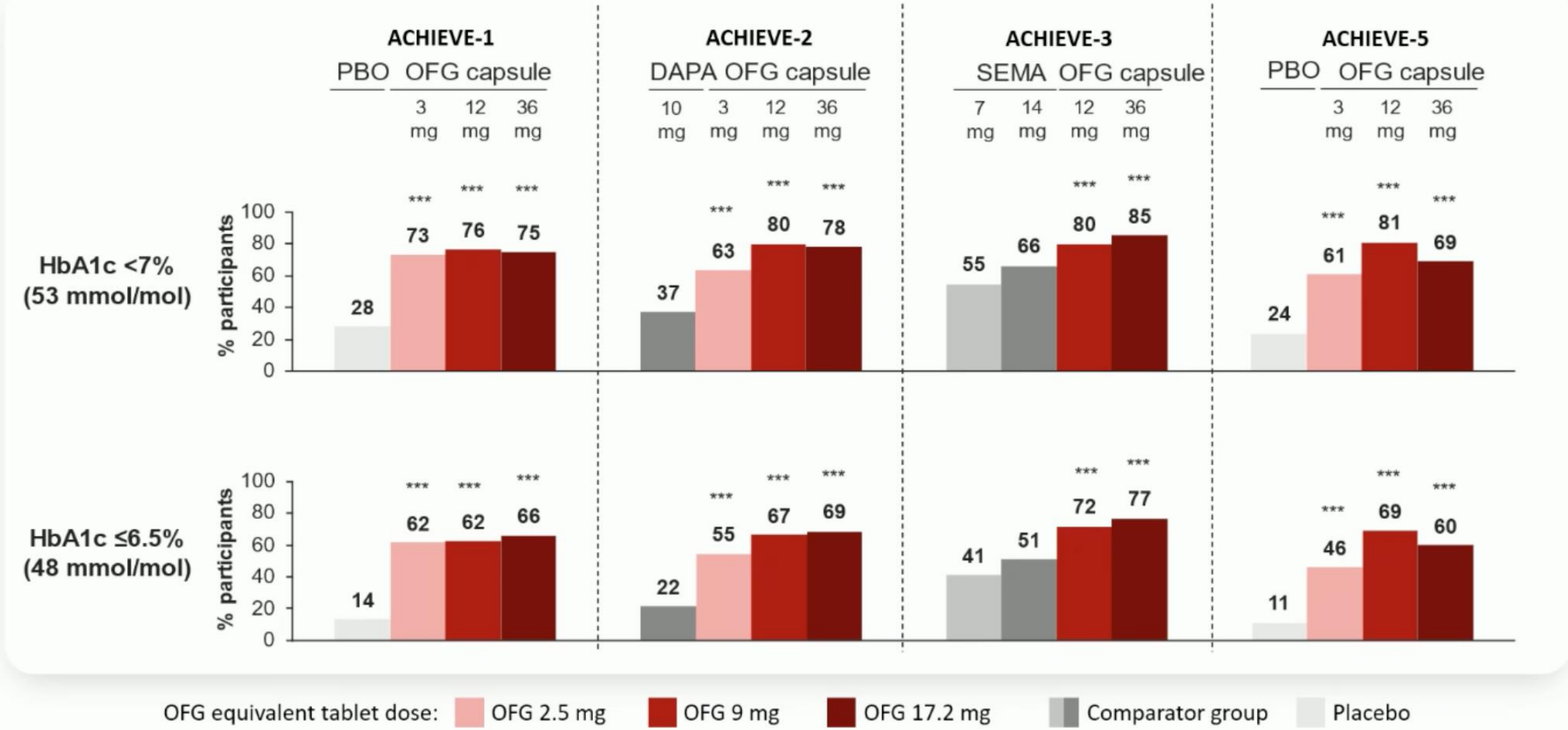
1. Ma X, et al. Diabetes Obesity and Metabolism. 2026; 0:1-7.

Orforglipron in T2D: HbA1c change from baseline (efficacy estimand)



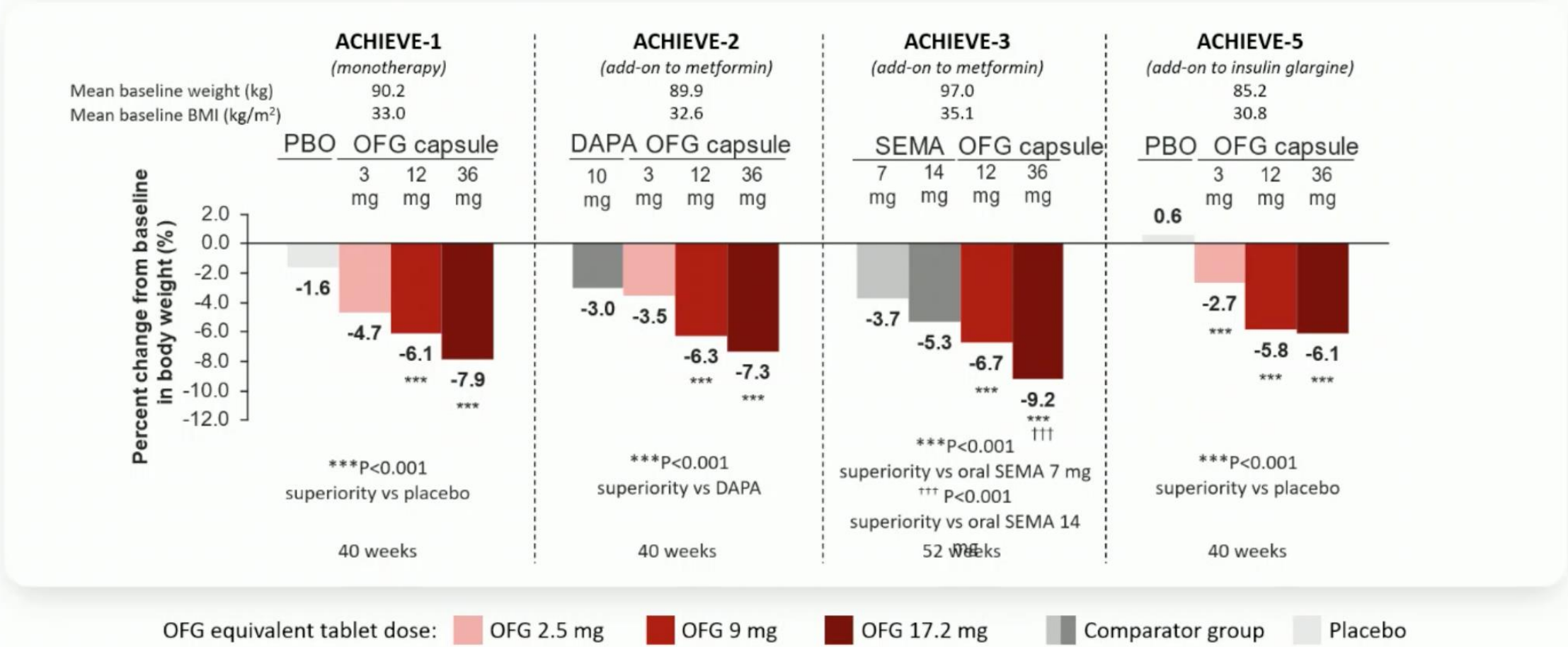
All endpoints controlled for Type I error. Efficacy estimand using mixed model repeated measures on randomized participants and efficacy estimand data points set. **Due to differences in study design, population, and methodology, direct comparisons between the results of different studies are not appropriate.** *DAPA=dapagliflozin; OFG=orforglipron; PBO=placebo; SEMA=oral semaglutide;*
Rosenstock J. et al. The New England Journal of Medicine. 2025; Welch M. et al. The Lancet. 2026; Rosenstock J. et al. The Lancet. 2026; Giorgino F. et al. JAMA. 2026

Orforglipron in T2D : HbA1c targets (efficacy estimand)



***p<0.001 OFG vs Comparator(s) or PBO. Endpoints for HbA1c <7% and ≤6.5% controlled for Type I error. Efficacy estimand using mixed model repeated measures on randomized participants. **Due to differences in study design, population, and methodology, direct comparisons between the results of different studies are not appropriate**. *DAPA=dapagliflozin; OFG=orforglipron; PBO=placebo; SEMA=oral semaglutide.* Rosenstock J. et al. The New England Journal of Medicine. 2025; Welch M. et al. The Lancet. 2026; Rosenstock J. et al. The Lancet. 2026; Giorgino F. et al. JAMA. 2026

Orforglipron in T2D: Body weight percent change from baseline (efficacy estim.)



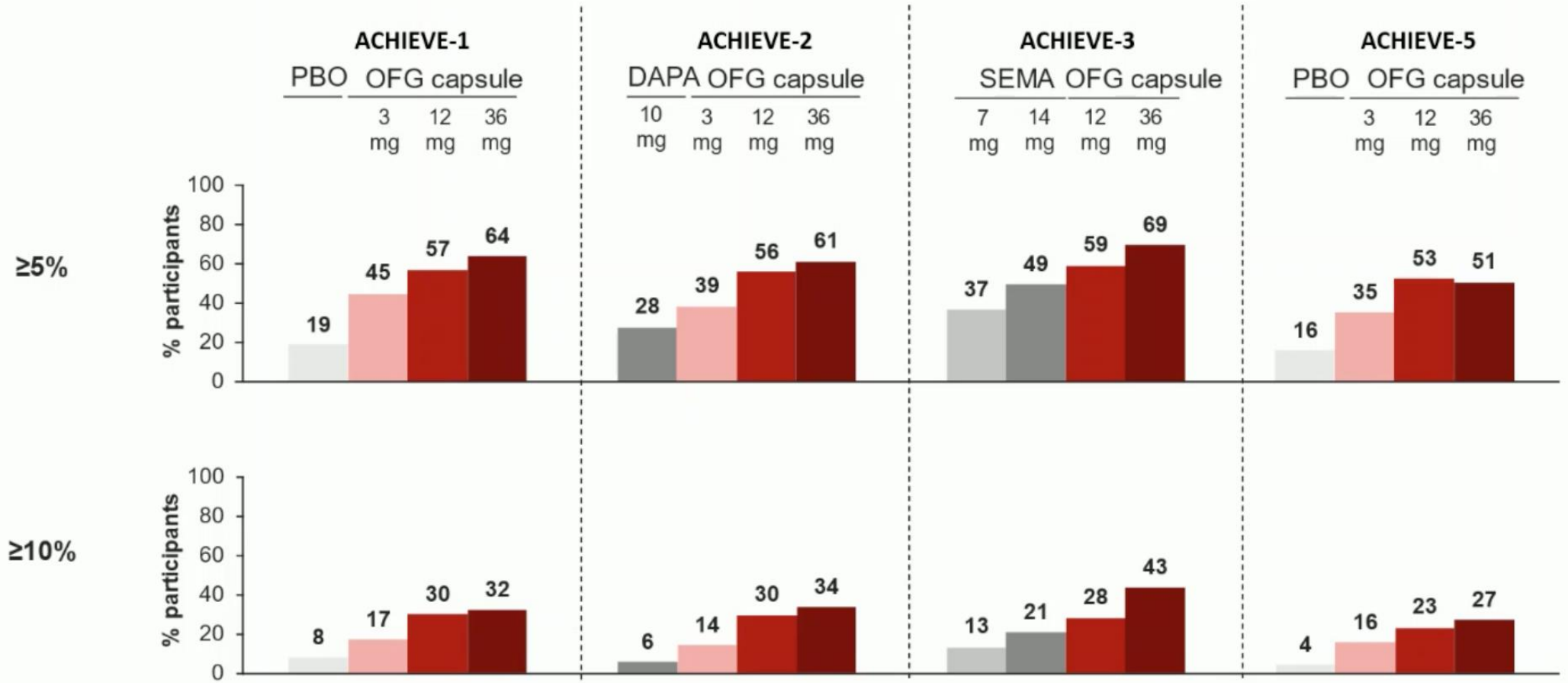
OFG equivalent tablet dose: OFG 2.5 mg | OFG 9 mg | OFG 17.2 mg | Comparator group | Placebo

Endpoints controlled for Type I error except OFG 3 mg in ACHIEVE-1 and -2, and OFG 12 mg vs SEMA 14 mg in ACHIEVE-3. Efficacy estimand using mixed model repeated measures on randomized participants and efficacy estimand data points set. **Due to differences in study design, population, and methodology, direct comparisons between the results of different studies are not appropriate.**

DAPA=dapagliflozin; OFG=orforglipron; PBO=placebo; SEMA=oral semaglutide;

Rosenstock J. et al. The New England Journal of Medicine. 2025; Welch M. et al. The Lancet. 2026; Rosenstock J. et al. The Lancet. 2026; Giorgino F. et al. JAMA. 2026

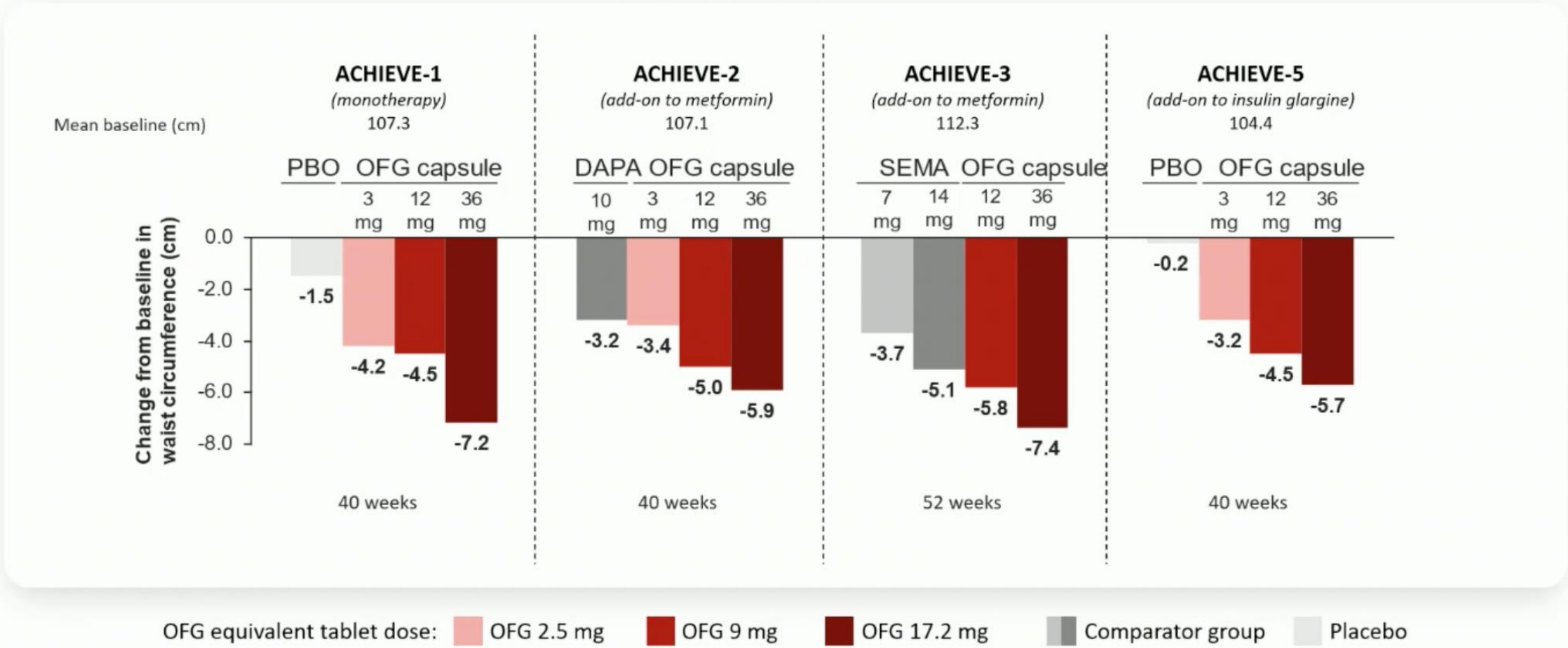
Orforglipron in T2D : Body weight reduction thresholds (efficacy estimand)



Endpoints not controlled for Type I error. Efficacy estimand using mixed model repeated measures on randomized participants and efficacy estimand data points set. **Due to differences in study design, population, and methodology, direct comparisons between the results of different studies are not appropriate.** *DAPA=dapagliflozin; OFG=orforglipron; PBO=placebo; SEMA=oral semaglutide*

Rosenstock J. et al. The New England Journal of Medicine. 2025; Welch M. et al. The Lancet. 2026; Rosenstock J. et al. The Lancet. 2026; Giorgino F. et al. JAMA. 2026

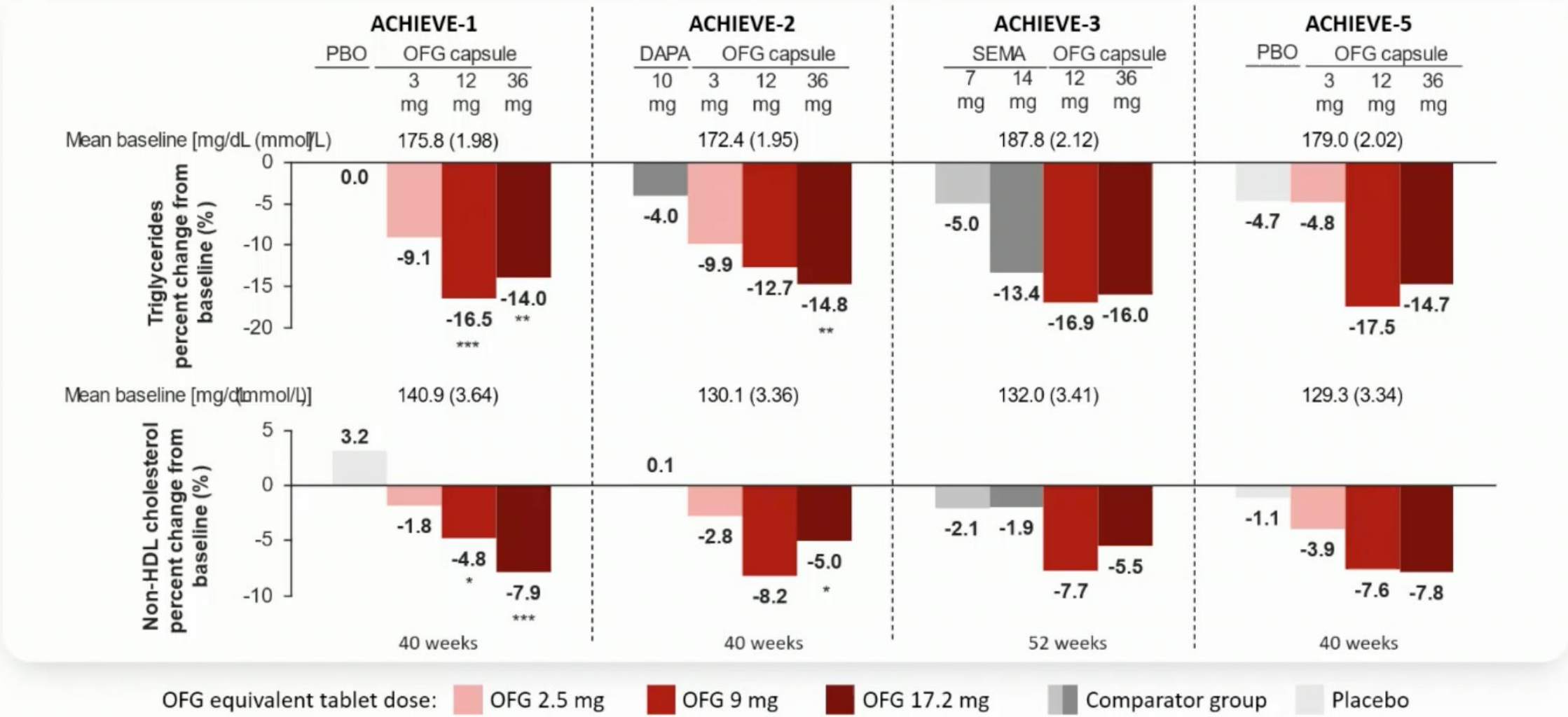
Orforglipron in T2D: Waist circumference change from baseline (efficacy estim.)



Endpoints not controlled for Type I error. Efficacy estimand using mixed model repeated measures on randomized participants and efficacy estimand data points set. **Due to differences in study design, population, and methodology, direct comparisons between the results of different studies are not appropriate**. *DAPA=dapagliflozin; OFG=orforglipron; PBO=placebo; SEMA=oral semaglutide*

Rosenstock J. et al. The New England Journal of Medicine. 2025; Welch M. et al. The Lancet. 2026; Rosenstock J. et al. The Lancet. 2026; Giorgino F. et al. JAMA. 2026

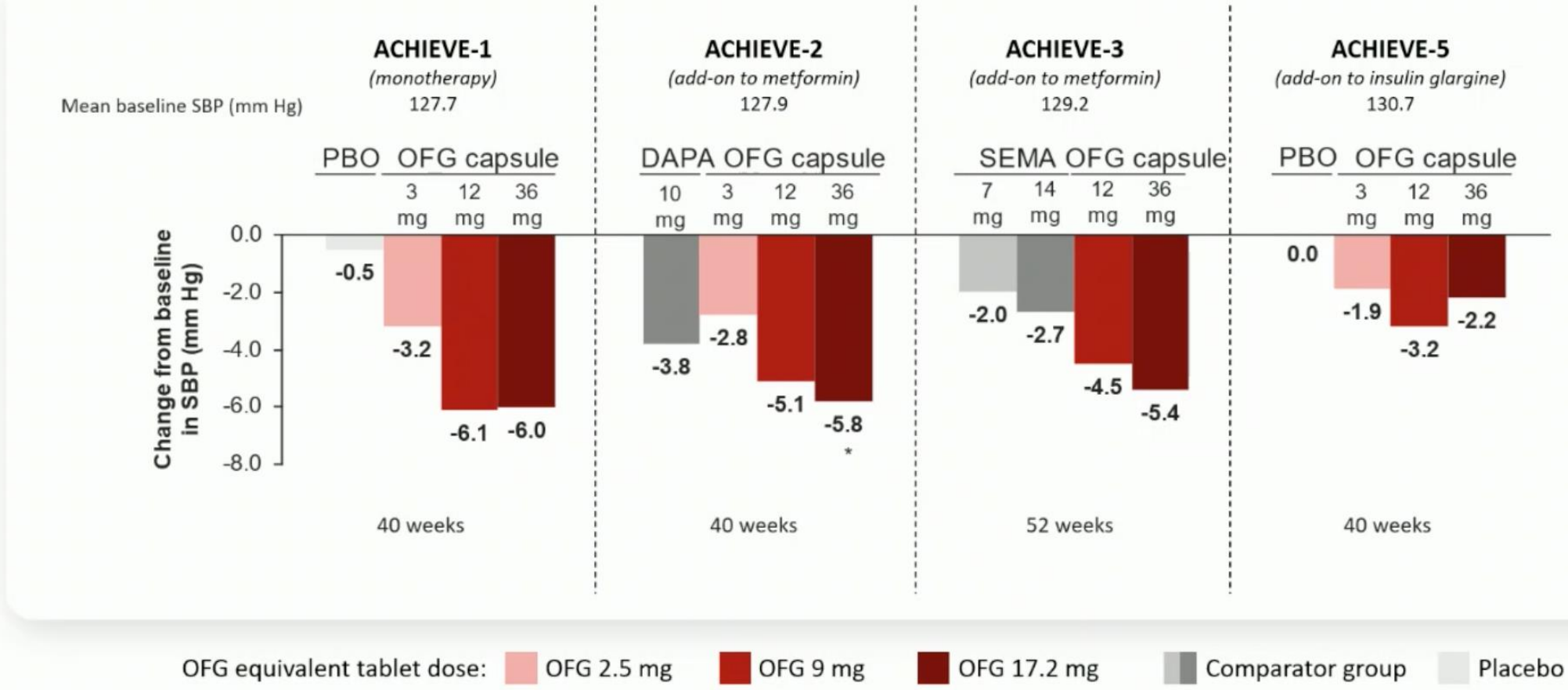
Orforglipron in T2D : Lipids percent change from baseline (efficacy estimand)



Endpoints not controlled for Type I error, except ACHIEVE-1 OFG 12 mg and 36 mg vs PBO, and ACHIEVE-2 OFG 36 mg vs DAPA. P-values only shown for endpoints controlled for Type I error. *P<0.05; **P<0.01; ***P<0.001. Efficacy estimand using mixed model repeated measures on randomized participants and efficacy estimand data points set. **Due to differences in study design, population, and methodology, direct comparisons between the results of different studies are not appropriate.** *DAPA=dapagliflozin; OFG=orforglipron; PBO=placebo; SEMA=oral semaglutide*

Rosenstock J. et al. The New England Journal of Medicine. 2025; Welch M. et al. The Lancet. 2026; Rosenstock J. et al. The Lancet. 2026; Giorgino F. et al. JAMA. 2026

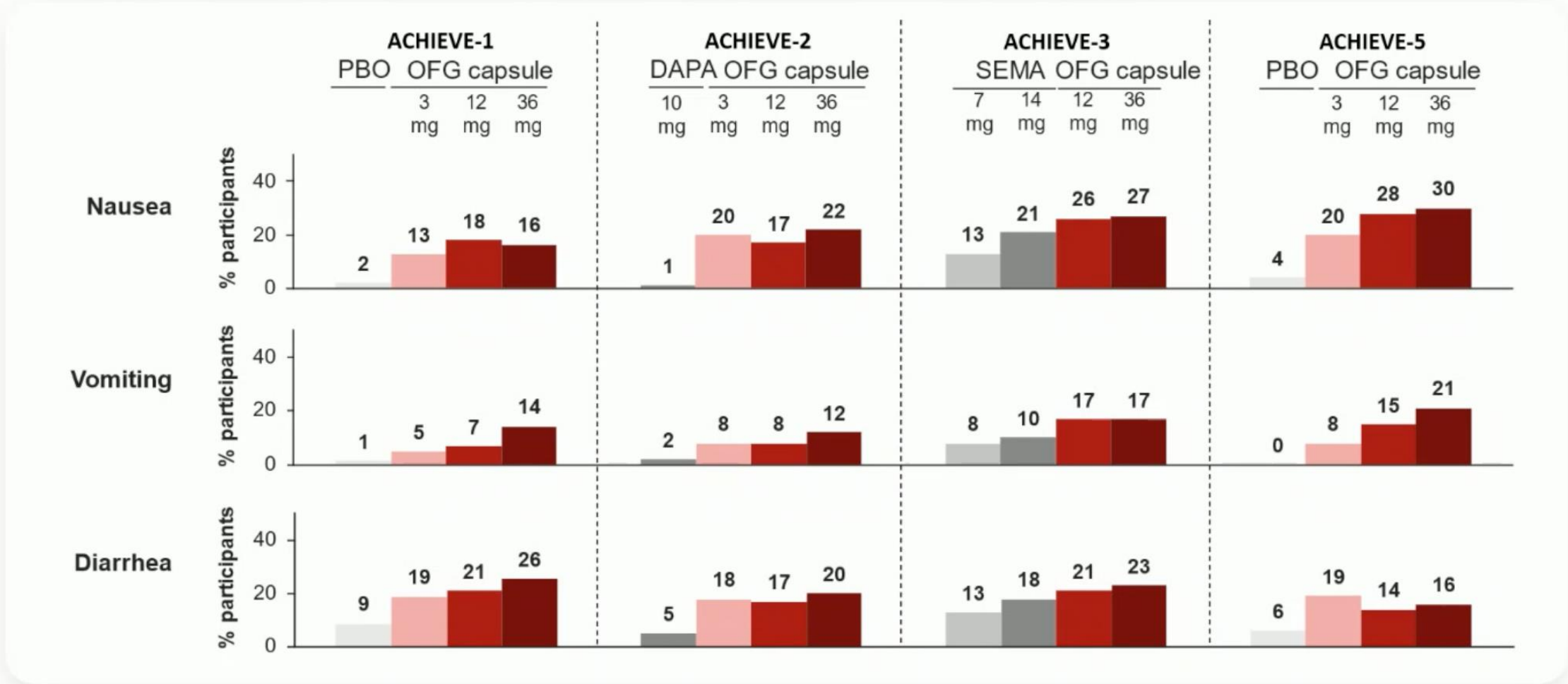
Orforglipron in T2D: Systolic blood pressure change from baseline (efficacy estimand)



Endpoints not controlled for Type I error, except ACHIEVE-2 OFG 36 mg vs DAPA. P-values only shown for endpoints controlled for Type I error. *P<0.05. Efficacy estimand using mixed model repeated measures on randomized participants and efficacy estimand data points set. ACHIEVE-1 and ACHIEVE-5 is data on file. **Due to differences in study design, population, and methodology, direct comparisons between the results of different studies are not appropriate**. *DAPA=dapagliflozin; OFG=orforglipron; PBO=placebo; SEMA=oral semaglutide*

Rosenstock J. et al. The New England Journal of Medicine. 2025; Welch M. et al. The Lancet. 2026; Rosenstock J. et al. The Lancet. 2026; Giorgino F. et al. JAMA. 2026

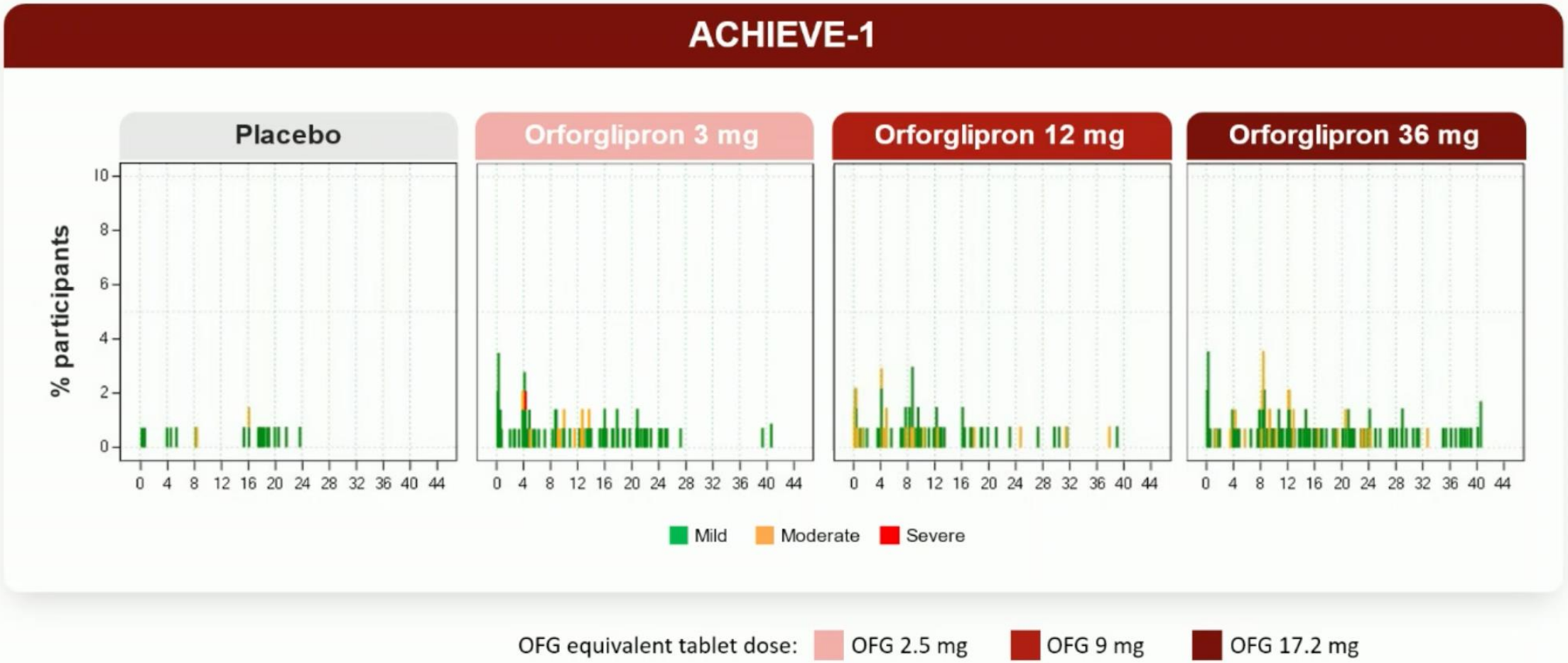
Orforglipron in T2D: Gastrointestinal adverse events overview



Safety analysis set. **Due to differences in study design, population, and methodology, direct comparisons between the results of different studies are not appropriate.**

Rosenstock J. et al. The New England Journal of Medicine. 2025; Welch M. et al. The Lancet. 2026; Rosenstock J. et al. The Lancet. 2026; Giorgino F. et al. JAMA. 2026

Orforglipron in T2D: Incidence and severity of nausea, vomiting and diarrhea



Nausea, vomiting, and diarrhea events combined. Proportions are based on number of participants at risk. Data on file.
N=number of participants in analysis population; OFG=orforglipron. Rosenstock J. et al. NEJM 2025

Summary of ACHIEVE-1, -2, -3 and -5

Efficacy

Orforglipron (12 mg and 36 mg capsule) demonstrated significant reductions in:

- HbA1c
- Body weight

...when compared to:

- Placebo [1,4]
- Active comparators (dapagliflozin 10 mg; oral semaglutide 7 mg and 14 mg) [2,3]

Safety

- Orforglipron tolerability and safety profile was generally consistent with the GLP-1 RA class. [1-4]
- Adverse events were predominantly gastrointestinal, mostly transient, and mostly mild-to-moderate in severity. [1-4]
- There was no liver toxicity signal across the entire clinical development program. [5]

1. Rosenstock J. et al. The New England Journal of Medicine. 2025; 2. Welch M. et al. The Lancet. 2026; 3. Rosenstock J. et al. The Lancet. 2026; 4. Giorgino F. et al. JAMA. 2026; 5. Wharton S. et al. Diabetes Obesity and Metabolism. 2026

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

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 Risk[1]

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

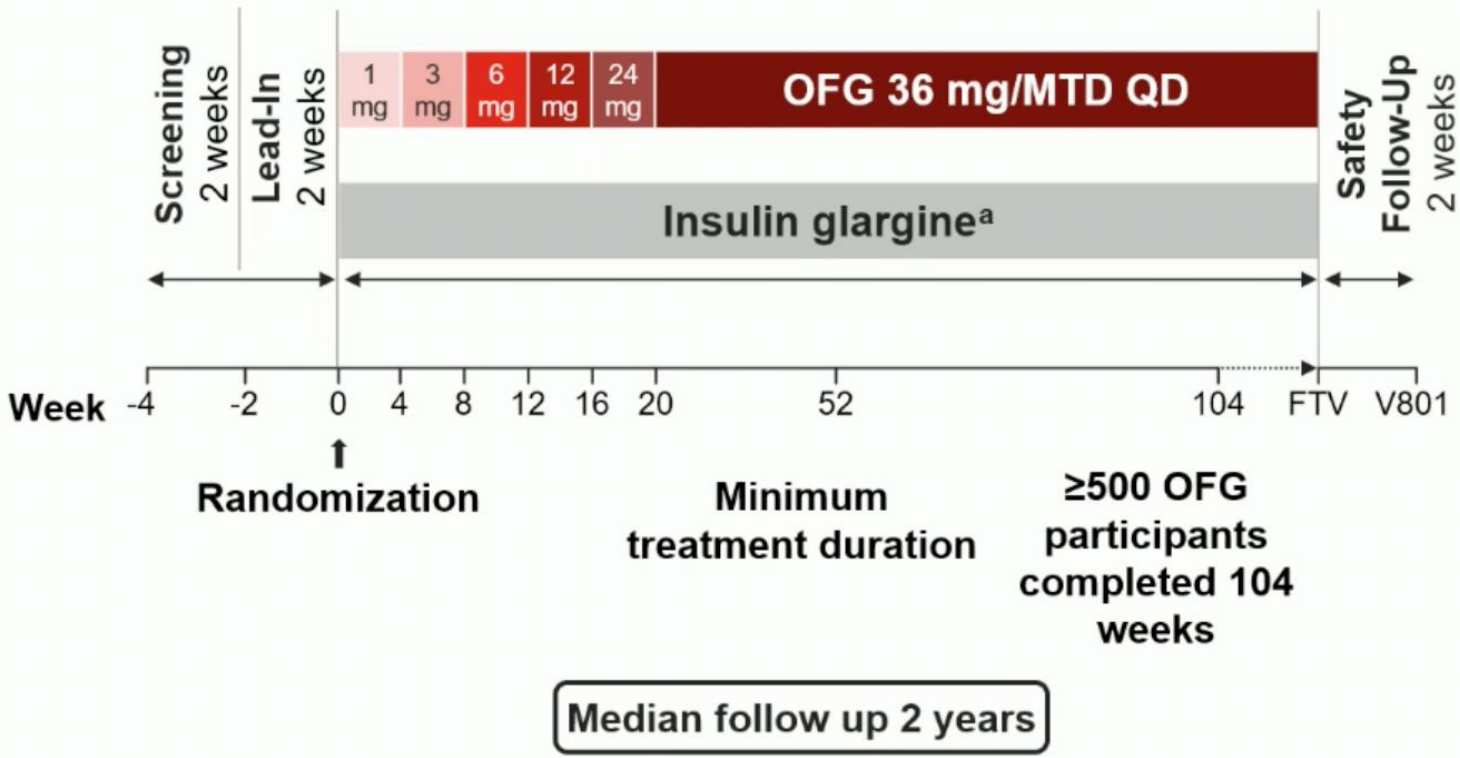
Insulin Glargine as Comparator

- Active control needed to ensure adequate glycemic control in a population with inadequate control
- Insulin glargine shown to have neutral effect on CV outcomes[2]

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 *Investigational use in study*	Orforglipron Tablet *Equivalent formulation**
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

[a]The 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**: ≥7.0% to ≤10.5% (or ≥7.5% if using SU)
- **BMI ≥25 kg/m²** with stable weight (±5%)
- Using stable doses of **1-3 oral glucose lowering medications** (± metformin ± SGLT-2i ± 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 m^2
- **ALT or AST** >5× 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**

[a]Participants 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)

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)

[a]Controlled for family-wise Type I error. [b]MACE-4 includes non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or CV death. [c]MACE-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

[a]Controlled for family-wise Type I error. [b]MACE-4 includes non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or CV death. [c]MACE-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.***

Weight and HbA1c endpoints

Population

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

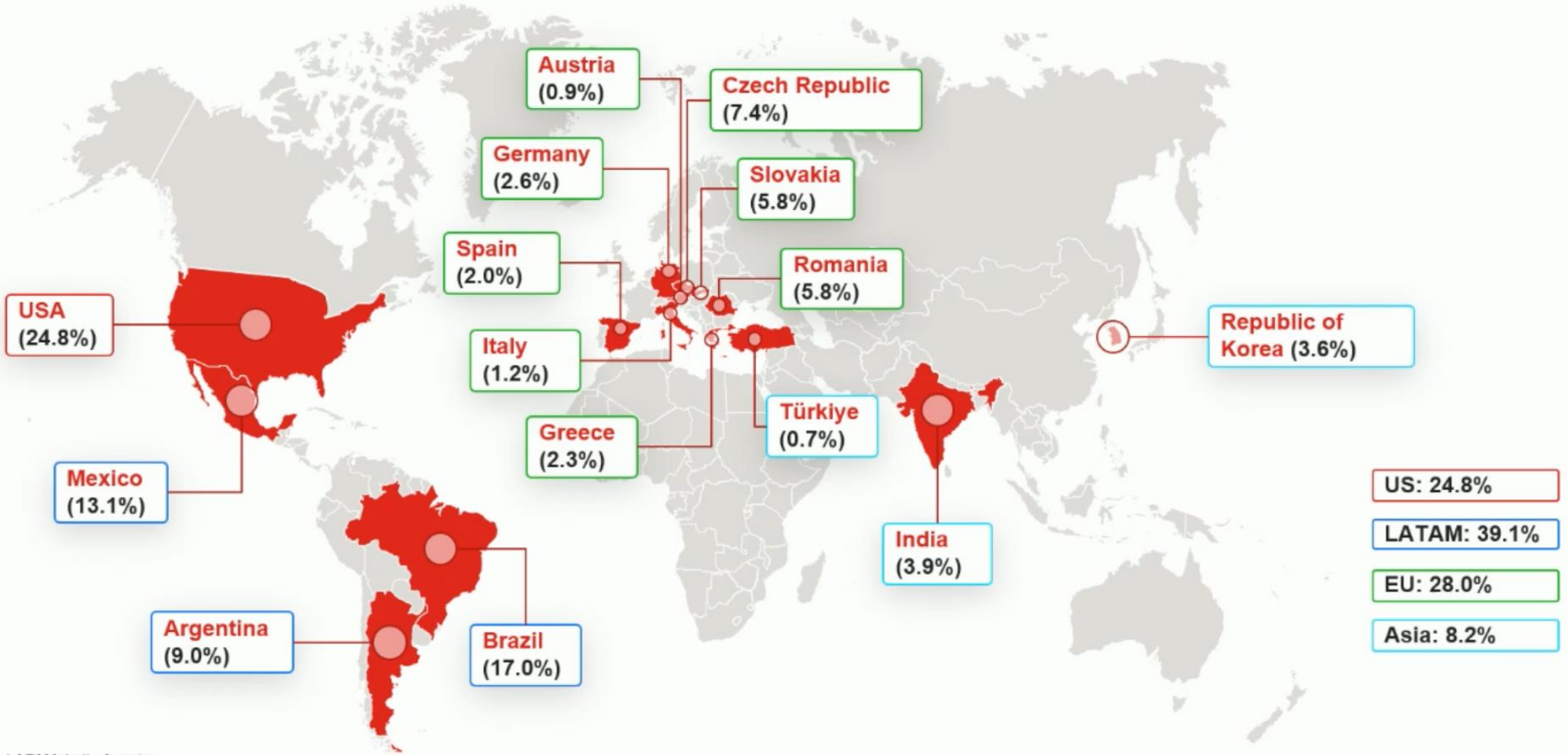
Treatment regimen estimand

Evaluates effect regardless of adherence or initiation of rescue therapy.

Efficacy estimand

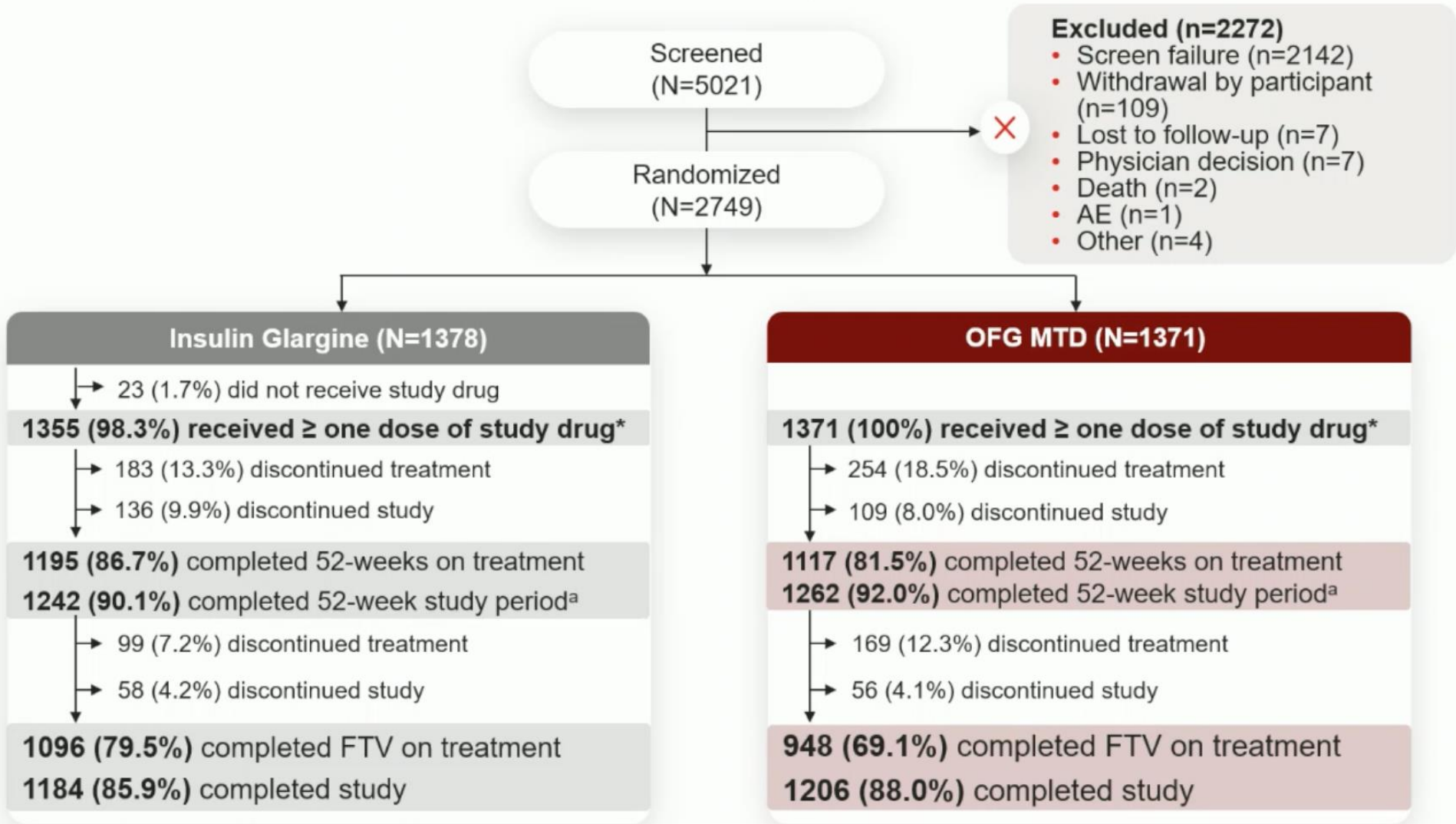
Effect if participants remained on assigned treatment without rescue therapy.

Country-Level Overview (N=2749)



EU=European Union; LATAM=Latin America;
Clinicaltrials.gov. NCT05803421.

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.

[a]Participants 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. [a]eGFR 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 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.

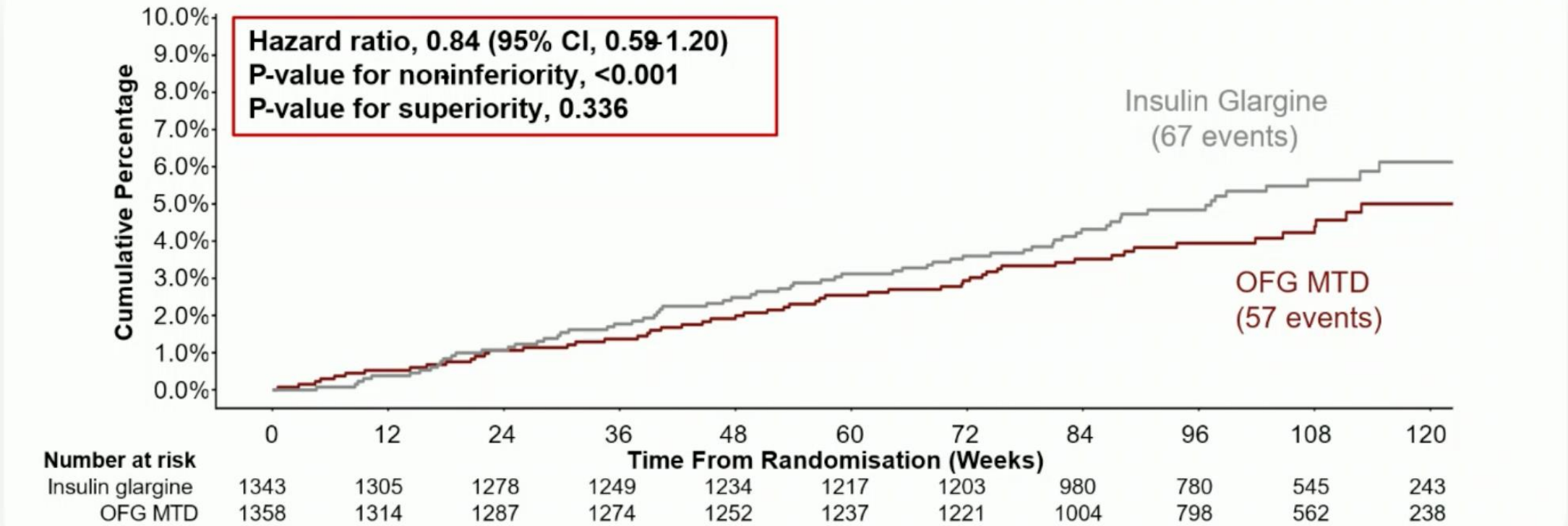
Baseline Cardiovascular and Kidney Disease

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.

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

Primary Endpoint



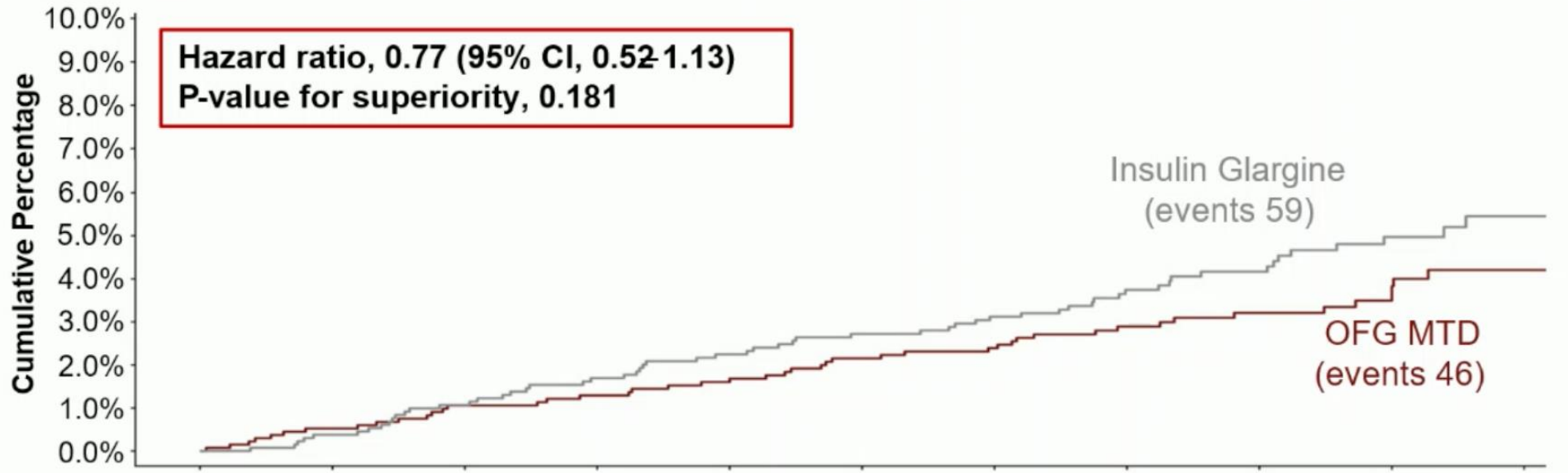
MACE-4 = composite of non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or CV death

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



Number at risk											
Insulin glargine	1366	1307	1280	1251	1238	1222	1209	987	788	548	245
OFG MTD	1358	1314	1287	1275	1256	1242	1228	1010	805	567	239

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)

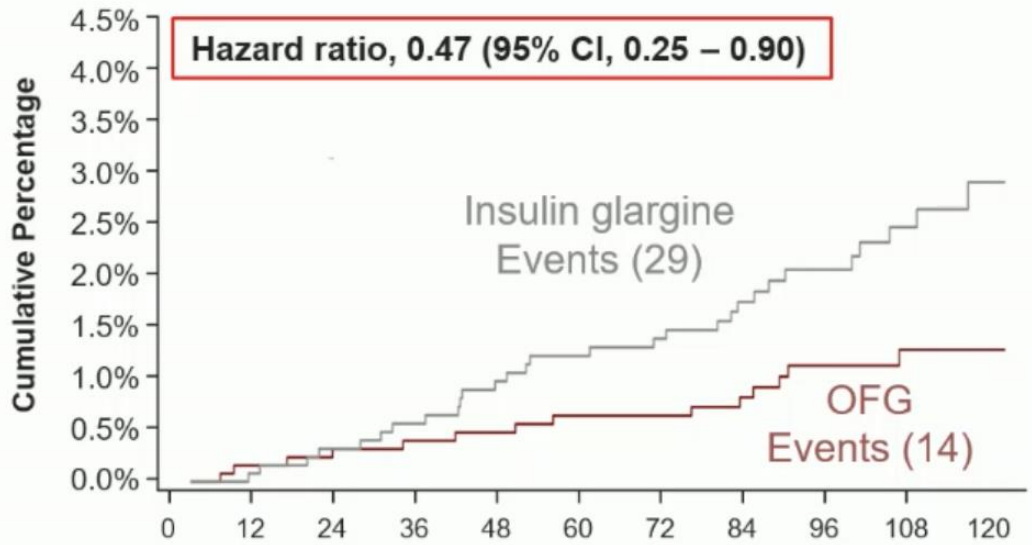
[a]Controlled for family-wise Type I error. [b]MACE-4 includes deaths due to cardiovascular cause, myocardial infarction, hospitalization for unstable angina, and stroke. Analysis set is all subjects taking ≥ 1 dose of study drug. [c]MACE-3 includes deaths due to cardiovascular cause, myocardial infarction, 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

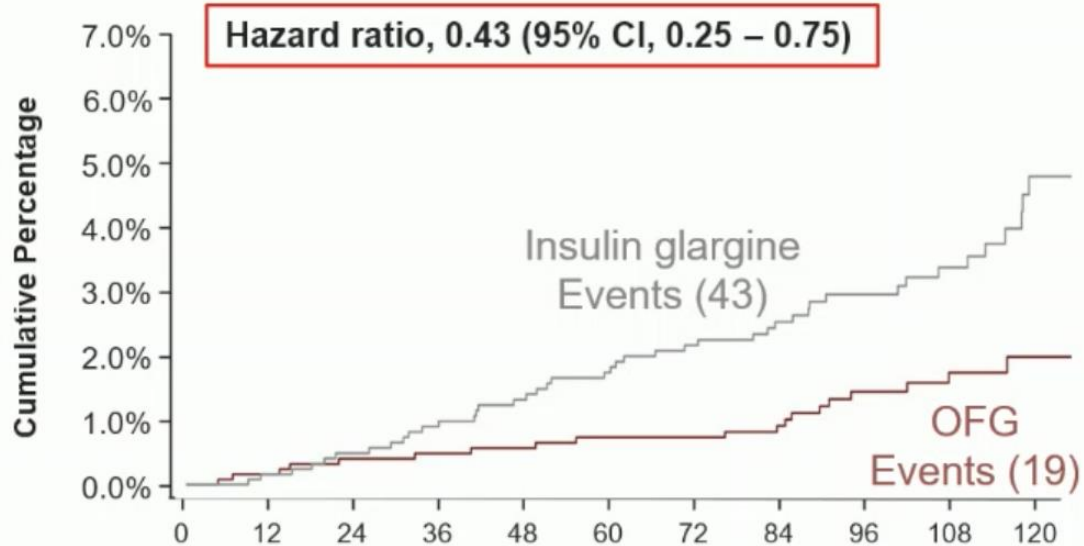
CV Death



Number at risk											
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

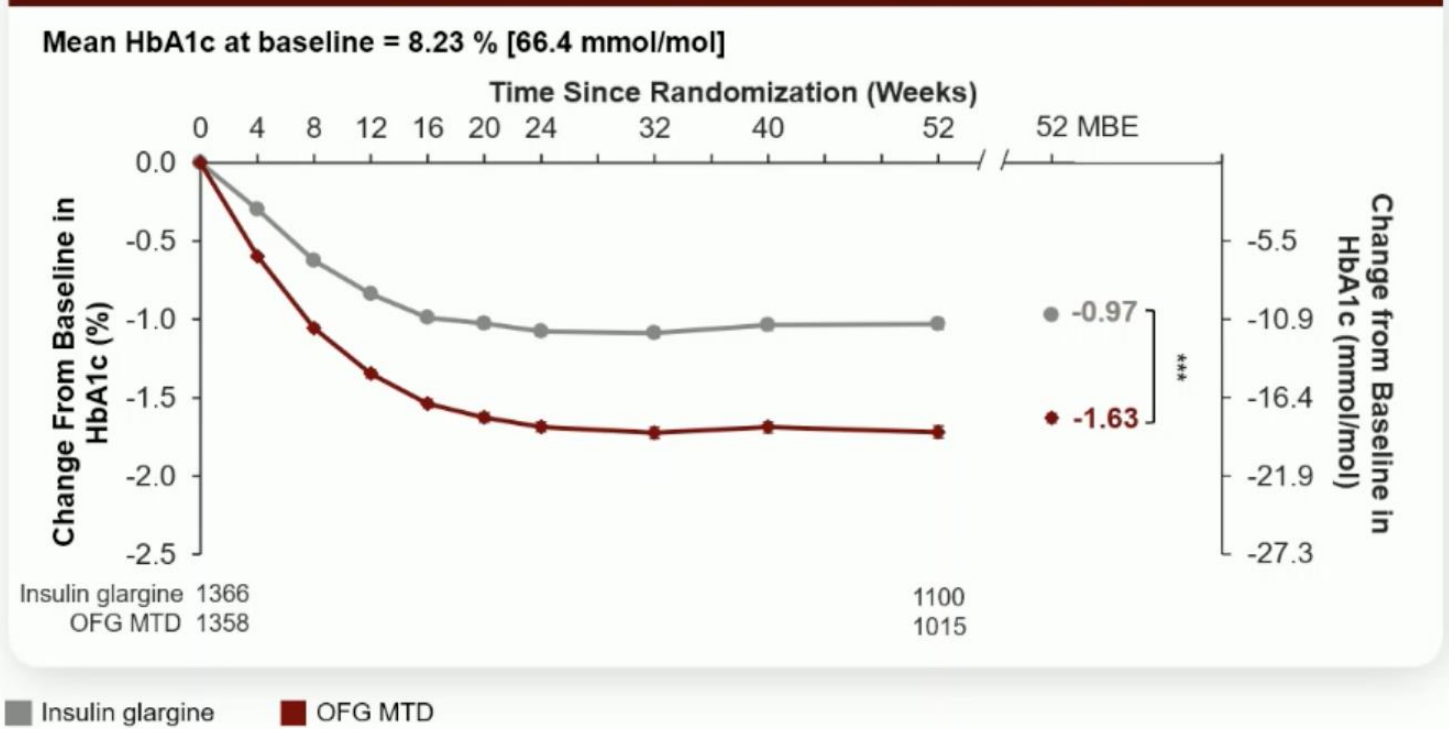
Notes: 1. All events confirmed by the CEC. 2. Point estimate and 95% CI of HR comparing OFG MTD and insulin glargine obtained from time-to-first-event analysis using Cox proportional hazards model; safety analysis set. 3. All cause death was an adjudicated outcome but was not a prespecified endpoint 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

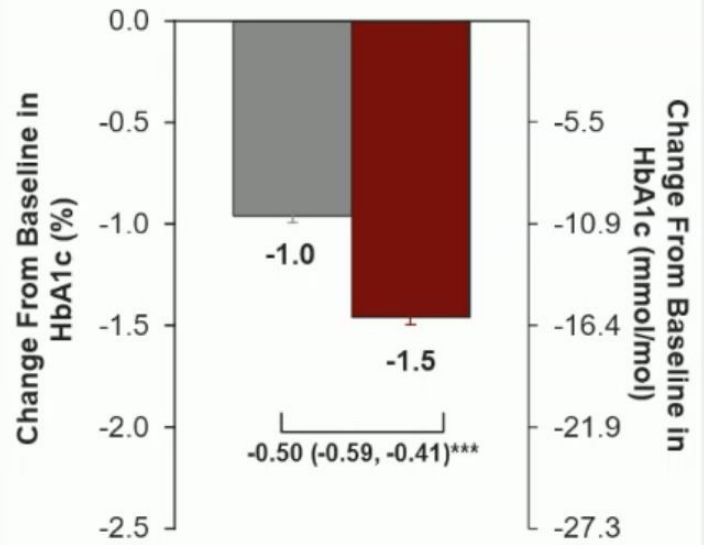
Orforglipron was Superior to Insulin Glargine for Reduction in HbA1c

Key Secondary Endpoint

Efficacy Estimand (Observed Mean + MBE)



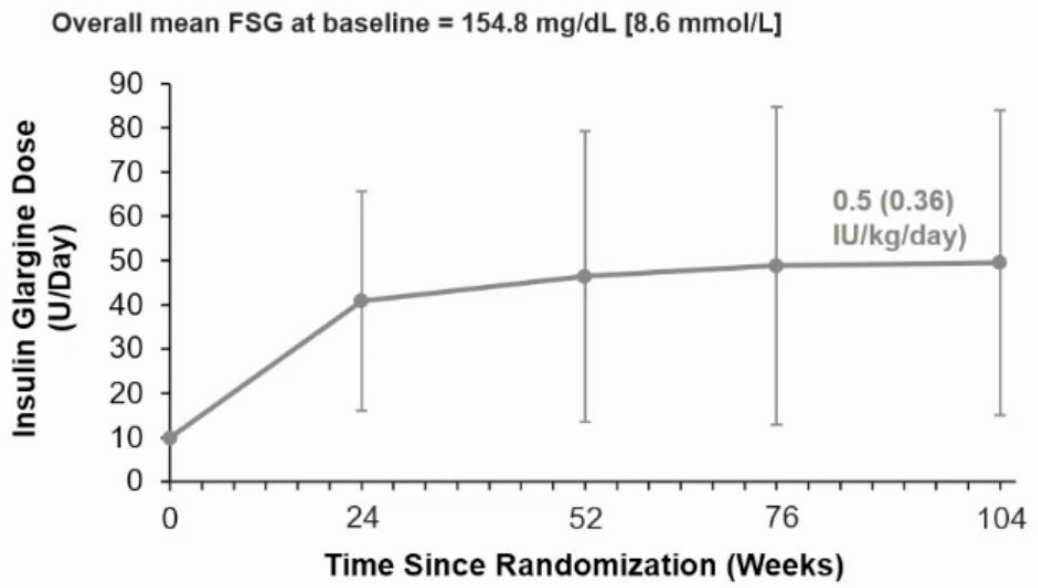
Treatment Regimen Estimand



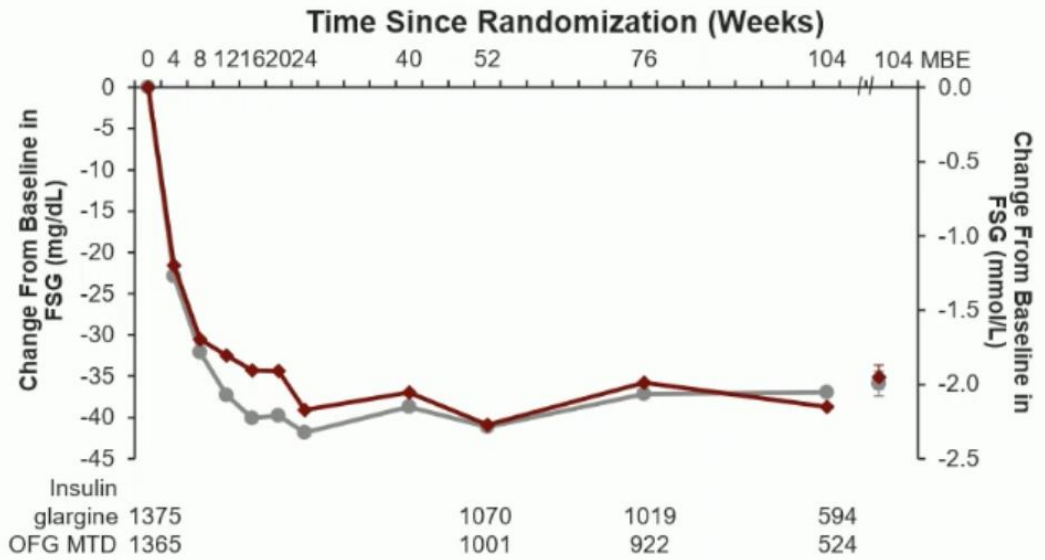
OFG MTD vs. insulin glargine: ***p<0.001. p-values are for MBE change difference vs. insulin glargine.
Notes: Data in line plot are raw mean (SE). EE analysis was conducted using MMRM on randomized participants and EE data points set. TRE analysis was conducted using ANCOVA on randomized participants 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



FSG



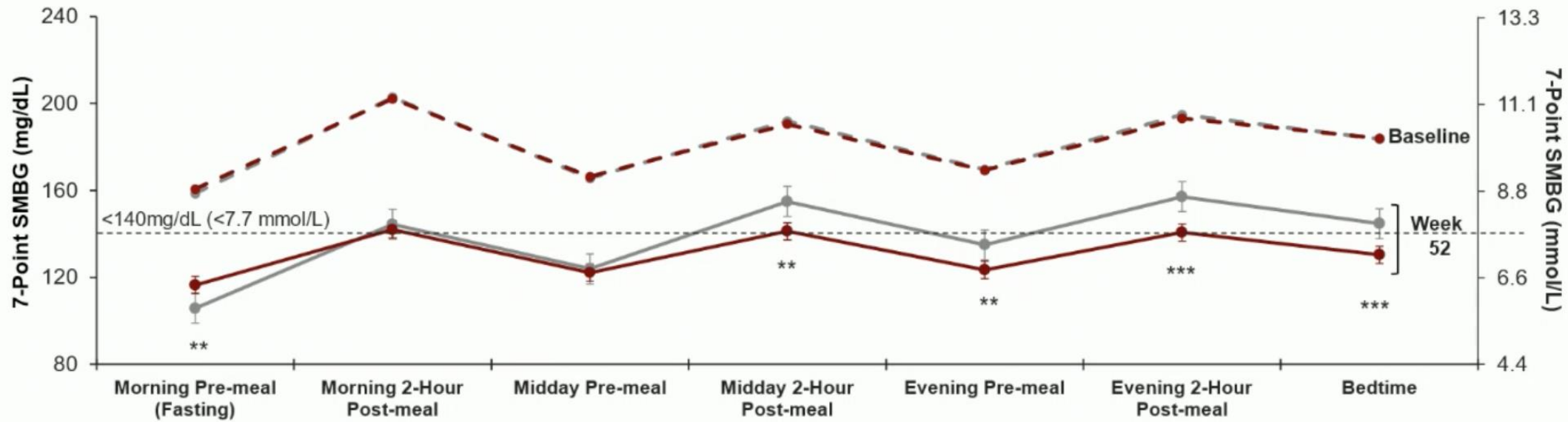
Insulin glargine OFG MTD

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

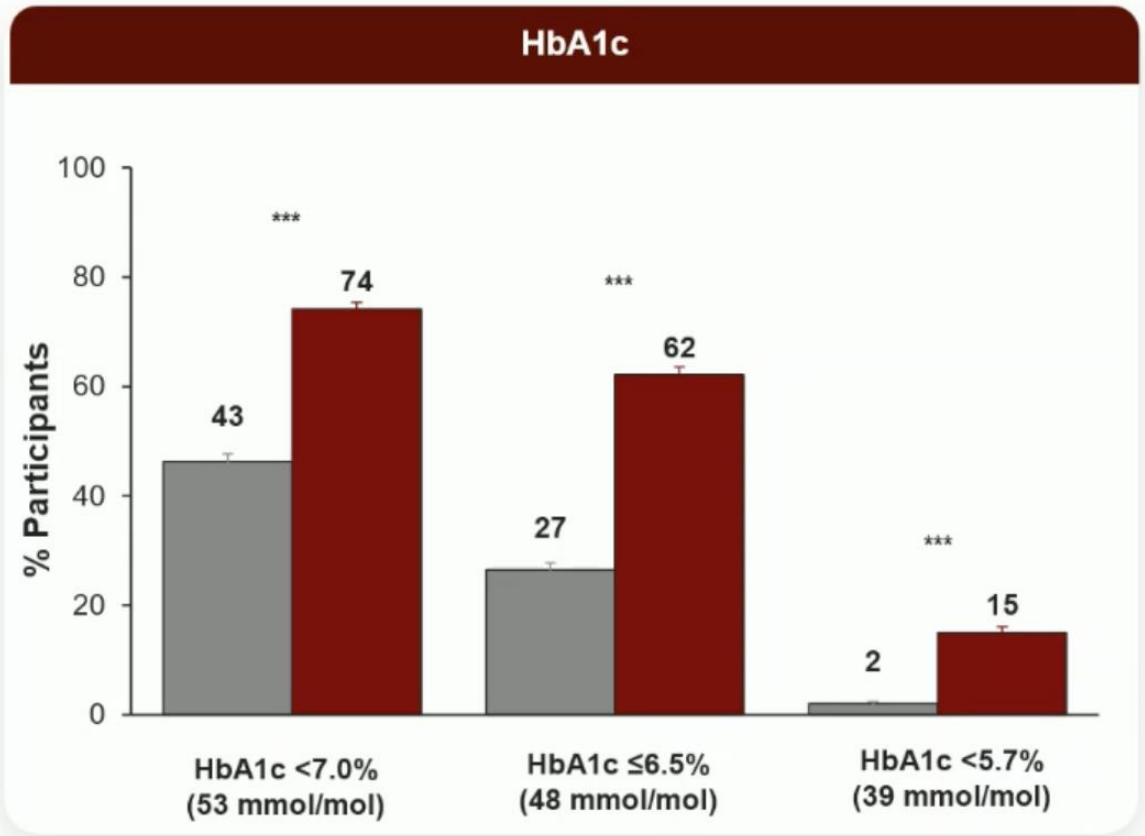
Efficacy Estimand

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)



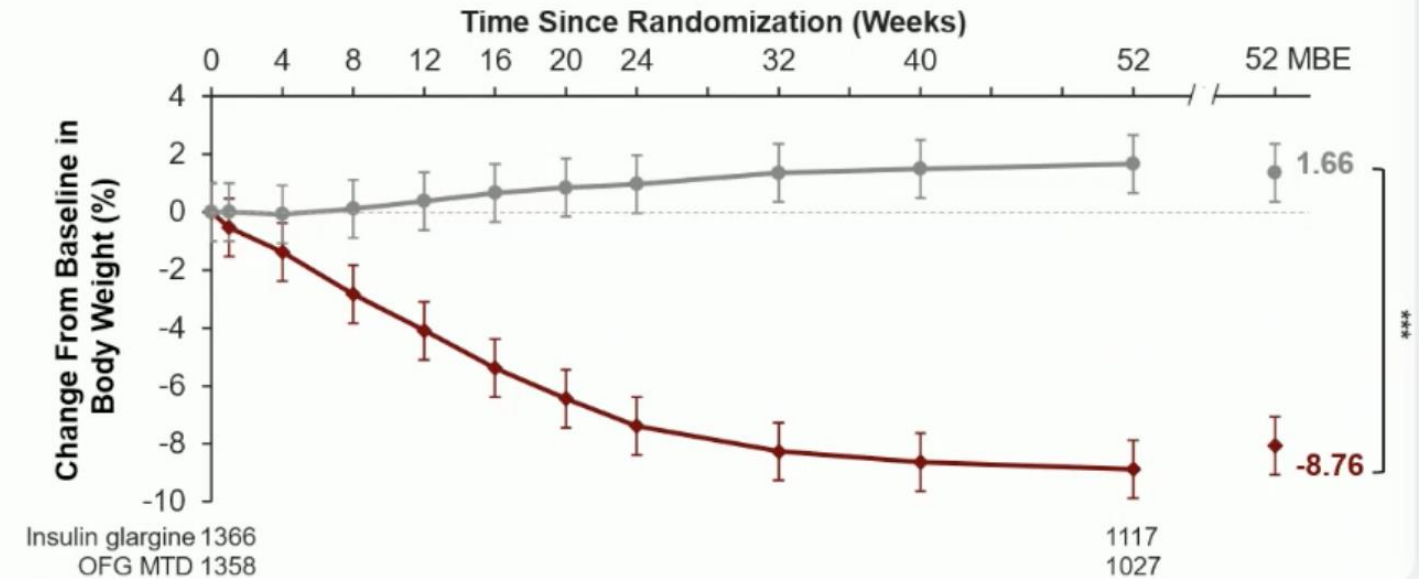
OFG vs. insulin glargine: ***p<0.001. p-values are for risk difference vs. insulin glargine.
Notes: Data are MBE (SE). EE analysis was conducted using logistic regression model on randomized participants and EE data points set, with missing data imputed. All analyses were pre-specified. Family-wise Type 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.

Orforglipron was Superior to Insulin Glargine for bodyweight reduction

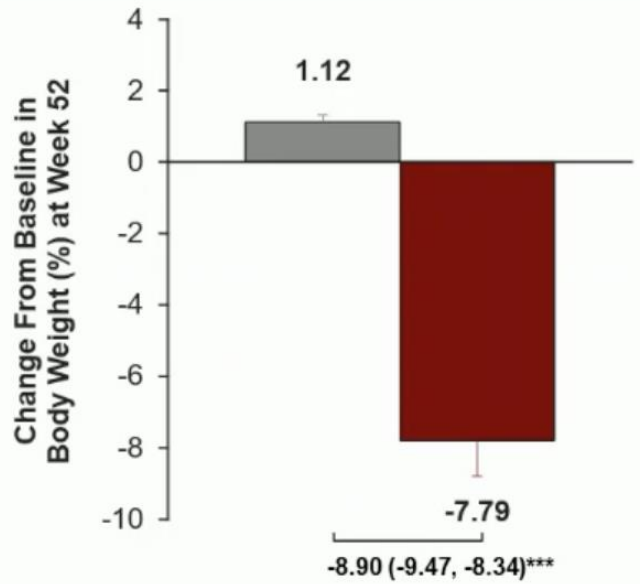
Key Secondary Endpoint

Efficacy Estimand

Mean body weight at baseline = 90.91 kg



Treatment Regimen Estimand



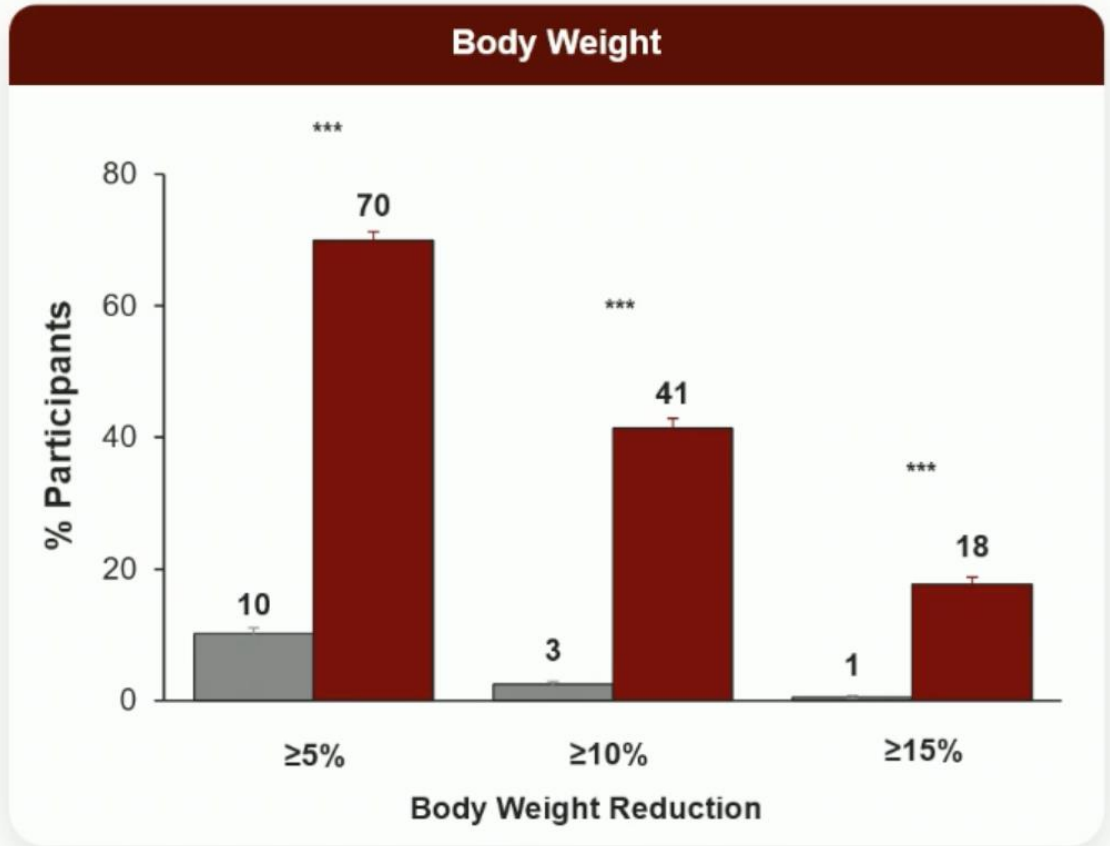
Insulin glargine OFG MTD

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); 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)

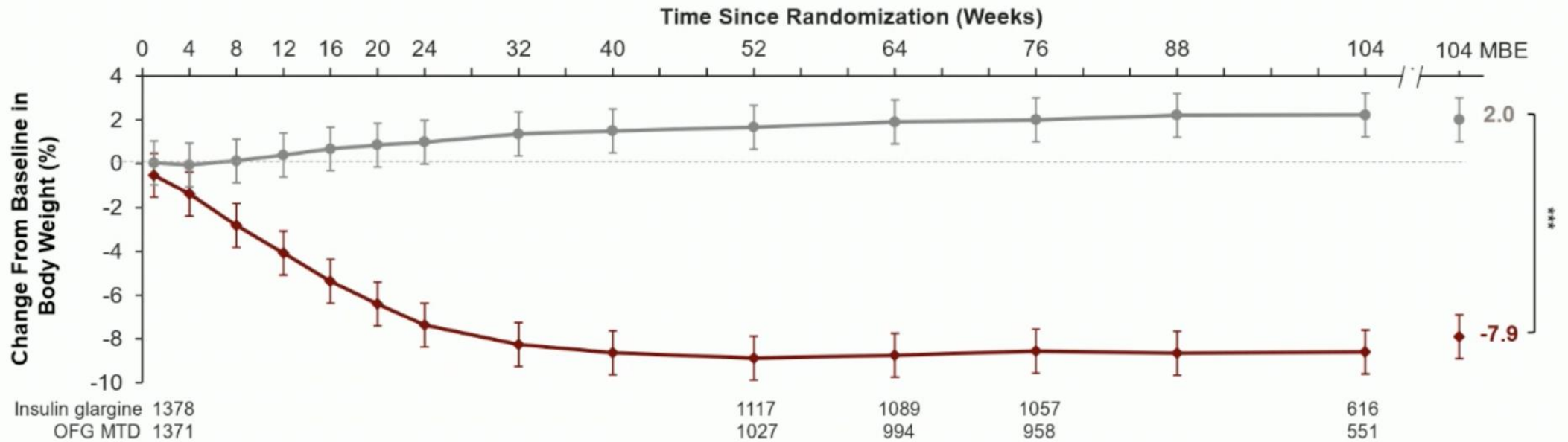


OFG vs. insulin glargine: ***p<0.001. p-values are for risk difference vs. insulin glargine.
Notes: Data are MBE (SE). EE analysis was conducted using logistic regression model on randomized participants and EE data points set, with missing data imputed. All analyses were pre-specified. Family-wise Type 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

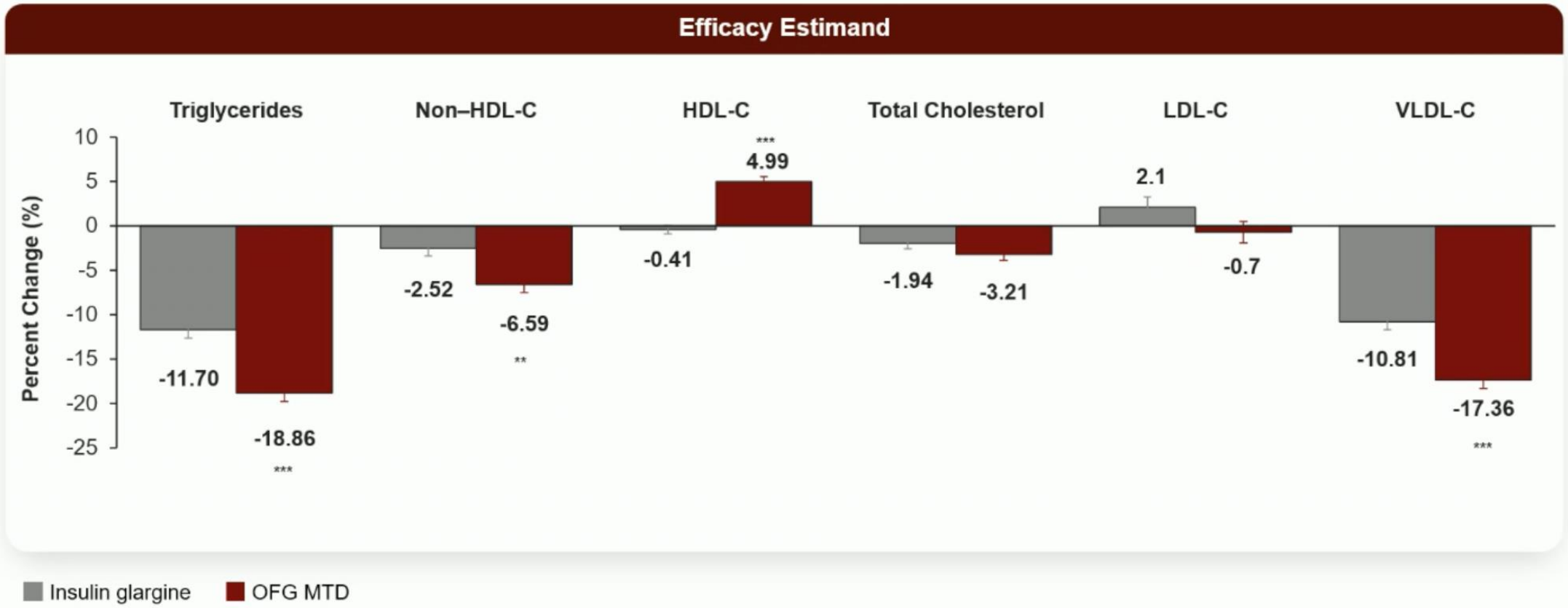
Overall mean body weight at baseline = 90.91 (20.04) kg



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.

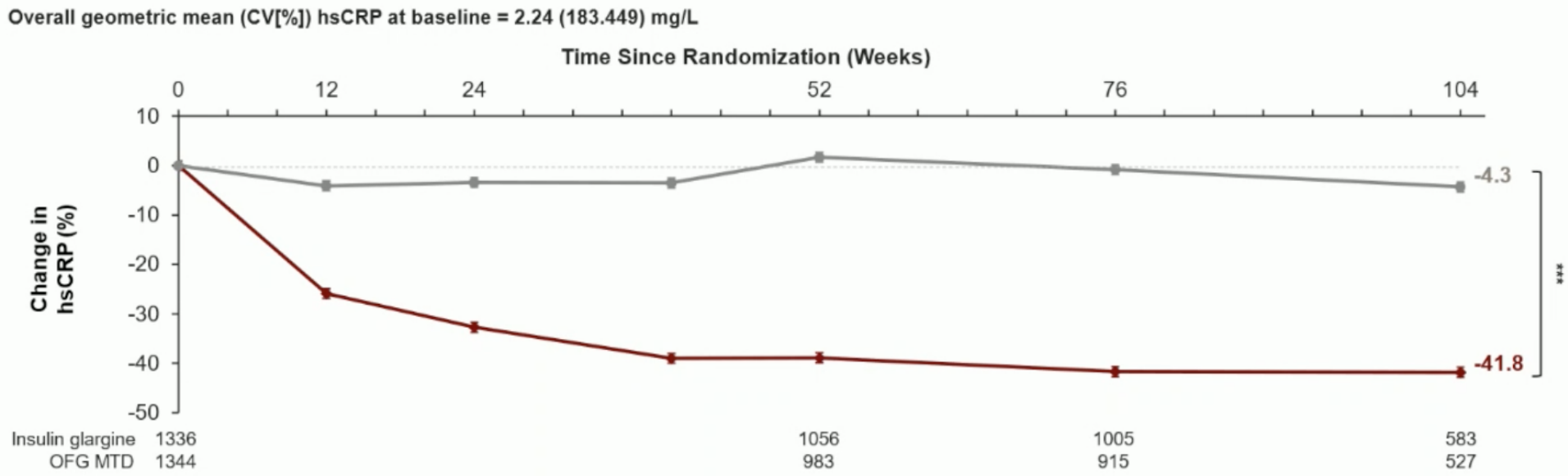
Favorable Lipid Profile Changes were Sustained Through Week 52



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

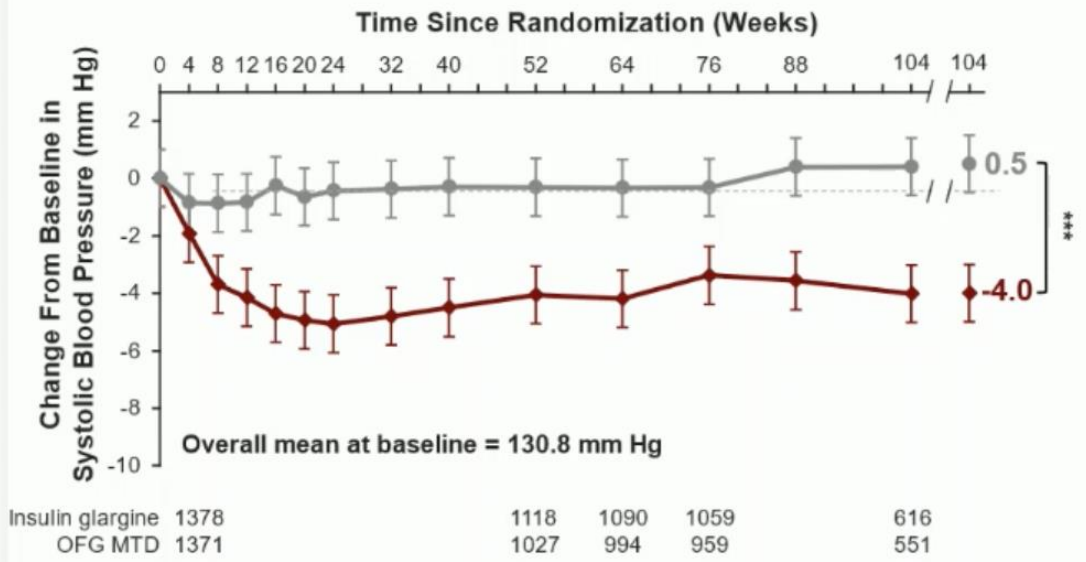


OFG MTD vs. insulin glargine: ***p<0.001. p-values are for MBE change difference vs. insulin glargine.
Data in line plot are MBE (SE). EE analysis was conducted using MMRM on randomized participants and EE data points set. Family-wise Type I error was not controlled.
EE=efficacy estimand; hsCRP=high-sensitivity C-reactive protein; 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

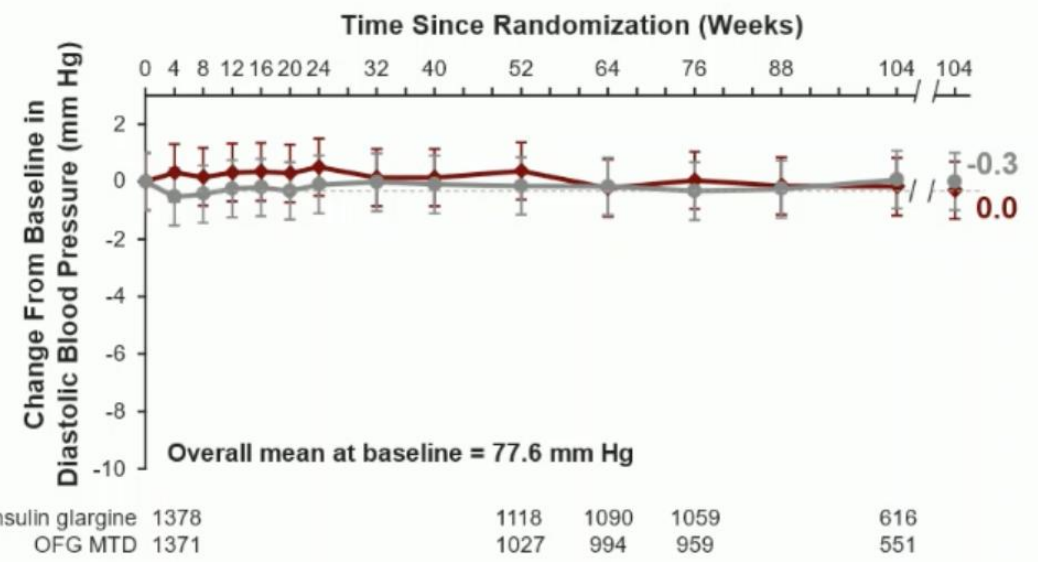
Changes in Blood Pressure

Efficacy Estimand

Systolic Blood Pressure



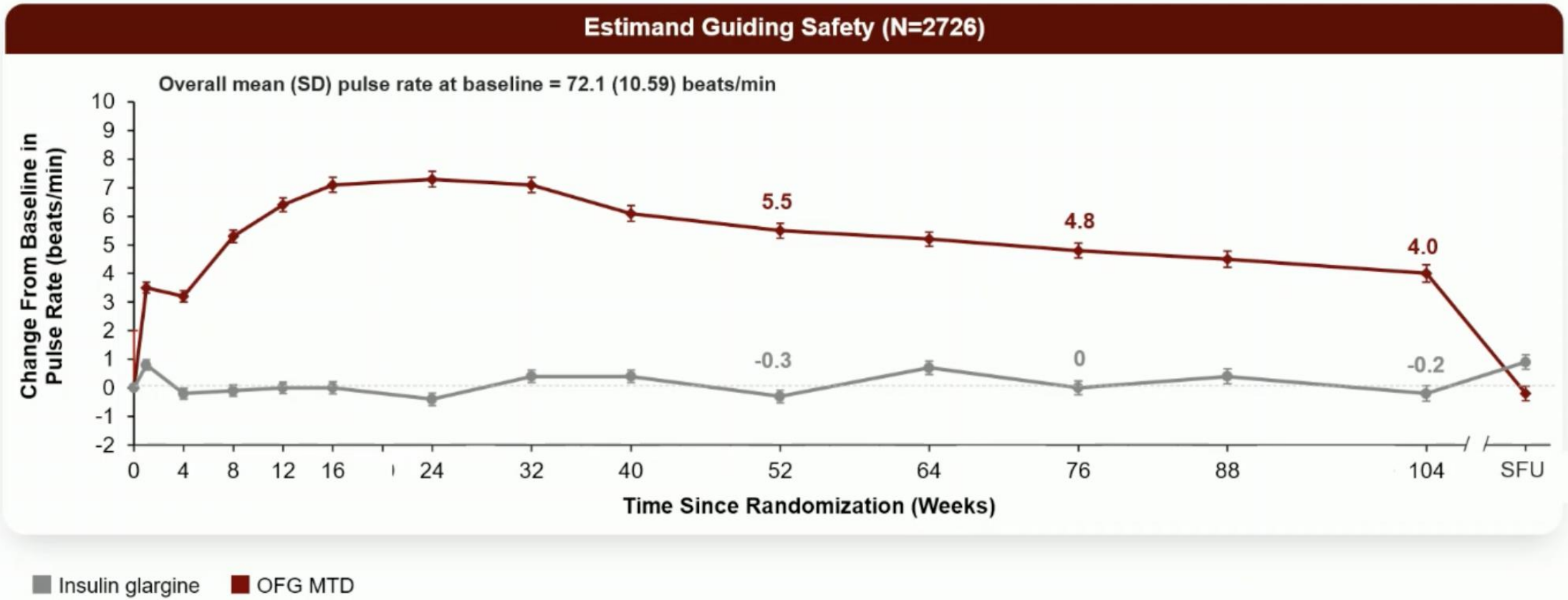
Diastolic Blood Pressure



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



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)

[a]Death 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.

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)

[a]Severe 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. [b]Hypoglycemia 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

CI=confidence interval; GLP-1 RA=glucagon-like peptide-1receptor agonist; HbA1c=glycated hemoglobin; HR=hazard ratio; hsCRP=high-sensitivity C-reactive protein; MACE-3=major adverse CV event-3 point; MACE-4=major adverse CV event-4 point; RA=receptor agonist.

Summary of ACHIEVE-4

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- 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.

CI=confidence interval; GLP-1 RA=glucagon-like peptide-1receptor agonist; HbA1c=glycated hemoglobin; HR=hazard ratio; hsCRP=high-sensitivity C-reactive protein; MACE-3=major adverse CV event-3 point; MACE-4=major adverse CV event-4 point; RA=receptor agonist.

Cardiovascular safety of orforglipron versus insulin glargine in adults with type 2 diabetes at increased cardiovascular risk (ACHIEVE-4): a phase 3, event-driven, randomised, open-label, non-inferiority, active comparator trial

Klara R Klein, Carol Wysham, Katherine R Tuttle, Melanie J Davies, David Cox, Jiaxun Chen, Wen-Shuo Wu, Max Denning, Rong Liu, Lisa Ludwig, Eric R Meskimen

15:30 - 15:45 CEST

PRESENTATION ID LBA 25

Effects of orforglipron versus insulin glargine on kidney outcomes in people with type 2 diabetes and high cardiovascular risk: results of the ACHIEVE-4 trial



Katherine Tuttle (Spokane, USA)

Effectiveness and safety of semaglutide in type 1 diabetes

A Danish nationwide study

Puriya Daniel Würtz Yazdanfard

MD, PhD fellow
Steno Diabetes Center Copenhagen, Denmark



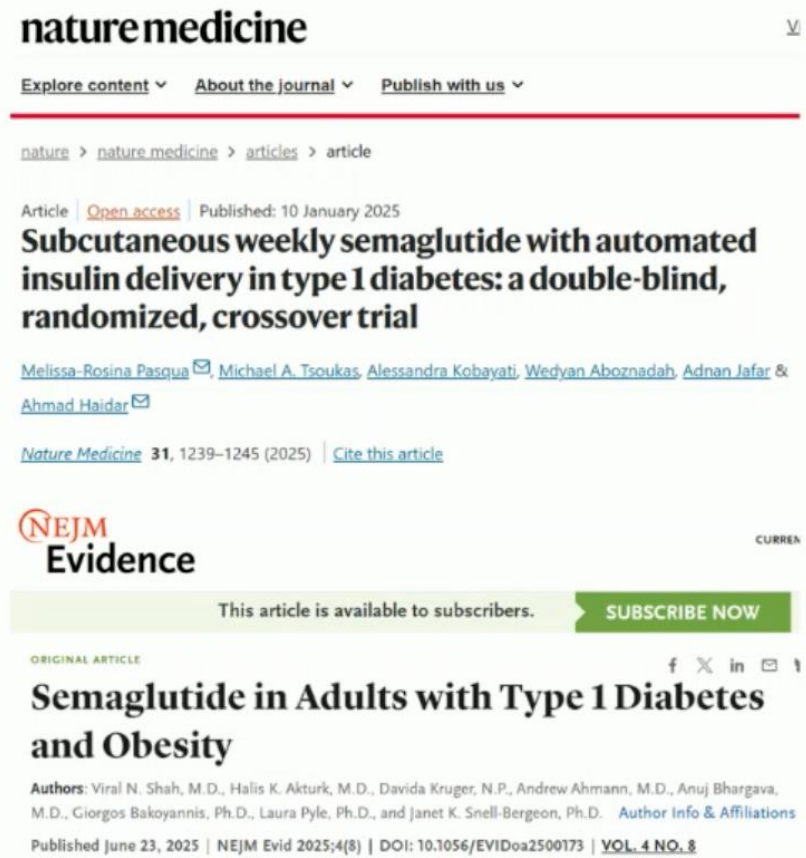
Puriya Yazdanfard

Effectiveness and safety of semaglutide in type 1 diabetes: a Danish nationwide study

Semaglutide in routine T1D care

Short-term trials suggest glycaemic benefit

Observational data suggest increasing uptake in routine T1D care.



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Subcutaneous weekly semaglutide with automated insulin delivery in type 1 diabetes: a double-blind, randomized, crossover trial

Melissa-Rosina Pasqua, Michael A. Tsoukas, Alessandra Kobayati, Wedyan Aboznadah, Adnan Jafar & Ahmad Haidar

Nature Medicine **31**, 1239–1245 (2025) | Cite this article

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ORIGINAL ARTICLE

Semaglutide in Adults with Type 1 Diabetes and Obesity

Authors: Viral N. Shah, M.D., Halis K. Akturk, M.D., Davida Kruger, N.P., Andrew Ahmann, M.D., Anuj Bhargava, M.D., Giorgos Bakoyannis, Ph.D., Laura Pyle, Ph.D., and Janet K. Snell-Bergeon, Ph.D. Author Info & Affiliations

Published June 23, 2025 | NEJM Evid 2025;4(8) | DOI: 10.1056/EVIDoa2500173 | VOL. 4 NO. 8

Use for glycaemic management in T1D is off-label.

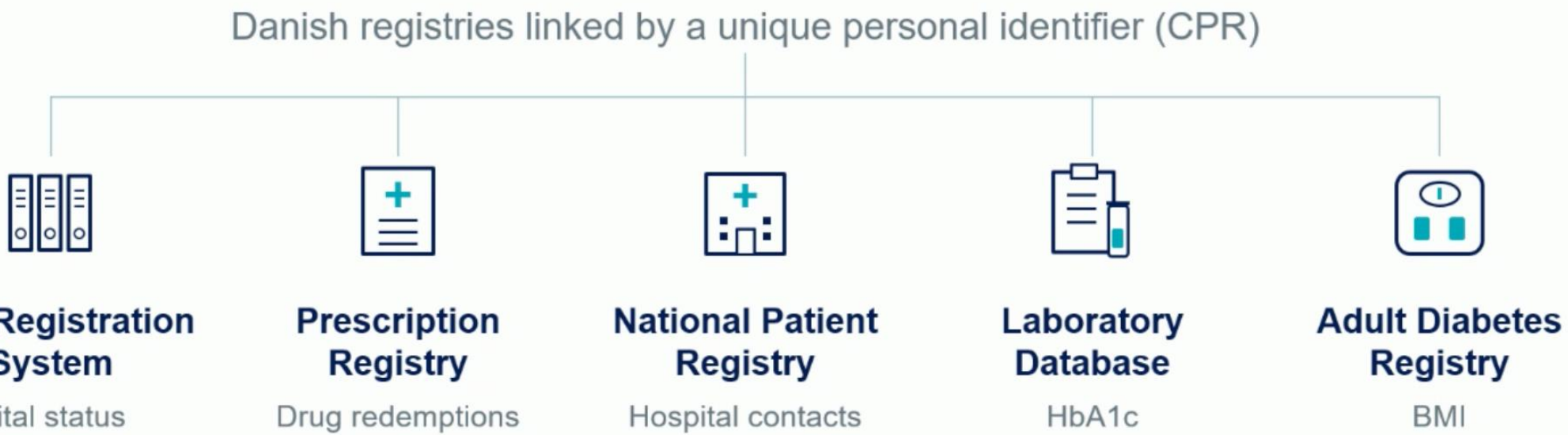
Pasqua et al. Nat Med 2025; Shah et al. NEJM Evid 2025; Yazdanfard et al. Lancet Reg Health Eur 2026

A nationwide setting for routine T1D care

Our routine care question

What happens after semaglutide initiation in T1D?

HbA1c · Treatment persistence · Hospital admissions
for hypoglycaemia or diabetic ketoacidosis



Yazdanfard et al. Lancet Reg Health Eur. 2026;66:101716 · Methods: data sources

Nationwide matched cohort

879 semaglutide initiators

3,516 matched controls with T1D

Initiation: January 2018 to June 2023
Follow-up: up to 2 years, ending January 2024

Analysis	Follow-up
HbA1c trajectory	Measurements during continued use
Hospital admissions	Regardless of discontinuation

The study population

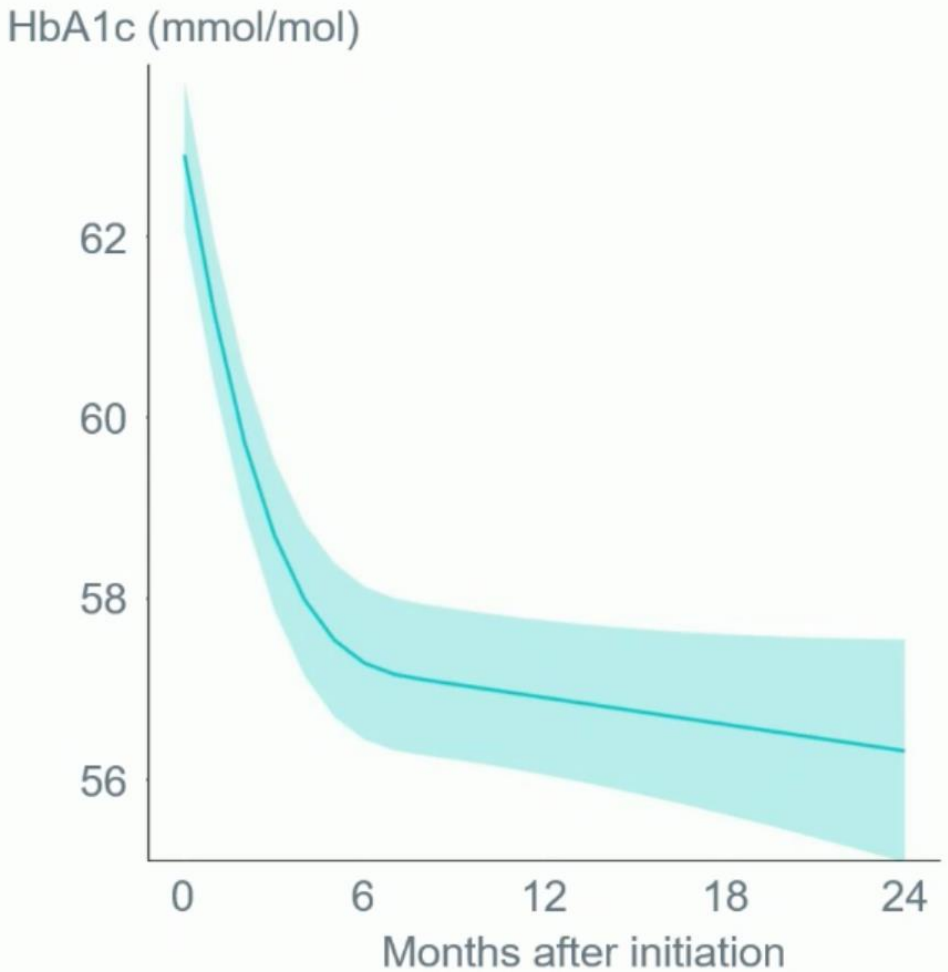
Baseline characteristic	Semaglutide n = 879	Controls n = 3,516
Age, median	48 years	48 years
Women	56%	56%
HbA1c, mean	63.0 mmol/mol	61.3 mmol/mol
Insulin pump use	29%	25%
BMI, mean*	32.1 kg/m²	30.5 kg/m²

71% of initiators used multiple daily injections.

*BMI was missing for 59% of initiators. The displayed mean uses available values.

Yazdanfard et al. Lancet Reg Health Eur. 2026;66:101716

HbA1c fell during the first six months



Yazdanfard et al. Lancet Reg Health Eur. 2026;66:101716

During continued use

−5.7 95% CI −6.3 to −5.0
−0.52 percentage points

mmol/mol at 6 months
No change thereafter up to 24 months

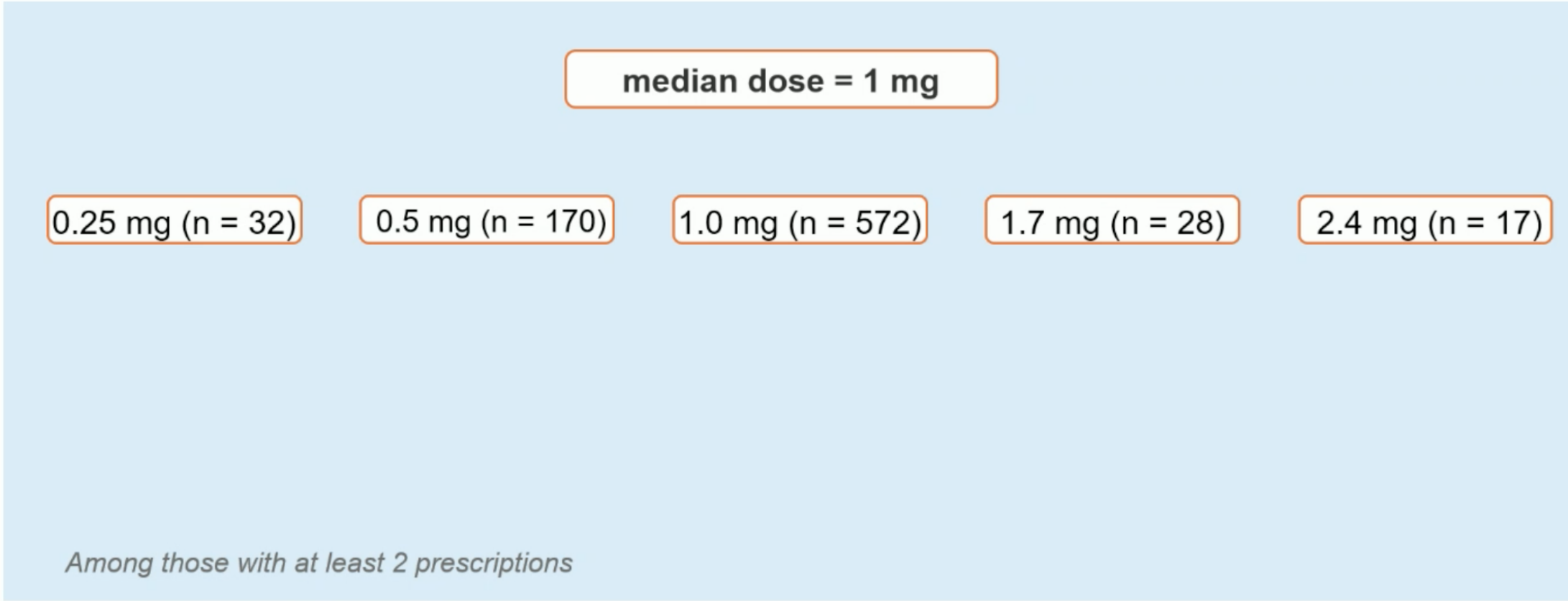
Stratified by baseline HbA1c

- ≥ 53: the decline was **6.8** mmol/mol *(95% CI: 6.1–7.6)*
- ≥ 63: the decline was **8.5** mmol/mol *(95% CI: 7.5–9.6)*

HbA1c change regardless of discontinuation
-4.4 mmol/mol (-4.9 to -3.8)

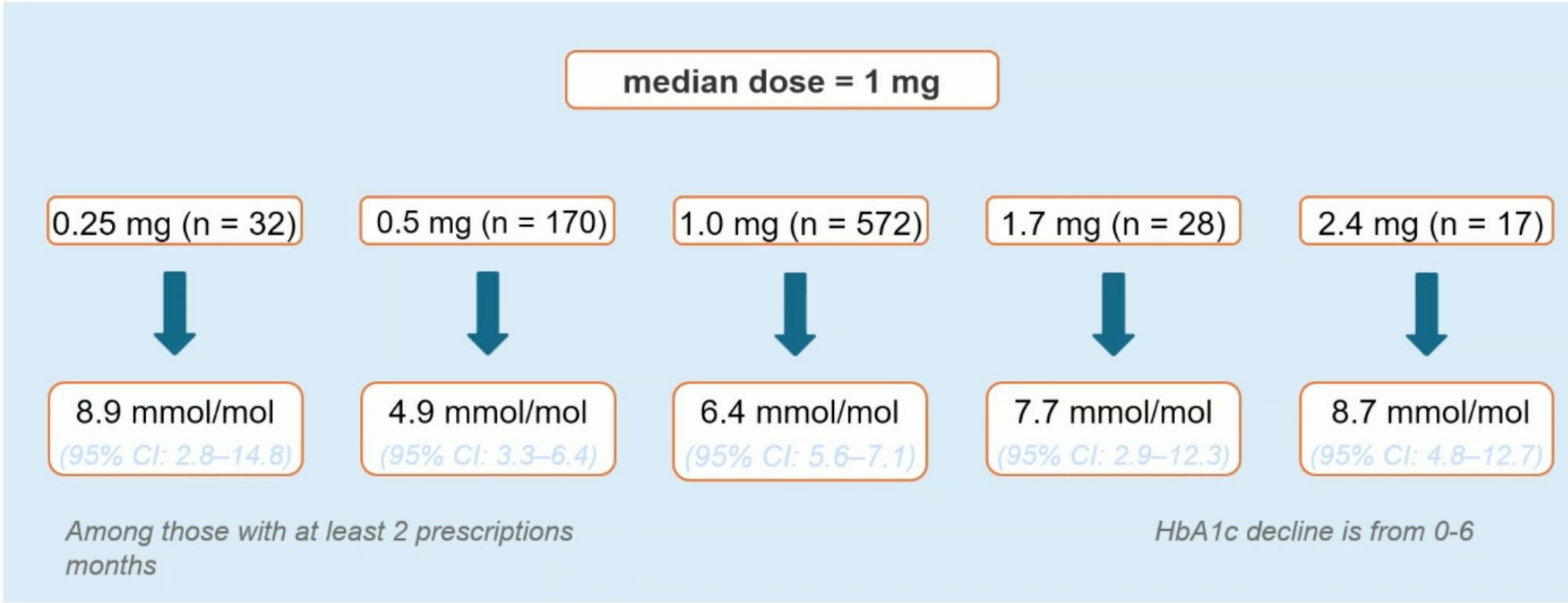
Method: Mixed-models in two segments from 0-6 months and 6-24 months.

Maximum dose prescription redeemed



Among those with at least 2 prescriptions

Maximum dose prescription redeemed



Half remained on treatment at one year



Prescription-based persistence

Expected supply based on prescriptions plus a 60-day grace period

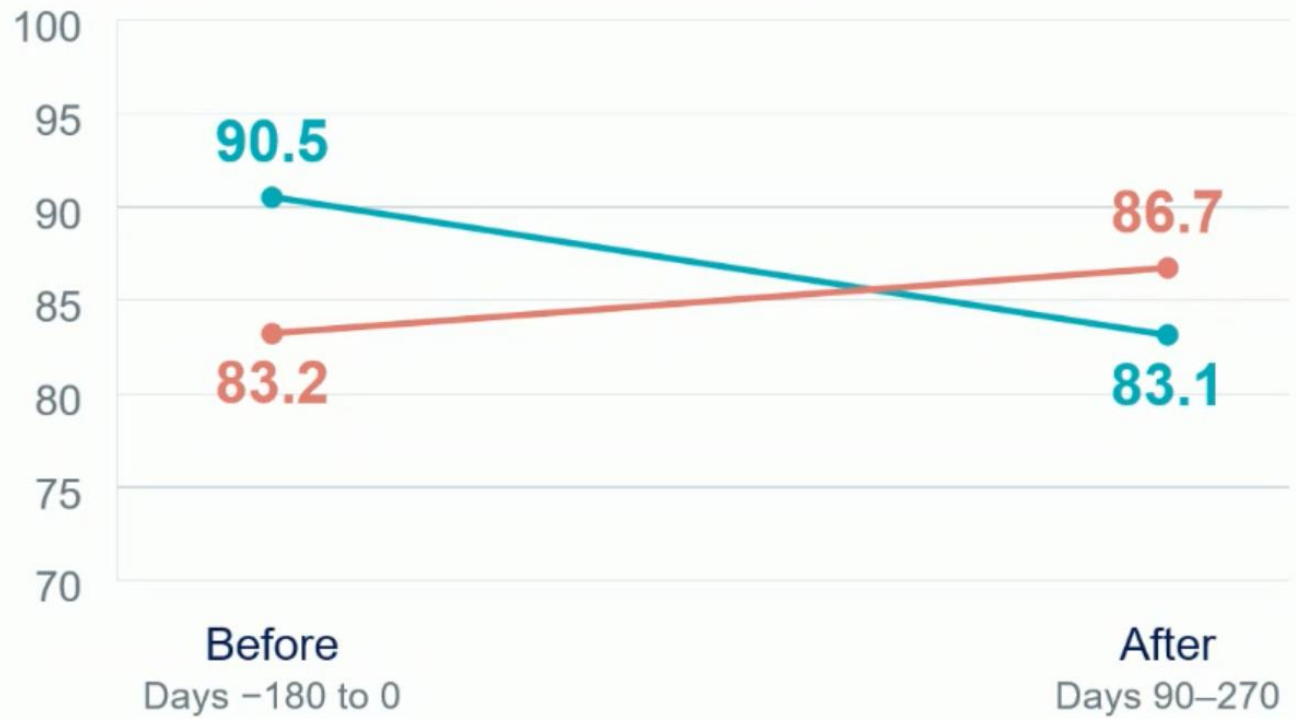
Method: Aalen-Johansen estimator. Death as a competing risk

95% CI: 6 months 69–74%, 12 months 47–54%, 24 months 22–29%.

Yazdanfard et al. Lancet Reg Health Eur. 2026;66:101716

Changes in insulin prescription redemptions

Mean insulin redeemed per 180-day period (mL)



Mean change

Semaglutide initiators

−7.4 mL

95% CI −11.2 to −3.6

Controls

+3.5 mL

95% CI 1.2 to 5.8

All insulin types combined; redeemed volume does not measure the daily dose taken.

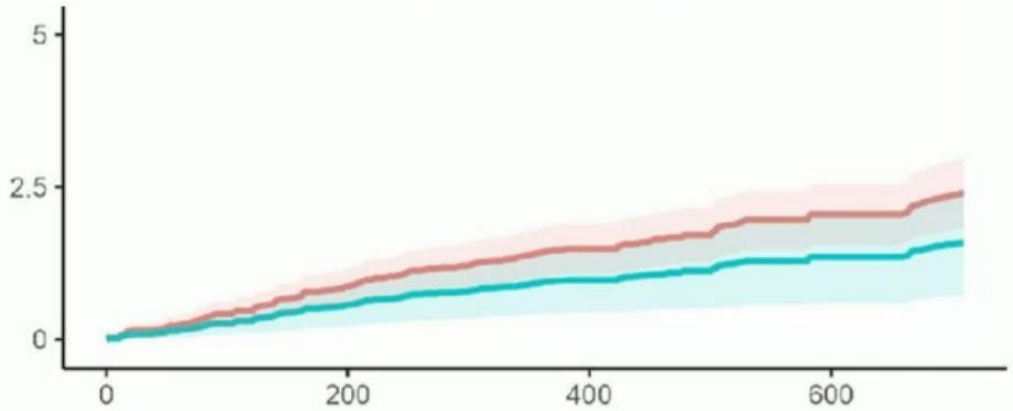
Yazdanfard et al. Lancet Reg Health Eur. 2026;66:101716

Hospital admission risk over two years

Adjusted cumulative risk (%) · Follow-up regardless of discontinuation

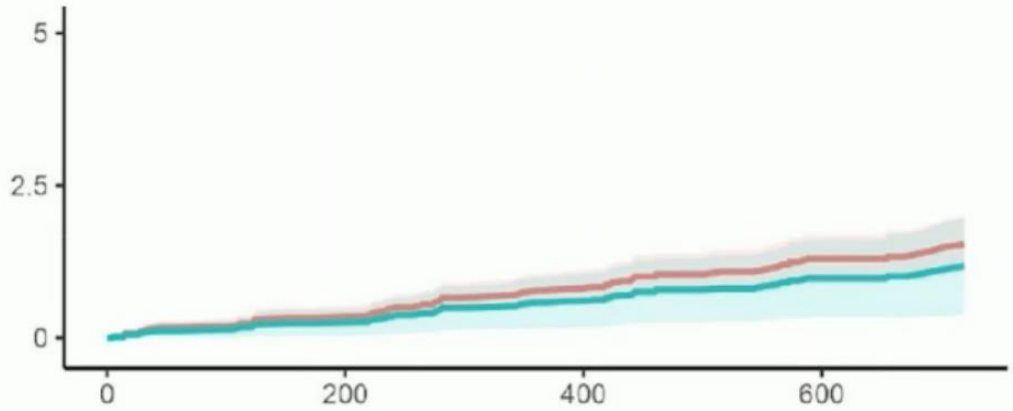
Hypoglycaemia

HR 0.64 (95% CI 0.35–1.19)



Diabetic ketoacidosis

HR 0.73 (95% CI 0.34–1.57)



Controls Semaglutide

Method: Adjusted cumulative incidence curves derived using parametric G-computation with all cause mortality as a competing risk. Adjusted Cox-propotional hazard models used for hazard ratios.

Yazdanfard et al. Lancet Reg Health Eur. 2026;66:101716, Fig. 4 (enlarged; 0–5% scale)

Conclusions

Clinically meaningful HbA1c improvement

−5.7 mmol/mol at six months during continued use. Likely partially weight loss related.

Limited long-term persistence

50% at one year and 25% at two years

No detected increase in admissions for severe hypoglycemia or diabetic ketoacidosis.

Yazdanfard et al. Lancet Reg Health Eur. 2026;66:101716 · doi:10.1016/j.lanepe.2026.101716

Thank you

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Full paper: doi:10.1016/j.lanepe.2026.101716

Joint ADA/EASD Consensus Report:
Management of Type 2 Diabetes

CO-CHAIR: JOHN B. BUSE, MD, PHD
CO-CHAIR: MELANIE J. DAVIES, MB CHB, MD

EASD

Figure 4: Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes

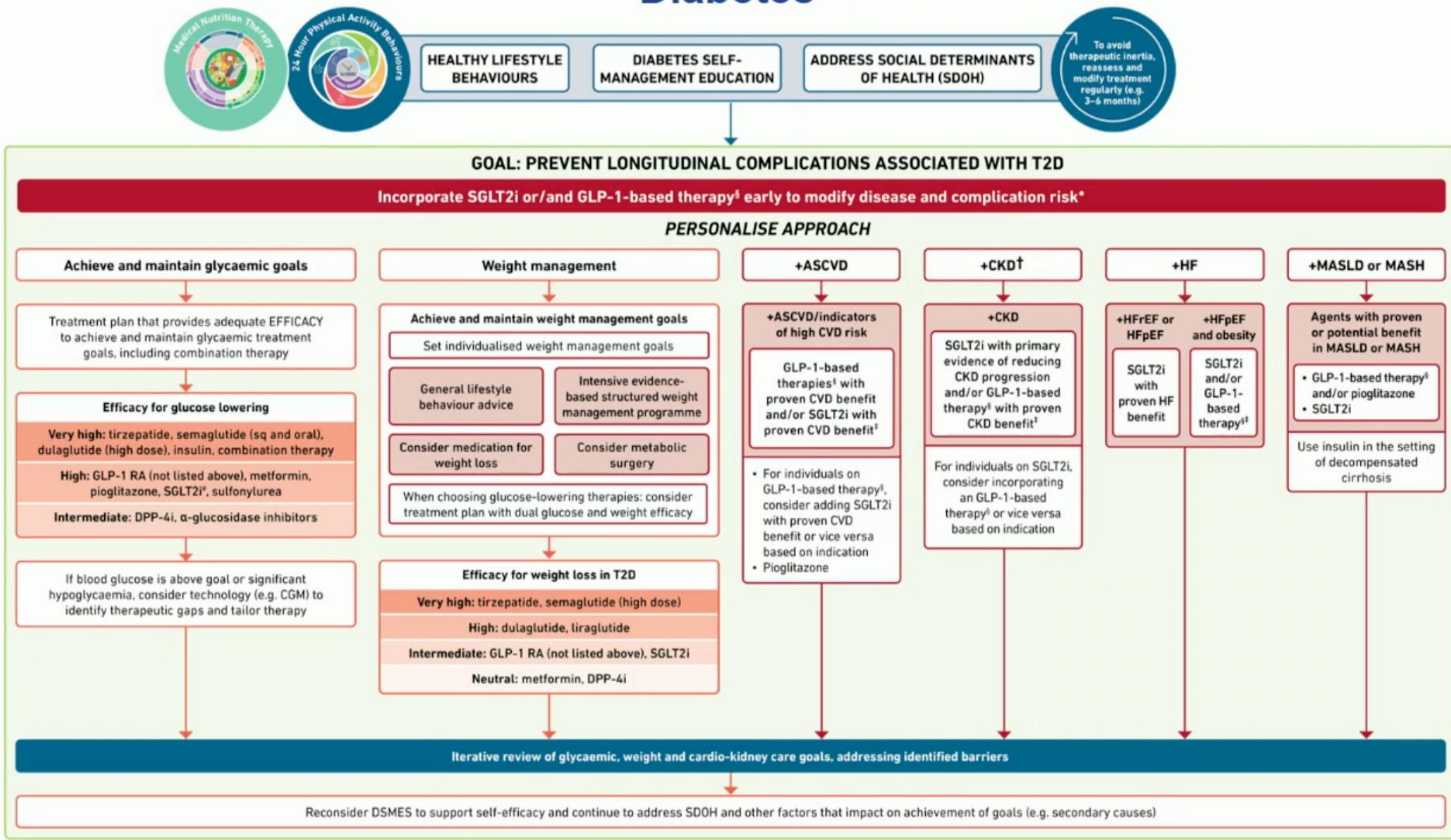
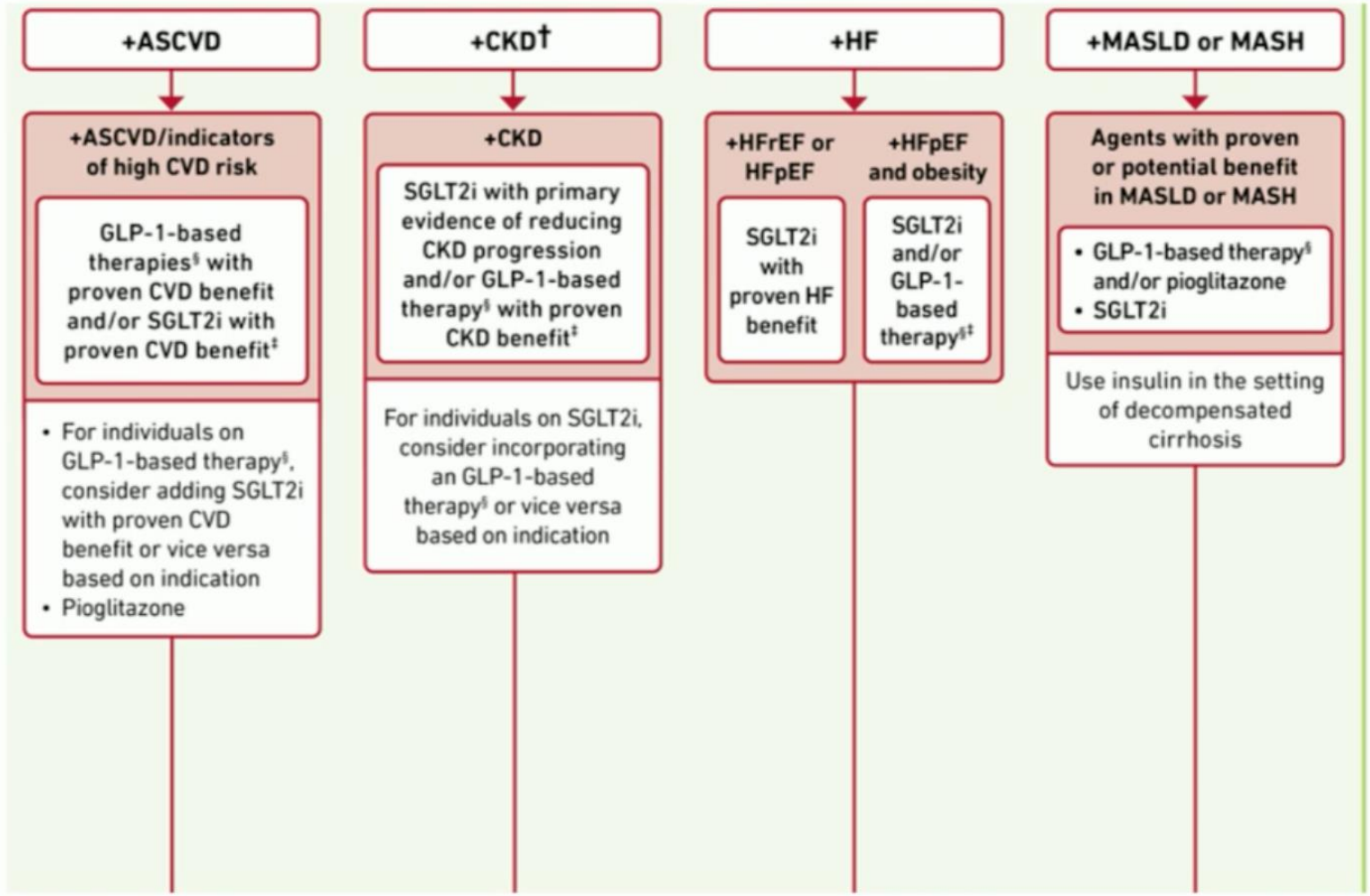
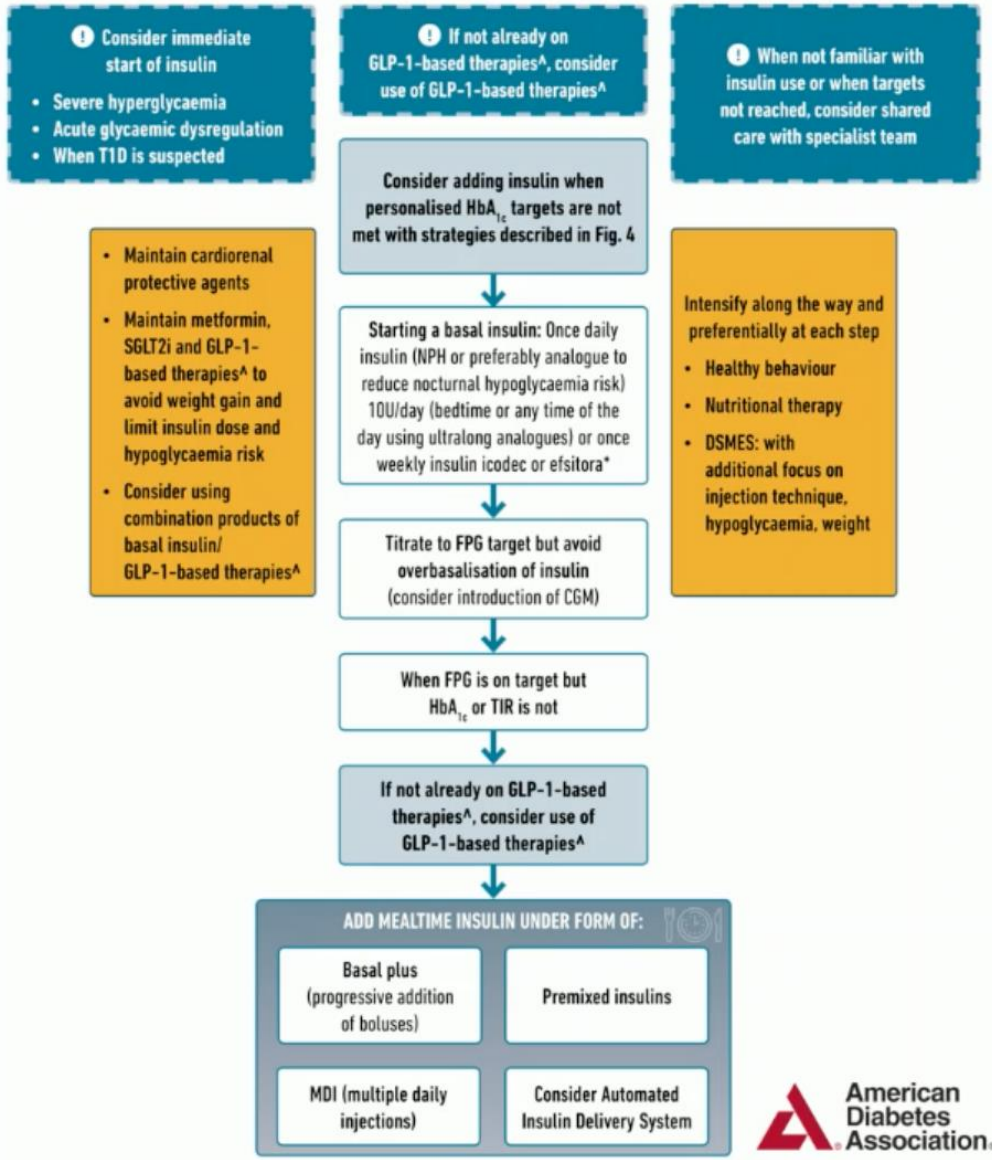


Figure 4: Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes



Place of Insulin



American Diabetes Association.

EASD European Association for the Study of Diabetes

Key Knowledge Gaps (1/4)

- Consensus is emerging that **early intensive therapy** in type 2 diabetes is associated with sustained benefits but trial evidence for glycaemic targets of <53 mmol/mol (<7%) is poorly developed and for CGM targets it is essentially non-existent. We need trials to provide convincing evidence for new targets.
- The aim of achieving **'remission'** should perhaps be rethought as not just achieving euglycaemia absent of glucose-lowering medications for 3 months but perhaps as a means to reduce the risk of developing associated complications/conditions. In that context, should the definition of remission be broadened to include modifications of associated long-term conditions, whether or not treatment with medications continues?
- We need to develop optimal strategies to maintain remission over time.
- We have burgeoning pharmacological and technologic applications in type 2 diabetes management. How can we optimally sequence them and **when is enough in fact enough**?

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Key Knowledge Gaps (2/4)

- Most studies of GLP-1-based therapies recruit people with overweight or obesity. How should GLP-1-based therapies be used in people where **weight loss is not desired**? Currently, in people with type 2 diabetes where GLP-1-based therapy is desired for glycaemic or cardiovascular benefit but weight loss is not desired, dulaglutide may be preferred.

- We need better trial evidence for early intensive therapy in **early-onset type 2 diabetes**, particularly in youth with type 2 diabetes in whom the lifetime risk of complications is highest. Similarly, there is inadequate understanding of how and when to de-intensify therapy **later in life**.

- **Women's health** approaches in the context of diabetes management have been understudied. A new issue is how GLP-1-based treatments should be managed in the context of **pregnancy**. GLP-1-based therapies are not recommended for use during pregnancy and could adversely affect a fetus. However, discontinuing GLP-1-based therapies may result in excessive weight gain and loss of glycaemic management during pregnancy with potential harms for both mother and baby. Further study is desperately needed.

Key Knowledge Gaps (3/4)

- **How should adiposity be measured** to best reflect the metabolic impact of adiposopathy and what should be targets for medical and surgical weight-loss programmes?
- What are **optimal lifestyle programmes** to support GLP-1-based therapy, including MNT and the five Ss to reach weight targets and preserve fat-free mass (particularly skeletal muscle mass and bone) and function? Furthermore, what are the best ways of tackling accelerated ageing, considering outcomes related to whole-body health and physical function?
- With the emergence of increasingly effective weight-loss drugs, we need to understand **whether high doses of moderately effective agents are equivalent to modest doses of highly effective agents** for outcomes, and also the optimum approaches for **maintenance of weight loss**.

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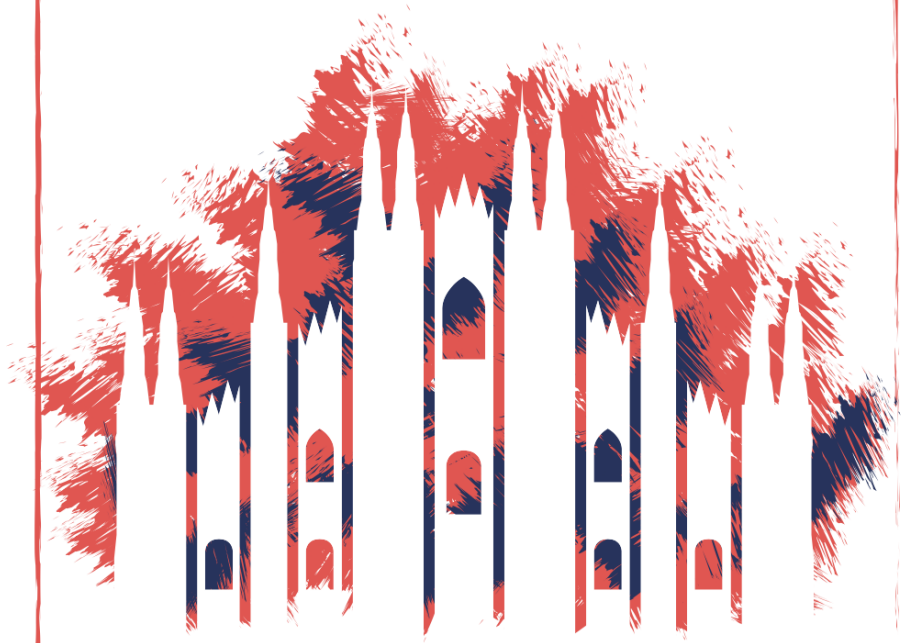
Key Knowledge Gaps (4/4)

- What should be the **evaluation strategy for people with inadequate responses to generally effective therapies**; recent studies suggest screening for hypercortisolism identifies a treatable cause in ~25%. There must be others.
- Developing a better understanding of the role of **cortisol-directed therapy** in type 2 diabetes is needed.
- We still do not have compelling evidence for whether **GLP-1-based therapy and SGLT2 inhibitors should be routinely combined**, or whether there is an optimal sequence by which they should be added.

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62nd Annual Meeting

European Association for the Study of Diabetes



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