Obesity/Overweight, Diabetes, and Heart Failure triad: novel treatments

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Faculty/Presenter Disclosure

- **Faculty: Kim Connelly**
- **Relationships with financial sponsors:**
  - **Any direct financial relationships including receipt of honoraria:** Merck, Astra Zeneca, Boehringer Ingelheim, Janssen, Servier, Eli Lilly and Novo Nordisk
  - **Memberships on advisory boards or speakers' bureau:** Merck, Astra Zeneca, Boehringer Ingelheim, Janssen, Servier, Eli Lilly and Novo Nordisk
  - **Patents for drugs or devices**: Boehringer Ingelheim - linaglitpin
  - **Other: financial relationships/investments**

Learning objectives

At the completion of this section, participants should be able to:

1. Present literature surrounding evidence-based therapy in the treatment of HF, Obesity and T2DM with RF and ASCVD

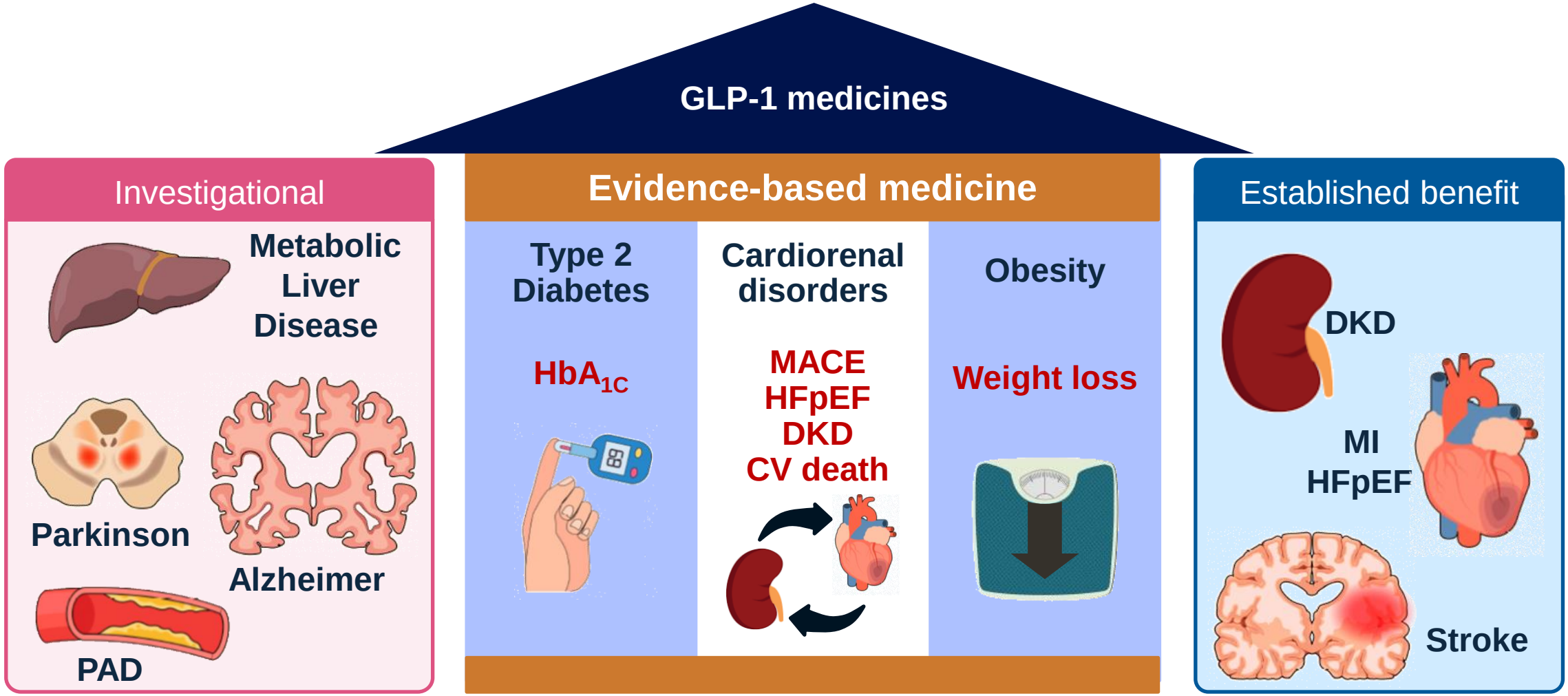
Let's start with a case!

Mrs. A.C.

- 66-year-old female with chronic stable hypertension and prior PCI of the mid-LAD for NSTEMI 2 years ago. She is referred because of atypical exertional symptoms of dyspnoea on exertion.
- Medications: ASA 81mg, ramipril 10 mg, rosuvastatin 20 mg, ezetimibe 10 mg, PCSK9i injected every 2 weeks.
- Physical examination: BMI 35, BP 136/84, JVP is difficult to assess but appears mildly elevated, normal S1 and S2, there is no edema.

	Age 66
EKG	NSR 65/min, QS V1, V2
A1C	6.6
TC	3.4
HDL-C	1
LDL-C	1.25
TG	1.24
apoB	0.55
eGFR/ UACR	63 1.9

Evolution of GLP-1 medicines …



Drucker DJ. Diabetes Care 2024 Jun 6:dci240003. doi: 10.2337/dci24-0003 (online ahead of print)

Canadian Journal of Cardiology 38 (2022) 1153–1167

Society Guidelines

2022 Canadian Cardiovascular Society Guideline for Use of GLP-1 Receptor Agonists and SGLT2 Inhibitors for Cardiorenal Risk Reduction in Adults

Primary Panel: G.B. John Mancini, MD (Co-chair),[a] Eileen O'Meara, MD (Co-chair),[b] Shelley Zieroth, MD,[c] Mathieu Bernier, MD,[d] Alice Y.Y. Cheng, MD,[e] David Z.I. Cherney, MD, PhD,[f] Kim A. Connelly, MD,[g] Justin Ezekowitz, MBBCh, MSc,[h] Ronald M. Goldenberg, MD,[i] Lawrence A. Leiter, MD,[j] Gihad Nesrallah, MD, MSc,[j,k] Breay W. Paty, MD,[l] Marie-Eve Piché, MD, PhD,[d] Peter Senior, MBBS, PhD,[m] Abhinav Sharma, MD,[n] Subodh Verma, MD, PhD,[o] Vincent Woo, MD,[c] **Secondary Panel:** Pol Darras, MD,[l] Jean Grégoire, MD,[b] Eva Lonn, MD,[p] James A. Stone, MD, PhD,[q] Jean-François Yale, MD,[r] Colin Yeung, MD, MPH,[s] and Deborah Zimmerman, MD, MSc[t]

Summary of relative (hazard ratios) in study populations with heart failure, chronic kidney disease, or type 2 diabetes

Table 1 Summary of hazard ratios (HR) for cardiorenal outcomes in study populations with heart failure, chronic kidney disease, or type 2 diabetes

Participant Groups		T2D	Class	MACE	All-cause mortality	CV death	Non-fatal MI	Non-fatal Stroke	HHF	CV Death or HHF	Kidney composite[¥]
HF	EF ≤ 40%*	+/-	SGLT2i	NA	0.84 (0.72, 0.97)	0.84 (0.71, 0.98)	NA	NA	0.69 (0.64, 0.75)	0.75 (0.69, 0.81)	0.59 (0.42, 0.83)
	EF > 40%	+/-	SGLT2i	NA	0.97 (0.89, 1.06)	0.96 (0.82, 1.14)	NA	NA	0.74 (0.67, 0.82)	0.79 (0.73, 0.86)	1.00 (0.82, 1.23)
CKD	Any EF	+/-	SGLT2i	0.85 (0.78, 0.92)	0.82 (0.75, 0.90)	0.85 (0.78, 0.93)	0.77 (0.62, 0.95)	0.78 (0.49, 1.25)	0.65 (0.59, 0.72)	0.75 (0.70, 0.79)	0.68 (0.60, 0.76)
		+/-	GLP1-RA	0.87	0.86	0.86	0.86	0.84	0.91	NA	0.85
T2D with ASCVD or multiple risk factors	Any EF or eGFR	+	SGLT2i	0.88 (0.82, 0.93)	0.87 (0.81, 0.94)	0.86 (0.80, 0.93)	0.90 (0.83, 0.98)	0.99 (0.88, 1.11)	0.70 (0.65, 0.75)	0.77 (0.73, 0.80)	0.67 (0.59, 0.75)
		+	GLP1-RA	0.86 (0.80, 0.93)	0.88 (0.82, 0.94)	0.87 (0.80, 0.94)	0.94 (0.88, 1.02)	0.84 (0.76, 0.94)	0.91 (0.83, 1.002)	0.89 (0.81, 0.98)	0.78 (0.70, 0.87)

ASCVD: atherosclerotic cardiovascular disease; CKD: chronic kidney disease; CV: cardiovascular; eGFR: estimated glomerular filtration rate; GLP-1RA: glucagon-like peptide-1 receptor agonists; HHF: hospitalization for heart failure; EF: ejection fraction; MACE: major adverse cardiac events; MI: myocardial infarction; NA: not applicable; SGLT2i, sodium-glucose co-transporter 2 inhibitors; T2D, type 2 diabetes; +/-, with/without. Light green indicates a significant HR and dark green indicates a significant HR that is statistically different than in the comparator group, namely participants with EF ≤ 40% versus > 40% in SGLT2i trials of participants with HF and SGLT2i versus GLP1-RA in participants with T2D with ASCVD or multiple risk factors

*DECLARE and VERTIS CV reported results using LVEF < 45% and LVEF ≥ 45.

¥ Renal death, progression to ESKD or reduced eGFR.

Process	Practice Statement	Strength of Recommendation	Quality of Evidence
Screening[1]	CV specialists are encouraged to assess kidney and glycemic status through measurement of eGFR, UACR, and A1c and to document LVEF when evaluating symptoms of HF.	–	–
	Recommendations		
Treatment of HF	In adults with HF and LVEF ≤ 40%, we recommend use of SGLT2i to reduce all-cause and CV mortality, hospitalization for HF, and the composite end point of significant decline in eGFR, progression to end-stage kidney disease or death due to kidney disease.	Strong	Moderate
	In adults with HF and LVEF > 40%, we recommend use of SGLT2i to reduce hospitalization for HF.	Strong	Moderate
Treatment of CKD	In adults with CKD (UACR > 20 mg/mmol, eGFR ≥ 25 mL/min/1.73m^2), we recommend use of SGLT2i to reduce the composite of significant decline in eGFR, progression to end-stage kidney disease or death due to kidney disease, all-cause and CV mortality, nonfatal MI, and hospitalization for HF.	Strong	Moderate
Prevention of cardiorenal events in adults with either T2D and ASCVD or multiple risk factors for ASCVD	In adults with T2D and either ASCVD or multiple risk factors for ASCVD, we recommend use of:		
	A. GLP-1RA or SGLT2i to reduce the risk of all-cause, or CV mortality or MACE;	Strong	Moderate
	B. SGLT2i to reduce the risk of hospitalization for HF or the composite of significant decline in eGFR, progression to end-stage kidney disease or death due to kidney disease;	Strong	Moderate
	C. GLP-1RA to reduce the risk of nonfatal stroke.	Strong	Moderate

What about new CKD data in persons with Type 2 DM?

The NEW ENGLAND JOURNAL of MEDICINE

Semaglutide, CKD, and Type 2 Diabetes

A PLAIN LANGUAGE SUMMARY

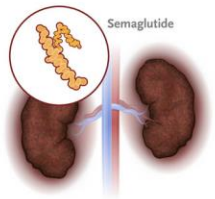
Based on the NEJM publication: Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes by V. Perkovic et al. (published May 24, 2024)

In this trial, researchers assessed whether the glucagon-like peptide 1 (GLP-1) receptor agonist semaglutide was effective in preventing progression of kidney disease in patients with type 2 diabetes and chronic kidney disease (CKD).

Type 2 diabetes is a frequent cause of chronic kidney disease, which can lead to kidney failure, cardiovascular events, and death.

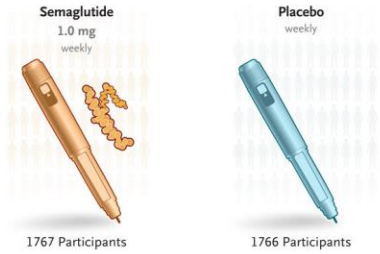
WHY WAS THE TRIAL DONE?

Semaglutide has been shown to improve glycemic control, lead to weight loss, and reduce cardiovascular events in patients with type 2 diabetes. Its effect on kidney outcomes in patients who also have chronic kidney disease is incompletely understood.



HOW WAS THE TRIAL CONDUCTED?

3533 participants with type 2 diabetes and chronic kidney disease were randomly assigned to receive weekly subcutaneous semaglutide (1.0 mg) or placebo. The primary outcome was major kidney disease events, a composite of the onset of kidney failure (initiation of dialysis, kidney transplantation, or an estimated glomerular filtration rate [eGFR] of <15 ml per minute per 1.73 m^2), at least a 50% reduction in eGFR from baseline, or death from kidney-related or cardiovascular causes.



PARTICIPANTS

WHO
- 3533 adults
- Mean age, 67 years
- Men: 70%; Women: 30%

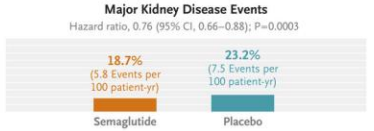
CLINICAL STATUS
- High-risk chronic kidney disease
- Type 2 diabetes

TRIAL DESIGN

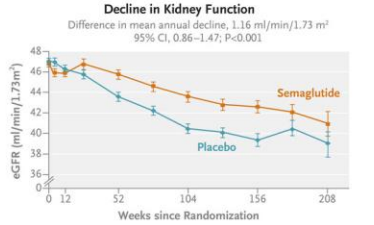
- DOUBLE-BLIND
- RANDOMIZED
- PLACEBO-CONTROLLED
- LOCATION: 387 SITES IN 28 COUNTRIES

RESULTS

The trial was stopped early at a median follow-up of 3.4 years after an interim analysis showed efficacy. The semaglutide group had fewer primary-outcome events than the placebo group, equivalent to a 24% lower risk with semaglutide.



Kidney function declined more slowly in the semaglutide group than in the placebo group.



Serious adverse events were less common in the semaglutide group than in the placebo group.

KIDNEY OUTCOMES

Twenty people would need to be treated with semaglutide over a 3-year period to prevent one major kidney disease event.

LIMITATIONS AND REMAINING QUESTIONS

- Sodium–glucose cotransporter 2 inhibitors and nonsteroidal mineralocorticoid-receptor antagonists were not yet approved for kidney protection when the trial began. Since few participants were receiving those drugs at baseline, the ability of the trial to assess the effects of combination therapy was limited.
- Kidney disease disproportionately affects Black and Indigenous people, who were underrepresented in this trial.
- The effects on kidney function may not be generalizable to other populations, such as persons at lower risk.

CONCLUSIONS

In adults with type 2 diabetes and chronic kidney disease, semaglutide reduced the risk of clinically important kidney outcomes and death from cardiovascular causes.

LINKS: FULL ARTICLE | NEJM QUICK TAKE | EDITORIAL

FURTHER INFORMATION

Trial registration: ClinicalTrials.gov number, NCT03819153

Trial funding: Novo Nordisk

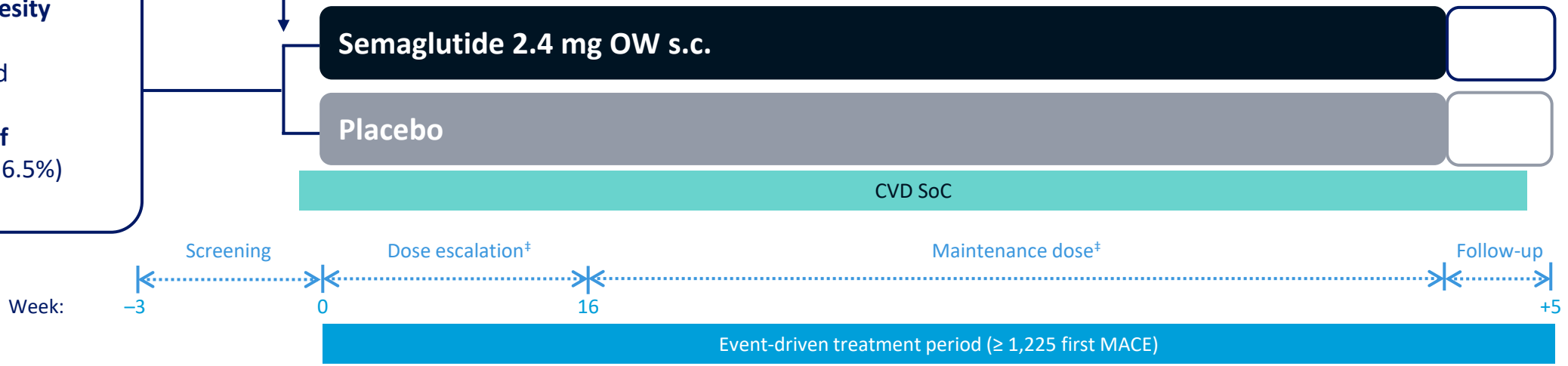
Full citation: Perkovic V, Tuttle KR, Rossing P, et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. N Engl J Med 2024;391:109-21. DOI: 10.1056/NEJMoa2403347

SELECT Trial design

Trial information[1–3]
- FPFV 24 October 2018
- Double-blind, placebo-controlled, superiority trial

- **Overweight** or **obesity** (BMI ≥ 27 kg/m^2)
- Age ≥ 45 years and **established CVD***
- **No prior history of diabetes** (HbA_{1c} < 6.5%)

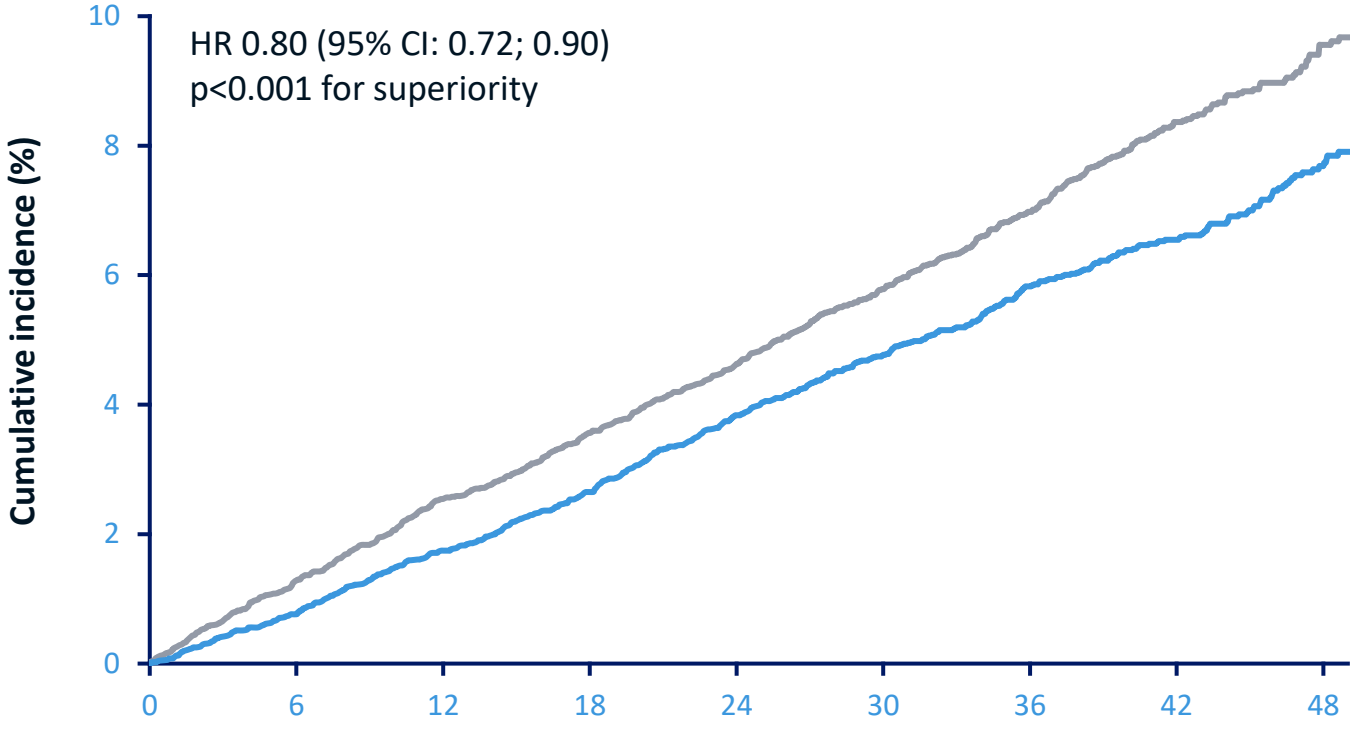
Randomisation (1:1)
N = 17,604†



Three-component MACE consisted of non-fatal MI, non-fatal stroke and CV death.
**Established CVD: MI ≥60 days prior to screening, stroke ≥60 days prior to screening or symptomatic PAD; NYHA class IV excluded. †Number of enrolled participants differs from number reported in baseline publication (17,605) as one participant was randomised twice in error and subsequently removed for the primary analysis. ‡Dose escalation is from week 4 to 16 with intervals of 4 weeks, and maintenance dose is event-driven to end of treatment period.*
BMI, body mass index; CV, cardiovascular; CVD, cardiovascular disease; FPFV, first patient first visit; HbA_{1c}, glycated haemoglobin; MACE, major adverse cardiovascular event; MI, myocardial infarction; NYHA, New York Heart Association; OW, once weekly; PAD, peripheral artery disease; s.c., subcutaneous; SoC, standard of care.
1. Ryan DH et al. Am Heart J 2020;229:61–9; 2. Lingvay I et al. Obesity (Silver Spring) 2023;31:111–22; 3. Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

Primary endpoint: Cumulative incidence of MACE

ARR = 1.5% over ~3.5 years, meaning for every **67 people treated**, **1 MACE event is prevented** (Number Needed to Treat, **NNT = 67**).



No. at risk									
Semaglutide	8,803	8,695	8,561	8,427	8,254	7,229	5,777	4,126	1,734
Placebo	8,801	8,652	8,487	8,326	8,164	7,101	5,660	4,015	1,672

Semaglutide 2.4 mg — Placebo

20%
reduction in risk of MACE*

Semaglutide 2.4 mg significantly reduced the risk of MACE by 20%

All three components (death from CV causes, non-fatal MI and non-fatal stroke) contributed to MACE risk reduction

Mean follow-up time was 39.8 months

Cumulative incidence (using the Aalen–Johansen method) of the composite MACE primary endpoint. The HR was estimated using a Cox proportional hazards regression model. The proportion of participants with MACE was 6.5% with semaglutide 2.4 mg and 8.0% with placebo. MACE was defined as death from CV causes, non-fatal myocardial infarction, or non-fatal stroke.
CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction.
1. Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563; 2. Novo Nordisk A/S. Company announcement, 8 August 2023. Available at: https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=166301. Accessed October 2023.

S/c Semaglutide: Wegovy

1 INDICATIONS

Wegovy® (semaglutide injection) is indicated as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in:

- Adult patients with an initial body mass index (BMI) of
  - 30 kg/m^2 or greater (obesity), or
  - 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus, dyslipidemia, or obstructive sleep apnea.
- Pediatric patients aged 12 to less than 18 years:
  - with an initial BMI at the 95th percentile or greater for age and sex (obesity; see Table 1), and
  - a body weight above 60 kg (132 lbs), and
  - an inadequate response to reduced calorie diet and physical activity alone.

Health Canada approves Wegovy® (semaglutide injection) to reduce the risk of non-fatal myocardial infarction

- *Wegovy® is the first-and-only medication indicated for both chronic weight management and to reduce the risk of non-fatal myocardial infarction (MI) in Canada.*[1]
- *Close to one in three Canadian adults are living with obesity, which is a risk factor for heart disease.*[2,3]

Tirzepatide! Or Mounjaro (type 2 DM) and Zepbound

- Tirzepatide is a **GIP receptor and GLP-1 receptor agonist**[1]
- Tirzepatide is a 39-amino-acid modified peptide based on the native GIP peptide sequence with a C20 fatty diacid moiety that enables albumin binding and prolongs the half-life (mean half-life is approximately 5 days)[1,2]
- Tirzepatide selectively binds to and activate both the GIP and GLP-1 receptors, the targets for native GIP and GLP-1[1,2]
- Tirzepatide **enhances first- and second-phase insulin secretion, and reduces glucagon levels,** both in a glucose-dependent manner[1,2]

GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1.

1. Mounjaro [US PI]. Indianapolis, IN, USA: Eli Lilly and Company, 2022. 2. Coskun T, et al. *Mol Metab.* 2018;18:3-14. 3. Urva S, et al. *Clin Pharmacokinet.* 2021;60(8):1049-1059. 4. Urva et al., *Clin Pharmacokinet.* 2022 Jul;61(7):1057-1067

Home

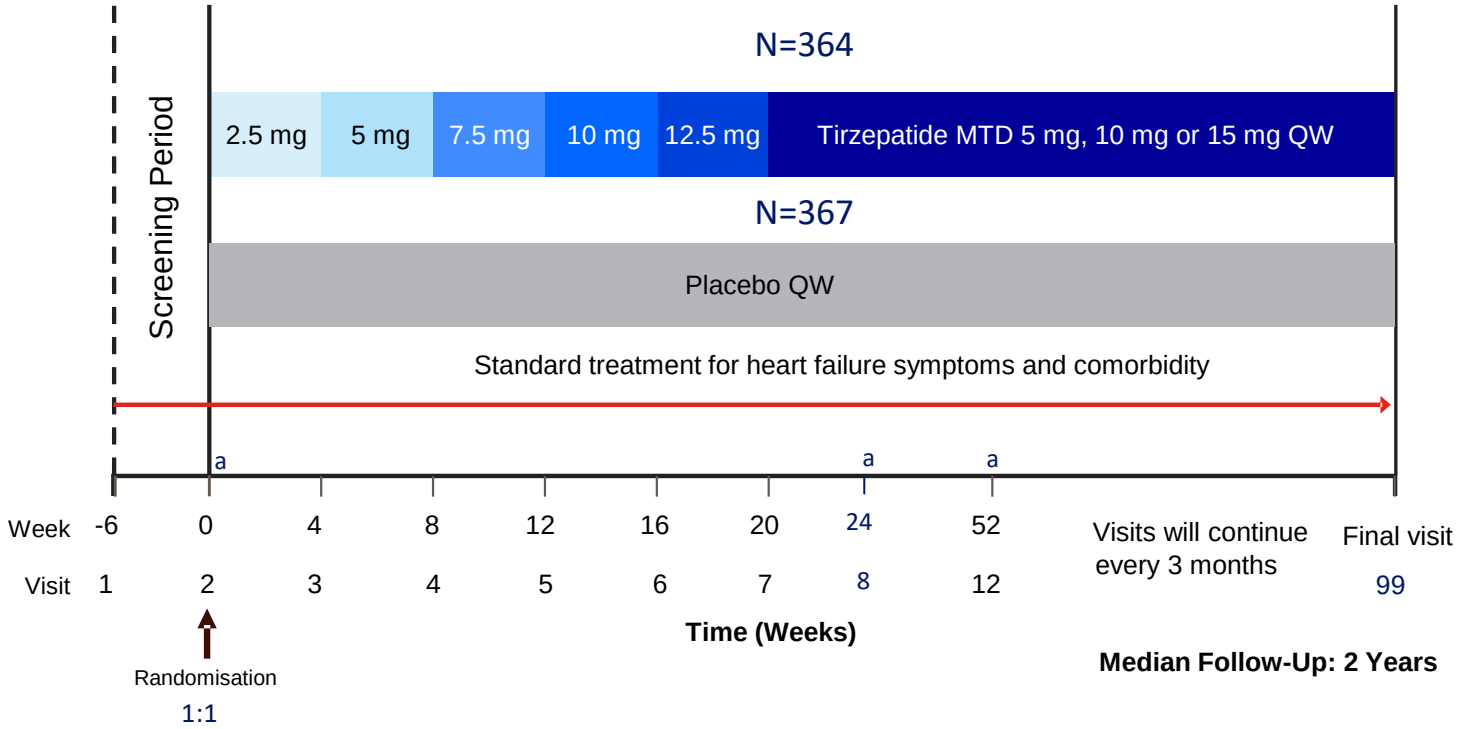
SUMMIT Trial Design

SUMMIT is a randomised, multicentre, international, placebo-controlled, double-blind, parallel-arm Phase 3 study. The study was designed to evaluate the efficacy and safety of once-weekly tirzepatide in participants with HFpEF and obesity.

Participants Enrolled: 731

Participating Countries

United States, Argentina, Brazil, China, India, Israel, Mexico, Russia and Taiwan[3]

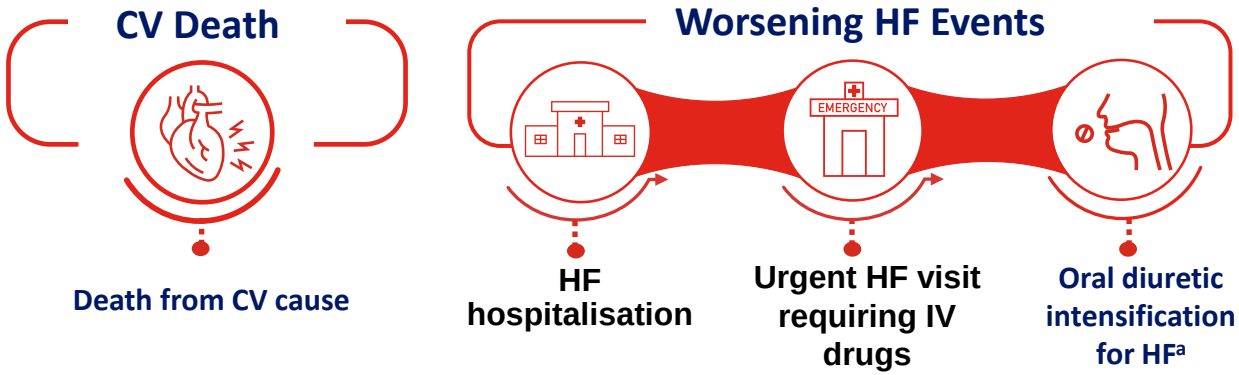


- [a]KCCQ, 6MWD and hsCRP were measured at baseline and 24 and 52 weeks.
- HFpEF=Heart Failure With Preserved Ejection Fraction; hsCRP=High-Sensitivity C-Reactive Protein; KCCQ=Kansas City Cardiomyopathy Questionnaire; MTD=Maximum Tolerated Dose; QW=Once Weekly; 6MWD=6-Minute Walk Distance.
- Packer M, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2410027 (Ahead of print).

SUMMIT Trial Endpoints

Dual Primary Endpoints

Time to the first occurrence of the composite endpoint of CV death or worsening HF events



Change in KCCQ-CSS from Baseline to Week 52

Key Secondary Endpoints

- Change from baseline to Week 52 in 6MWD
- Percent change from baseline to Week 52 in body weight
- Change from baseline to Week 52 in hsCRP

- [a]Diuretic intensification in the absence of worsening heart failure was not designated as an event.
- CV=Cardiovascular; HF=Heart Failure; hsCRP=High-Sensitivity C-Reactive Protein; IV=Intravenous; KCCQ-CSS=Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; 6MWD=6-Minute Walk Distance.
- Packer M, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2410027 (Ahead of print).

SUMMIT: Key Inclusion and Exclusion Criteria

Key Inclusion Criteria

- Age ≥40 years and BMI ≥30 kg/m^2
- Chronic HF NYHA class II-IV, LVEF ≥50%, on stable guideline-directed medical therapy
- At least one of the following as documented evidence of heart failure
  - Structural heart disease (LA enlargement)
  - Elevated NT-proBNP (defined as >200 pg/mL for participants without AF or >600 pg/mL for participants with AF)
  - Elevated LV filling pressure
- eGFR <70 mL/min/1.73 m^2 at screening, or HF decompensation within 12 months of screening
- 6MWD ≥100 m to ≤425 m
- KCCQ CSS ≤80

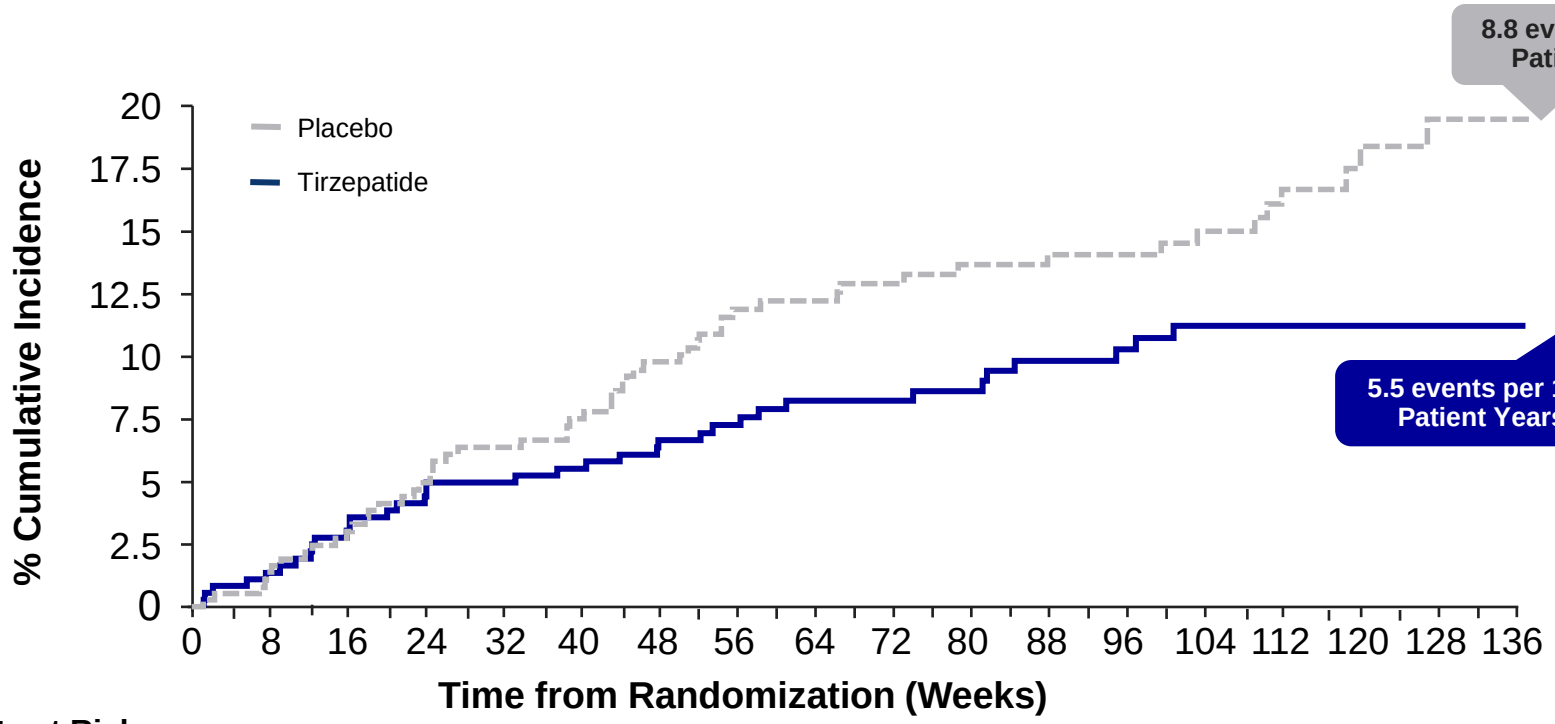
Key Exclusion Criteria

- Acute decompensated HF within 4 weeks
- MI, stroke, or major CV surgery/intervention within 90 days
- Hypertrophic cardiomyopathy, cardiac amyloidosis, and valvular diseases requiring surgery
- Atrial fibrillation or atrial flutter with a resting heart rate >110 bpm
- LVEF <40% within 2 years
- eGFR <15 mL/min/1.73 m^2 or requiring dialysis
- Severe lung diseases (COPD, PAH, and CTEPH)
- T1D or uncontrolled T2D HbA1c >9.5%

- AF=Atrial Fibrillation; BMI=Body Mass Index; COPD=Chronic Obstructive Pulmonary Disease; CTEPH=Chronic Thromboembolic Pulmonary hypertension; CV=Cardiovascular; eGFR=Estimated Glomerular Filtration Rate; HbA1c=Glycated Hemoglobin; HF=Heart Failure; HFpEF=Heart Failure With Preserved Ejection Fraction; KCCQ-CSS=Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LA=Left Atrial; LV=Left Ventricular; LVEF=Left Ventricular Ejection Fraction; MI=Myocardial Infarction; NT-proBNP=N-terminal Pro B-Type Natriuretic Peptide; NYHA=New York Heart Association; PAH=Pulmonary Arterial Hypertension; T1D=Type 1 Diabetes; T2D=Type 2 Diabetes; 6MWD=Six-Minute Walk Distance.
- Packer M, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2410027 (Ahead of print).

SUMMIT Primary Endpoint: Time to First Event for CV Death or Worsening HF Event[a]

Assuming an event rate was 20% in the placebo group and 12.4% in the tirzepatide group (reflecting a 38% relative reduction), the ARR would be 7.6%, leading to an NNT of approximately 13 (1 / 0.076)



HR 0.62
(95% CI 0.41-0.95)
P=.026

RRR 38%

Participants at Risk

Placebo	367	361	349	339	332	328	318	268	259	240	219	215	195	165	145	94	73	45
Tirzepatide	364	359	349	344	340	338	333	284	275	251	228	220	196	167	146	105	82	46

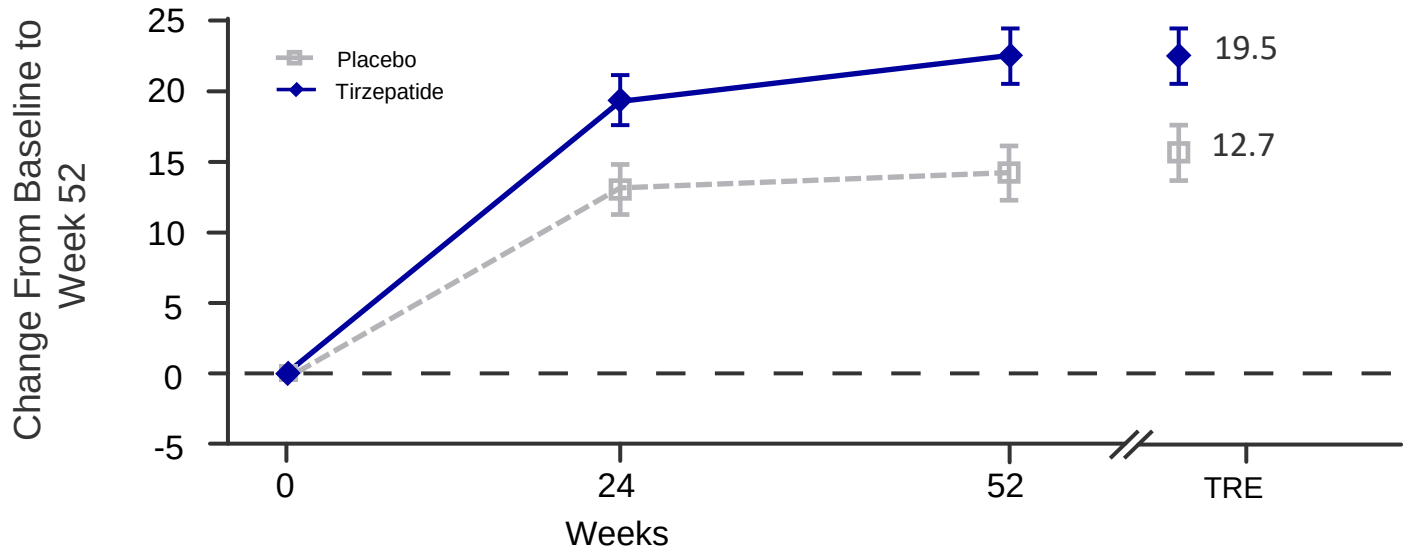
- [a]Worsening HF event was defined as heart failure symptoms requiring hospitalization, intravenous drugs for HF in an urgent care setting or intensification of oral diuretics. Changes in oral diuretics without worsening HF was not designated as an event.
- CI=Confidence Interval; CV=Cardiovascular; HF=Heart Failure; HR=Hazard Ratio; RRR=Relative Risk Reduction.
- Packer M, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2410027 (Ahead of print).

Overview of Primary Endpoint of CV Death or Worsening HF Event[a] (and Components)

	Placebo (N=367)		Tirzepatide (N=364)		Hazard Ratio or Difference (95% CI)
	Number (%)	Events/100 patient-yr	Number (%)	Events/100 patient-yr	
Primary end points and components					
Adjudicated death from CV causes or a worsening HF event resulting in hospitalisation, intravenous drugs in an urgent care setting or intensification of oral diuretic therapy	56 (15.3)	8.8	36 (9.9)	5.5	0.62 (0.41-0.95); *p*=.026
Adjudicated death from cardiovascular causes	5 (1.4)	0.7	8 (2.2)	1.2	1.58 (0.52-4.83)
Adjudicated death from an undetermined cause	0	0	2 (0.5)	0.3	----
Adjudicated worsening HF event resulting in hospitalisation, intravenous drugs in an urgent care setting or intensification of oral diuretic therapy	52 (14.2)	8.2	29 (8.0)	4.5	0.54 (0.34-0.85)
Adjudicated worsening HF event resulting in hospitalisation	26 (7.1)	3.9	12 (3.3)	1.8	0.44 (0.22-0.87)
Adjudicated worsening HF event resulting in intravenous diuretic therapy in an urgent care setting	12 (3.3)	1.8	5 (1.4)	0.7	0.41 (0.14-1.16)
Adjudicated worsening HF event resulting in intensification of oral diuretic therapy in an outpatient setting	21 (5.7)	3.2	17 (4.7)	2.6	0.80 (0.42-1.52)

- [a]Worsening HF event was defined as heart failure symptoms requiring hospitalisation, intravenous drugs for HF in an urgent care setting or intensification of oral diuretics. Changes in oral diuretics without worsening HF was not designated as an event.
- CI=Confidence Interval; CV=Cardiovascular; HF=Heart Failure; KCCQ-CSS=Kansas City Cardiomyopathy Questionnaire - Clinical Summary Score.
- Packer M, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2410027 (Ahead of print).

SUMMIT Co-Primary Endpoint: Effect of Tirzepatide on Health Status (KCCQ-CSS)



Treatment Regimen Estimand

ETD 6.9
(95% CI 3.3-10.6)[a]
P<.001

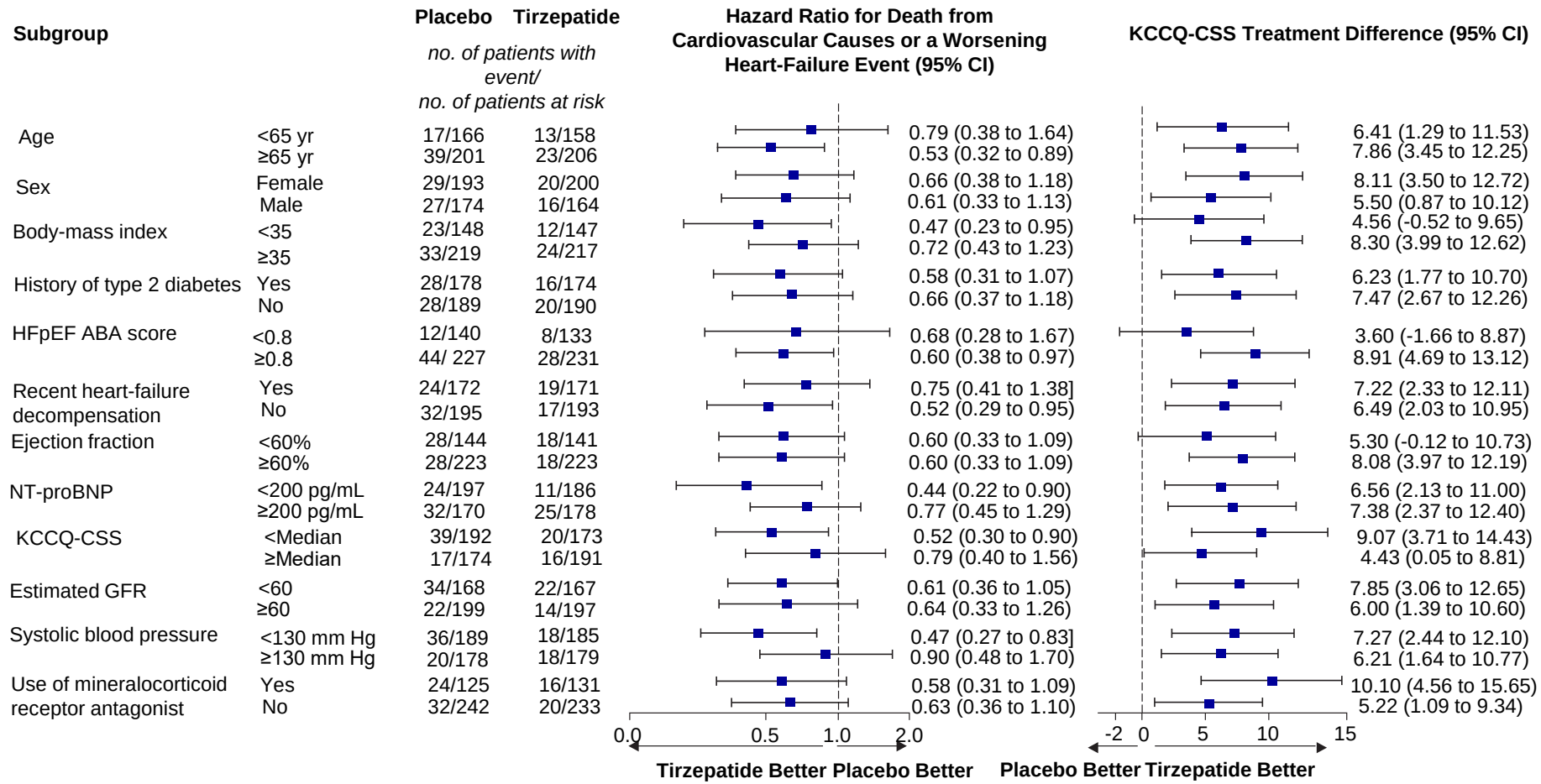
No. of Participants

Placebo	337	326	313
Tirzepatide	341	330	301

Treatment with tirzepatide significantly improved heart failure symptoms and physical limitations.

- [a]Hodges-Lehmann estimate of location shift and corresponding CI.
- Tirzepatide vs. placebo: ***P<0.001.
- Randomised population, on-treatment period. MMRM analysis. Data presented are LSM±SE with 95% CI.
- CI=Confidence Interval; ETD=Estimated Treatment Difference; KCCQ-CSS=Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LSM=Least-Square Mean; MMRM=Mixed Model Repeated Measures; SE=Standard Error; TRE=Treatment Regimen Estimand.
- Packer M, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2410027 (Ahead of print).

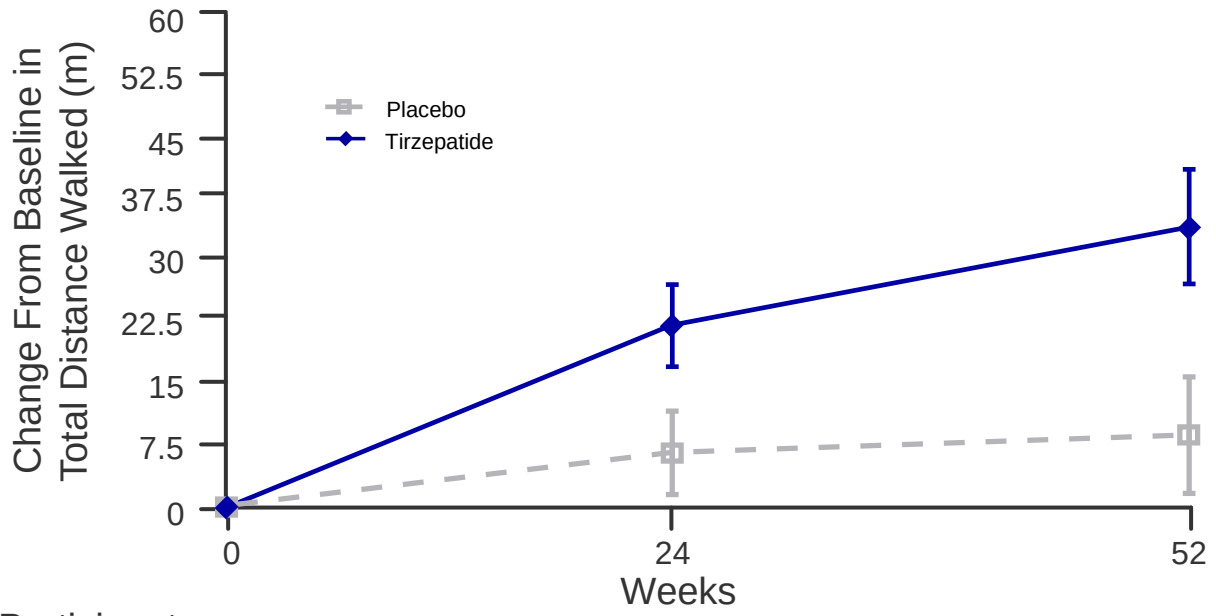
The Effects of Tirzepatide on Primary Outcomes Were Consistent Across Pre-specified Subgroups



- [a]Worsening HF event was defined as heart failure symptoms requiring hospitalisation, intravenous drugs for HF in an urgent care setting or intensification of oral diuretics. Changes in oral diuretics without worsening HF was not designated as an event.
- BMI=Body Mass Index; BP=Blood Pressure; CI=Confidence Interval; CV=Cardiovascular; eGFR=Estimated Glomerular Filtration Rate; HF=Heart Failure; HFpEF=Heart Failure With Preserved Ejection Fraction; KCCQ-CSS=Kansas City Cardiomyopathy Questionnaire - Clinical Summary Score; MRA=Mineralocorticoid Receptor Antagonist; NT-proBNP=N-terminal Prohormone of Brain Natriuretic Peptide; T2D=Type 2 Diabetes.
- Packer M, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2410027 (Ahead of print).

Change From Baseline to Week 52 in 6 MWD

- Key Secondary Endpoint



No. of Participants

Placebo	335	330	314
Tirzepatide	344	340	326

Treatment Regimen Estimand

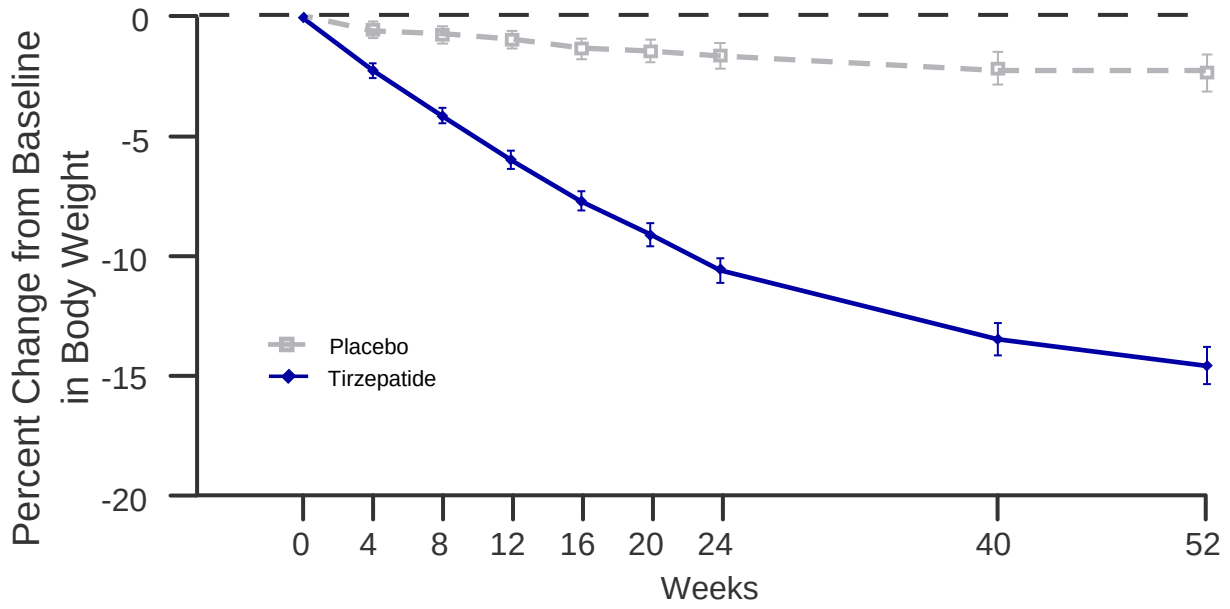
ETD 18.3
(95% CI 9.9-26.7)[a]
P<.001

A significant improvement in 6MWD was observed in patients on tirzepatide compared to placebo

- [a]Hodges-Lehmann estimate of location shift and corresponding CI.
- Data presented are LSM±SE with 95% CI.
- CI=Confidence Interval; ETD=Estimated Treatment Difference; LSM=Least-Square Mean; MMRM=Mixed Model Repeated Measures; SE=Standard Error; TRE=Treatment Regimen Estimand; 6MWD=6-Minute Walk Distance.
- Packer M, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2410027 (Ahead of print).

Change From Baseline to Week 52 in Body Weight

- Key Secondary Endpoint



No. of Participants

Placebo	363	339	333
Tirzepatide	364	341	331

Treatment Regimen Estimand

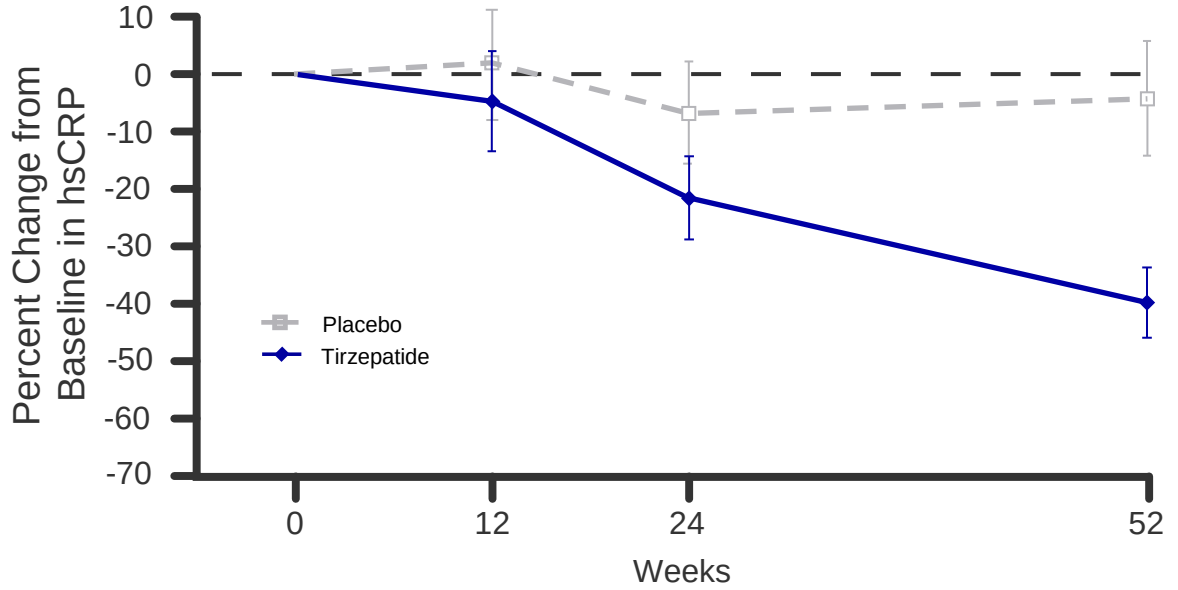
ETD -11.6
(95% CI -12.9 to -10.4)
P<.001

A greater reduction in body weight was observed in patients on tirzepatide compared to placebo.

- Tirzepatide vs. placebo: ***P<0.001.
- Data presented are LSM±SE with 95% CI.
- CI=Confidence Interval; ETD=Estimated Treatment Difference; LSM=Least-Square Mean; MMRM=Mixed Model Repeated Measures; SE=Standard Error; TRE=Treatment Regimen Estimand.
- Packer M, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2410027 (Ahead of print).

Change From Baseline to Week 52 in hsCRP

- Key Secondary Endpoint



No. of Participants				
Placebo	332	323	313	298
Tirzepatide	344	332	323	305

Treatment Regimen Estimand

ETD -34.9
(95% CI -45.6 to -22.2)[a]
P<.001

A greater reduction in hsCRP was observed in patients on tirzepatide compared to placebo.

- [a]Data were log-transformed before analysis.
- Tirzepatide vs. placebo: ***P<0.001.
- Data presented are LSM±SE with 95% CI.
- CI=Confidence Interval; ETD=Estimated Treatment Difference; hsCRP=High Sensitivity C-reactive Protein; LSM=Least-Square Mean; MMRM=Mixed Model Repeated Measures; SE=Standard Error; TRE=Treatment Regimen Estimand.
- Packer M, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2410027 (Ahead of print).

Non-Fatal AEs Leading to Discontinuation of Study Medication, Occurring in ≥2 Patients

AEs	Placebo (N=367)	Tirzepatide (N=364)
Patients who discontinued study medication due to non-fatal adverse event	5 (1.4%)	23 (6.3%)
Constipation	0 (0%)	3 (0.8%)
Diarrhoea	0 (0%)	2 (0.5%)
Dyspepsia	0 (0%)	2 (0.5%)
Vomiting	0 (0%)	2 (0.5%)
Blood calcitonin increased	0 (0%)	2 (0.5%)

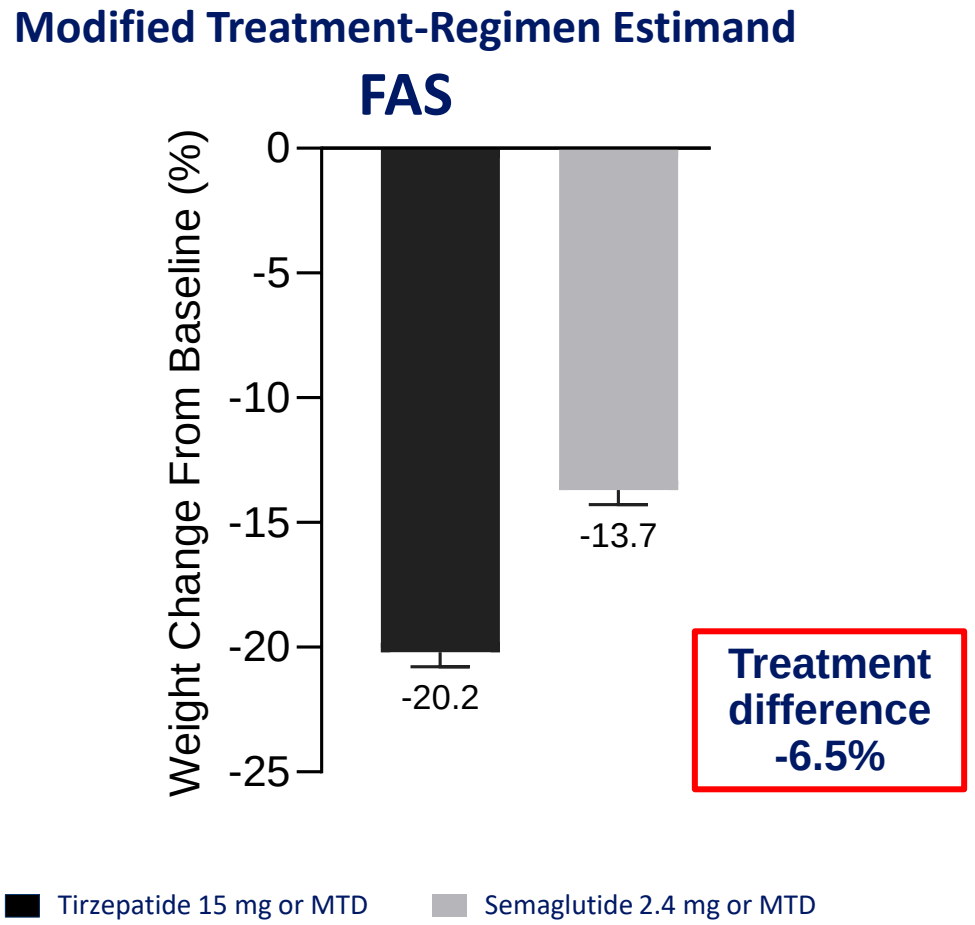
- AE=Adverse Events.
- Packer M, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2410027 (Ahead of print).

Objective

SURMOUNT-5 is a 72-week Phase 3b, randomized controlled study to evaluate the efficacy and safety of tirzepatide 15 mg or MTD (10 mg or 15 mg) compared to semaglutide 2.4 mg or MTD (1.7 mg or 2.4 mg) in adults with obesity or overweight with weight-related comorbidities, without type 2 diabetes.

- MTD=Maximum Tolerated Dose.
- https://clinicaltrials.gov/study/NCT05822830 (Accessed October 25, 2024).
- Eli Lilly and Company. 2024. Available at: https://investor.lilly.com/news-releases/news-release-details/lillys-zepboundr-tirzepatide-superior-wegovyr-semaglutide-head. Accessed 04 December 2024.

Primary Endpoint: Percentage Change in Body Weight From Baseline to 72 Weeks



- Tirzepatide shows a 47% greater relative weight loss compared to semaglutide

FAS=Full Analysis Set; MTD=Maximum Tolerated Dose.

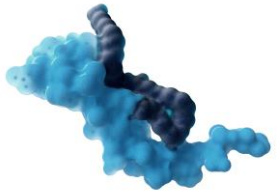
- Eli Lilly and Company. 2024. Available at: https://investor.lilly.com/news-releases/news-release-details/lillys-zepboundr-tirzepatide-superior-wegovyr-semaglutide-head. Accessed 04 December 2024.

Summary of Efficacy

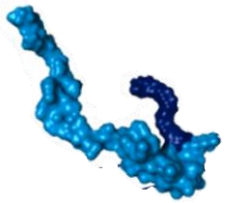
- In SURMOUNT-5, all primary and key secondary endpoints were met
- Over 72 weeks, tirzepatide MTD was statistically and clinically superior to semaglutide MTD for weight reduction with the mean difference for tirzepatide MTD versus semaglutide MTD being 6.5% for treatment-regimen estimand
- Tirzepatide showed a 47% greater relative weight loss compared to semaglutide
- 31.6% of tirzepatide MTD participants had ≥ 25% body weight reduction versus 16.1% of semaglutide MTD participants

- MTD=Maximum Tolerated Dose.
- Eli Lilly and Company. 2024. Available at: https://investor.lilly.com/news-releases/news-release-details/lillys-zepboundr-tirzepatide-superior-wegovyr-semaglutide-head. Accessed 04 December 2024.

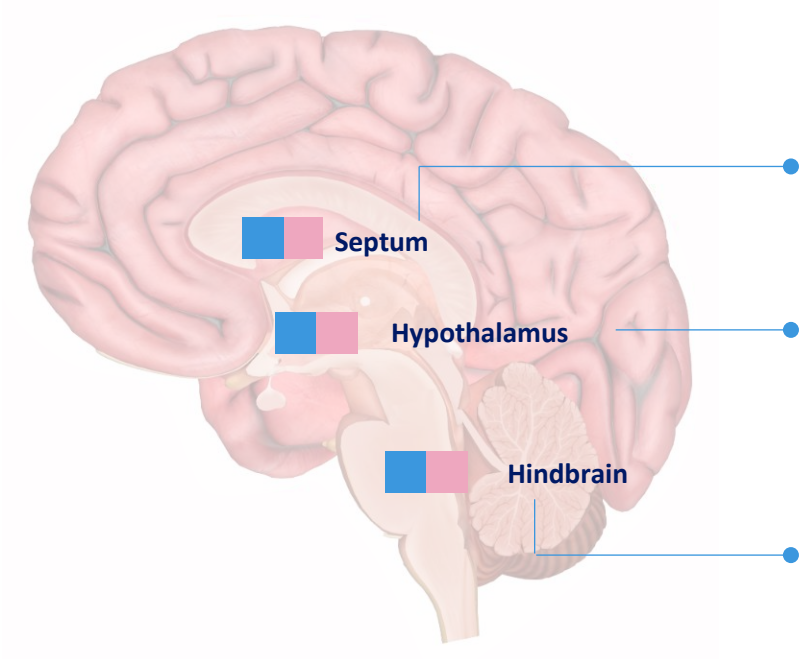
The potential of combination therapy for weight management with CagriSema



Semaglutide



Cagrilintide



Direct targets in the brain

In the **septum**, semaglutide targets GLP-1R expressing cells. The identity of these cells have yet to be defined

In the **hypothalamus**, cagrilintide target populations are currently being explored

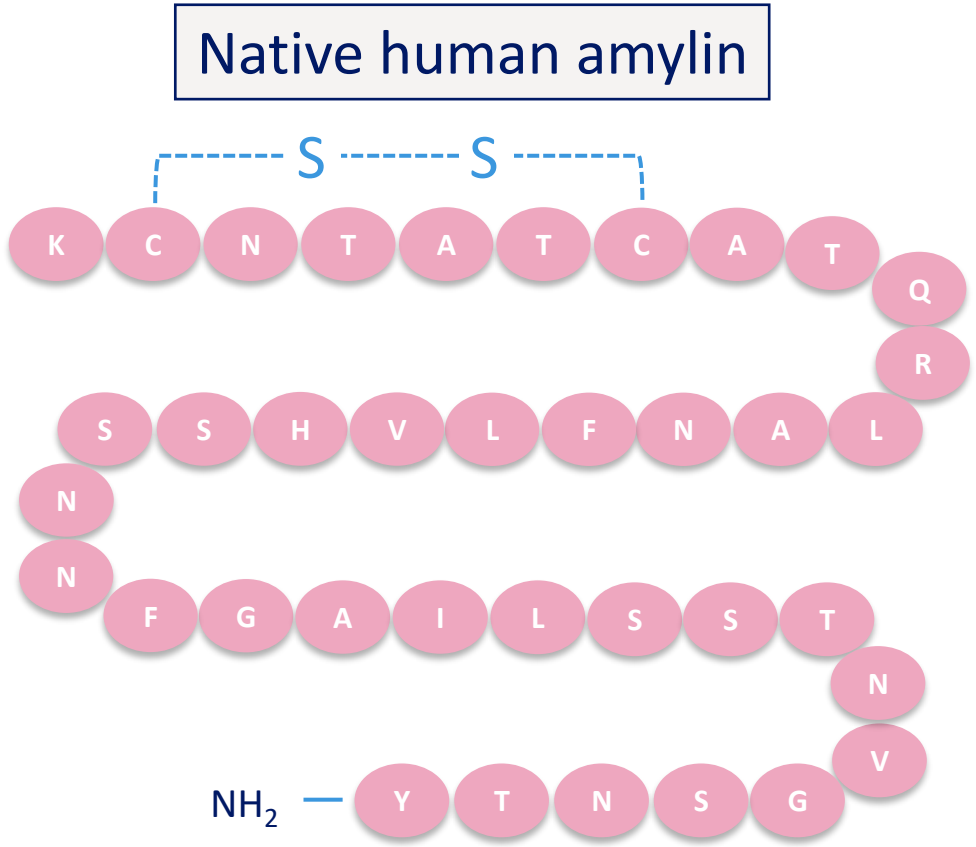
In the **hindbrain**, semaglutide and cagrilintide targets both common and distinct sets of cell populations expressing the GLP-1R and/or the AMYRs

AMYRs, Amylin receptors; GLP-1R, Glucagon like peptide receptors

Jensen et al. Diabetes 2017;66:A305; 2. adapted from : Boccia et al. Peptides 2020; 132: 170366; Ludwig et al. Nature Metabolism 2021; 3(4): 530-545; Secher A. et al. (2022), Poster #177, Poster Abstracts. Obesity (Silver Spring), 30: 55-293

What is amylin?

- Amylin is a **neuroendocrine** peptide hormone comprised of 37 amino acids[1]
- Co-secreted with insulin from **pancreatic β-cells** in response to food intake[1]
- Endogenous amylin has strong fibrillating properties[2]
- It is difficult to estimate the $t_{1/2}$ of endogenous amylin (few reports in humans indicated range could be between 2-11 mins)[3-4]
- Circulating plasma $t_{½}$ of the amylin analogue pramlintide is 20-45 mins[5]

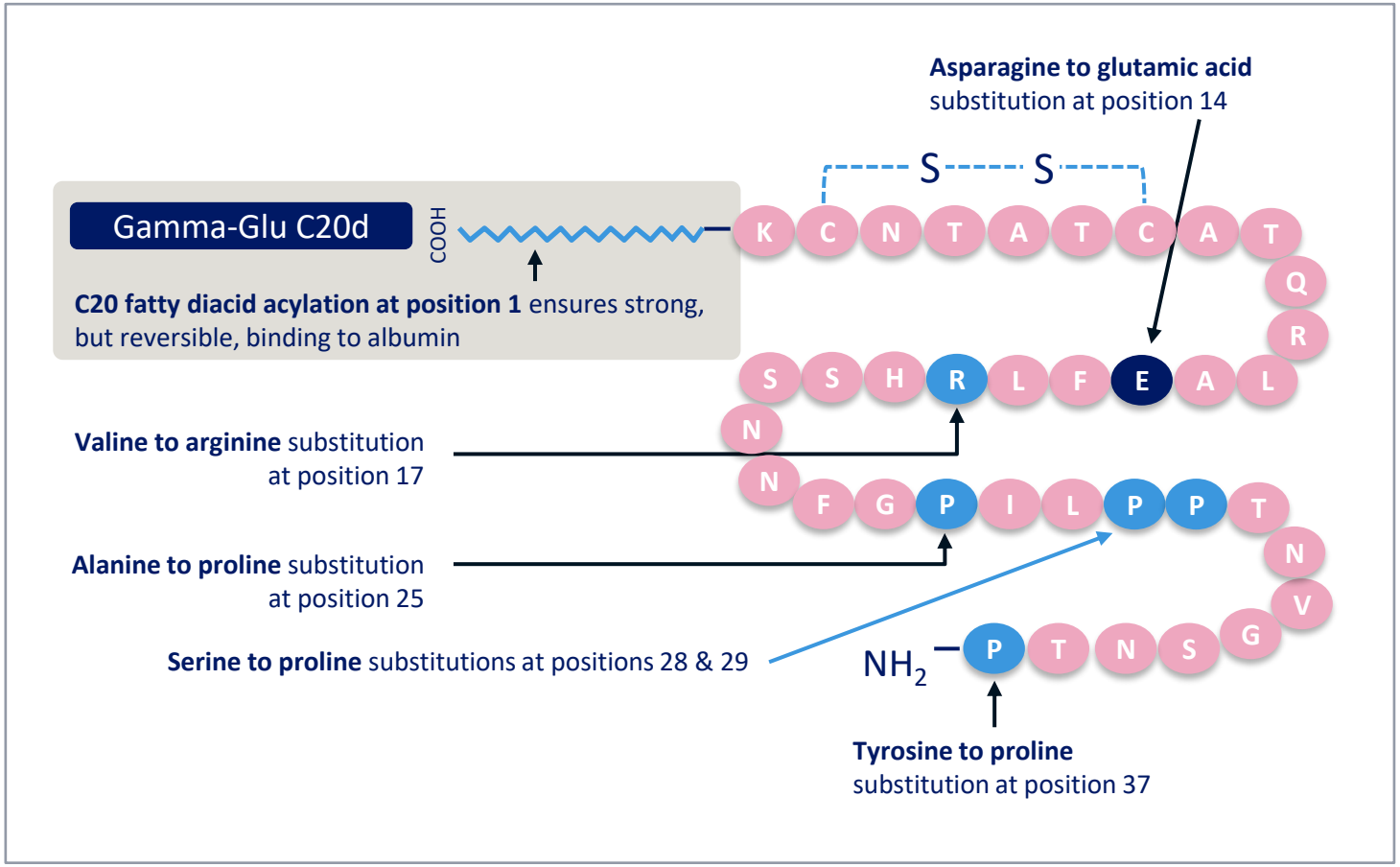


$t_{½}$, half-life

1. Hay et al. Pharmacol Rev 2015;67:564–600; 2. Lorenzo et al. Nature 1994; 368(6473): 756-760; 3. Bretherton-Watt et al. Diabetologia 1990; 33(2): 115-117; 4. Clodi et al. American Journal of Physiology-Endocrinology and Metabolism 1998; 274(5): E903-E908; 5. Colburn et al. J Clin Pharmacol 1996; 36(1): 13-24;

Cagrilintide is a human long acting amylin analogue

- 84% homology to native human amylin
- The purpose of the amino acid substitutions and acylation were primarily to remove the fibrillating properties of human amylin and ensure stability
- t½ of approximately 180 hours



Glu, glutamic acid

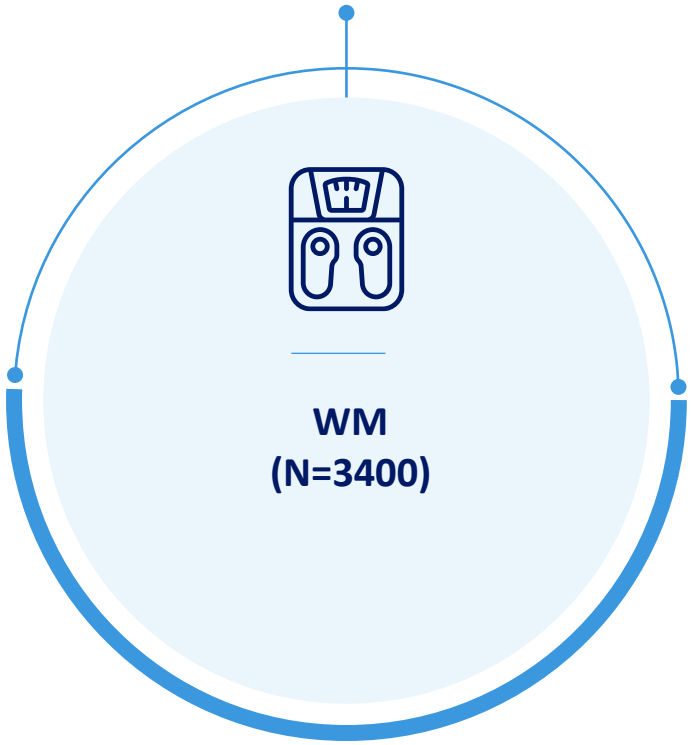
1. Kruse et al. Journal of Medicinal Chemistry 2021; 64(15): 11183-11194

CagriSema Phase 3a programme[1,2]

Weight management

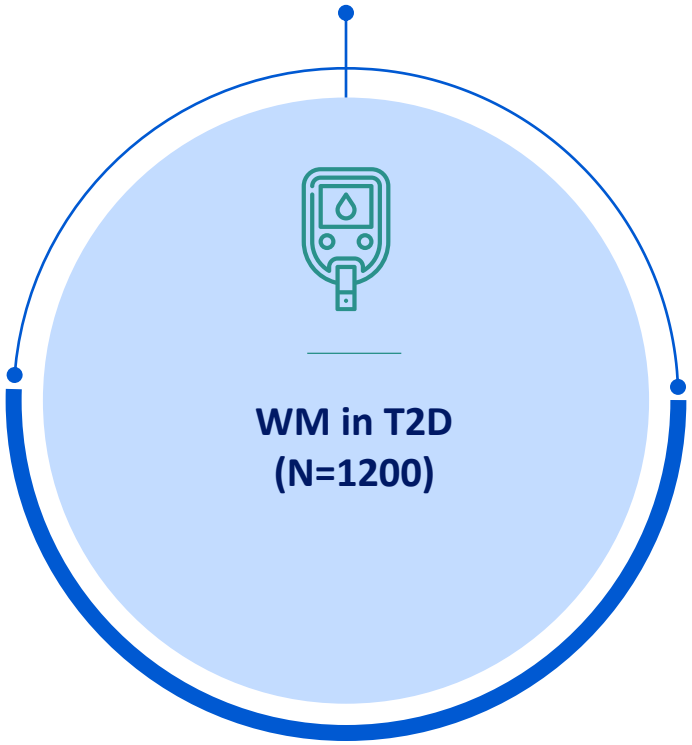
Global phase 3a

4608 – REDEFINE 1



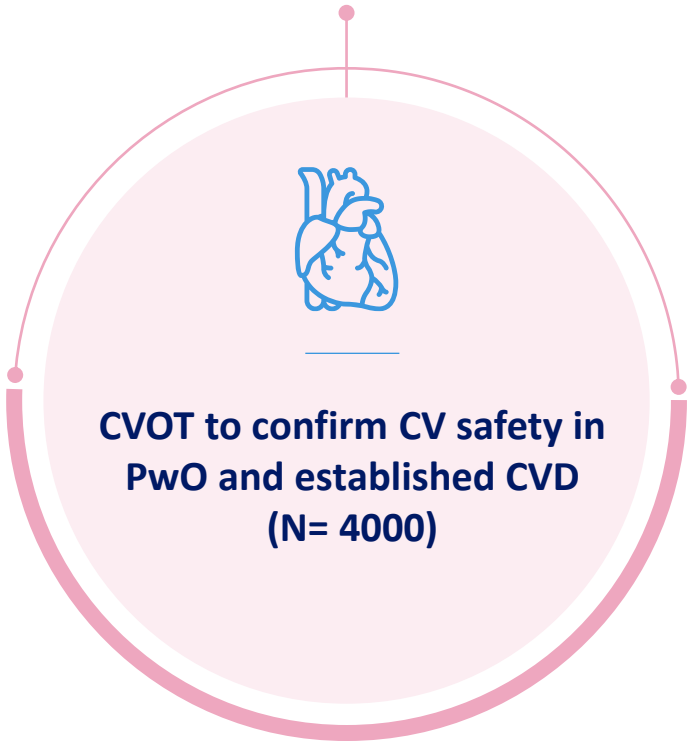
WM
(N=3400)

4609 – REDEFINE 2



WM in T2D
(N=1200)

4942 – REDEFINE 3



CVOT to confirm CV safety in PwO and established CVD
(N= 4000)

CV, cardiovascular; CVOT, cardiovascular outcomes; PwO, people with obesity; T2D, type 2 diabetes; WM, weight management; REDEFINE, REDEfining treatment oF obesity with cagrilINtide and semaglutidE combination

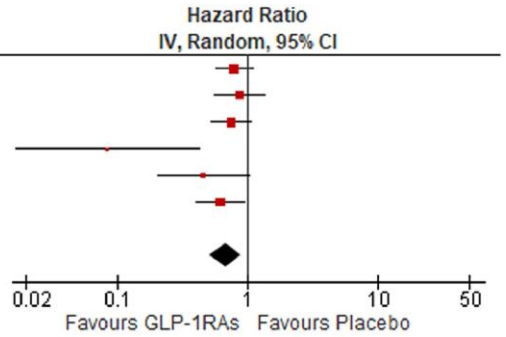
1. https://clinicaltrials.gov/ct2/show/NCT05567796 2. https://clinicaltrials.gov/ct2/show/NCT05394519 3. https://clinicaltrials.gov/ct2/show/NCT05669755

Are GLP-1RA safe across LVEF spectrum in HF?

A) Composite of CV Death or Worsening HF event

Study or Subgroup	log[Hazard Ratio]	SE	GLP-1RAs Total	Placebo Total	Weight	Hazard Ratio IV, Random, 95% CI
EXSCEL	-0.2357	0.1674	499	561	25.0%	0.79 [0.57, 1.10]
FLOW	-0.1462	0.224	167	158	19.5%	0.86 [0.56, 1.34]
SELECT	-0.2877	0.183	1174	1099	23.4%	0.75 [0.52, 1.07]
STEP HFpEF	-2.4663	0.8216	263	266	2.7%	0.08 [0.02, 0.42]
STEP HFpEF DM	-0.7853	0.4082	310	306	9.1%	0.46 [0.20, 1.01]
SUMMIT	-0.478	0.216	364	367	20.2%	0.62 [0.41, 0.95]
Total (95% CI)			**2777**	**2757**	**100.0%**	**0.68 [0.51, 0.89]**

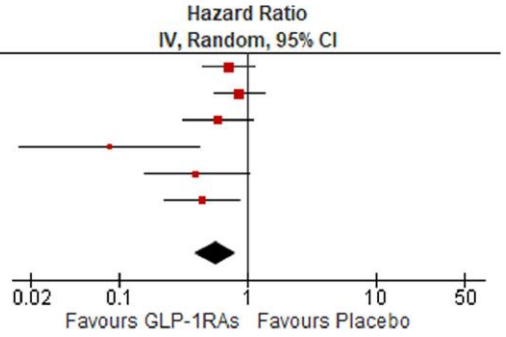
Heterogeneity: Tau² = 0.05; Chi² = 9.51, df = 5 (P = 0.09); I² = 47%
Test for overall effect: Z = 2.77 (P = 0.006)



B) Worsening HF event

Study or Subgroup	log[Hazard Ratio]	SE	GLP-1RAs Total	Placebo Total	Weight	Hazard Ratio IV, Random, 95% CI
EXSCEL	-0.3425	0.2327	499	561	23.8%	0.71 [0.45, 1.12]
FLOW	-0.1473	0.2243	167	158	24.4%	0.86 [0.56, 1.34]
SELECT	-0.5344	0.3183	1174	1099	18.5%	0.59 [0.31, 1.09]
STEP HFpEF	-2.4769	0.826	263	266	4.9%	0.08 [0.02, 0.42]
STEP HFpEF DM	-0.9263	0.4819	310	306	11.4%	0.40 [0.15, 1.02]
SUMMIT	-0.821	0.349	364	367	16.9%	0.44 [0.22, 0.87]
Total (95% CI)			**2777**	**2757**	**100.0%**	**0.56 [0.38, 0.82]**

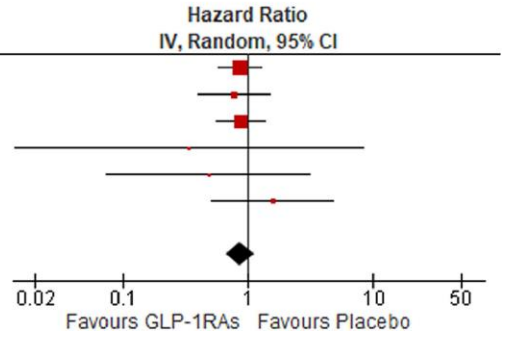
Heterogeneity: Tau² = 0.11; Chi² = 10.22, df = 5 (P = 0.07); I² = 51%
Test for overall effect: Z = 2.95 (P = 0.003)



C) CV Death

Study or Subgroup	log[Hazard Ratio]	SE	GLP-1RAs Total	Placebo Total	Weight	Hazard Ratio IV, Random, 95% CI
EXSCEL	-0.1485	0.2057	499	561	41.3%	0.86 [0.58, 1.29]
FLOW	-0.2485	0.3369	167	158	15.4%	0.78 [0.40, 1.51]
SELECT	-0.1393	0.2221	1174	1099	35.4%	0.87 [0.56, 1.34]
STEP HFpEF	-1.0873	1.6307	263	266	0.7%	0.34 [0.01, 8.24]
STEP HFpEF DM	-0.7215	0.9541	310	306	1.9%	0.49 [0.07, 3.15]
SUMMIT	0.4574	0.57	364	367	5.4%	1.58 [0.52, 4.83]
Total (95% CI)			**2777**	**2757**	**100.0%**	**0.86 [0.67, 1.12]**

Heterogeneity: Tau² = 0.00; Chi² = 1.91, df = 5 (P = 0.86); I² = 0%
Test for overall effect: Z = 1.10 (P = 0.27)



EF >40% - semaglutide, exanetide and tirzepatide

https://onlinejcf.com/article/S1071-9164(25)00091-0/fulltext

Are GLP-1RA safe across LVEF spectrum in HF?

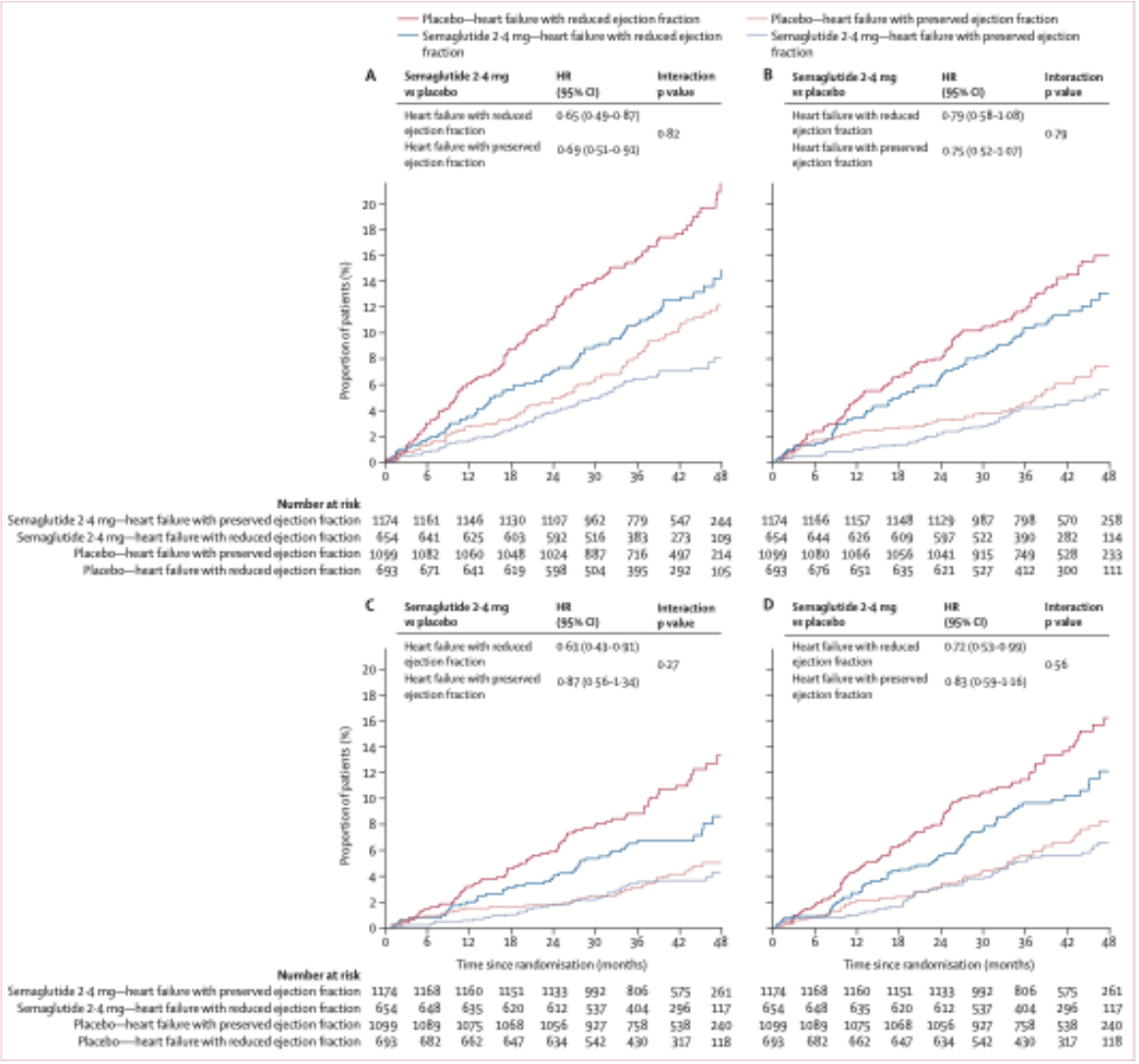
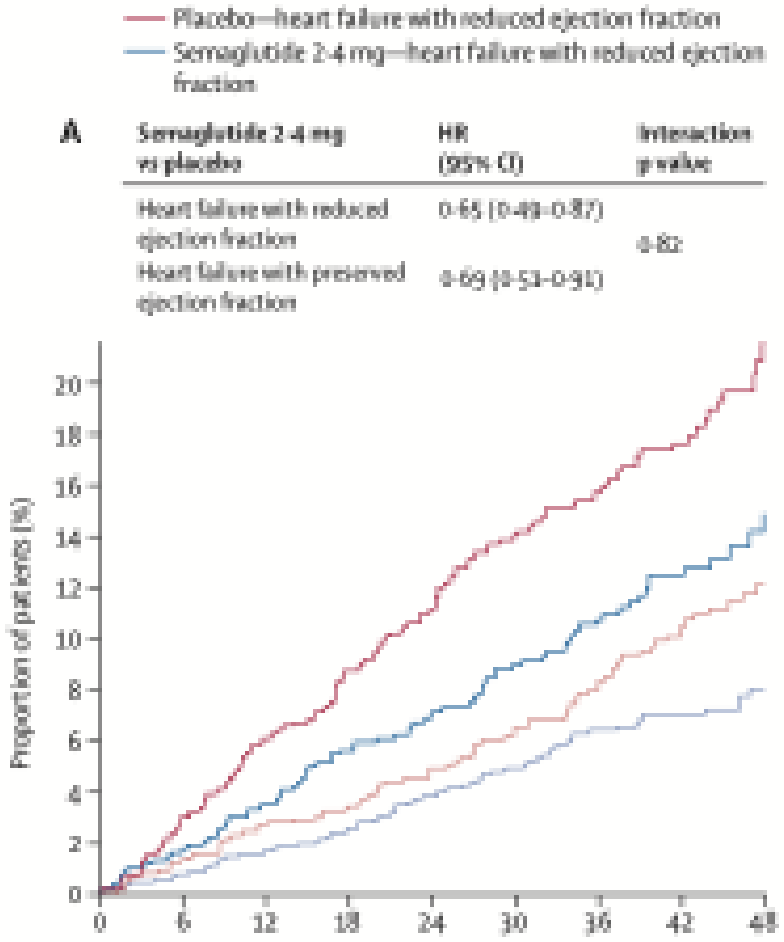


Figure 2: The effect of semaglutide versus placebo according to heart failure subtype
Cumulative incidence curves comparing the risk of major adverse cardiovascular events (A), heart failure composite (B), cardiovascular death (C), and all-cause death (D) comparing semaglutide with placebo according to heart failure subtype. The cumulative incidence rate is calculated using the Aalen-Johansen method. HR=hazard ratio.

EF <40%



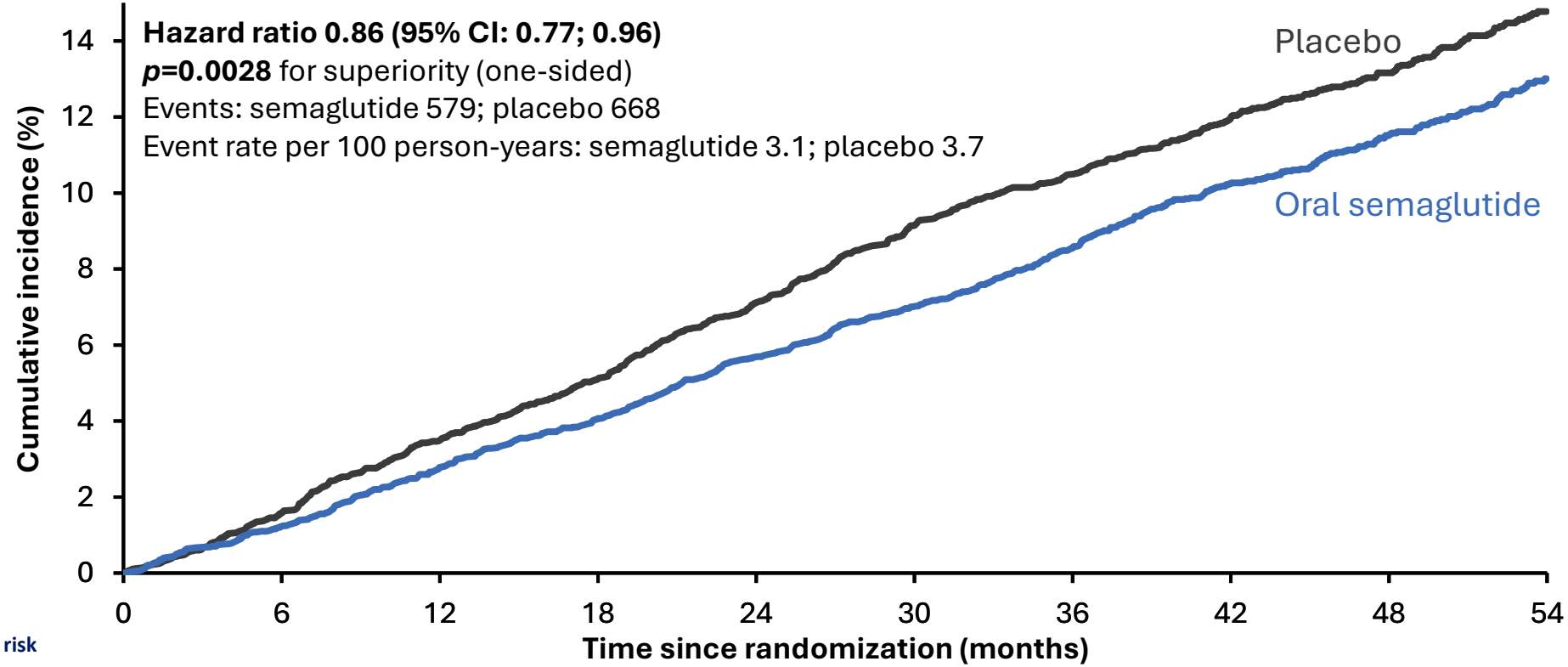
company announcement

Oral semaglutide demonstrates a 14% reduction in risk of major adverse cardiovascular events in adults with type 2 diabetes in the SOUL trial

Bagsværd, Denmark, 21 October 2024 — Novo Nordisk today announced the headline results from the SOUL cardiovascular outcomes trial. The double-blinded, randomised trial compared oral semaglutide to placebo as an adjunct to standard of care for the prevention of major adverse cardiovascular events (MACE). The trial enrolled 9,650 people with type 2 diabetes and established cardiovascular disease (CVD) and/or chronic kidney disease (CKD). As part of standard of care, 49% of patients received SGLT2i at some point during the trial.

SOUL trial – ORAL GLP1RA: 3-point MACE composite

Primary outcome



No. at risk										
Placebo	4825	4718	4583	4455	4322	4194	4101	3727	2517	1346
Semaglutide	4825	4743	4835	4542	4438	4346	4239	3831	2555	1346

Components:

- CV death
- Nonfatal MI
- Nonfatal stroke

- Results consistent across pre-specified sensitivity analyses
- Absolute risk reduction 2% over 3 years
- **NNT = 50**

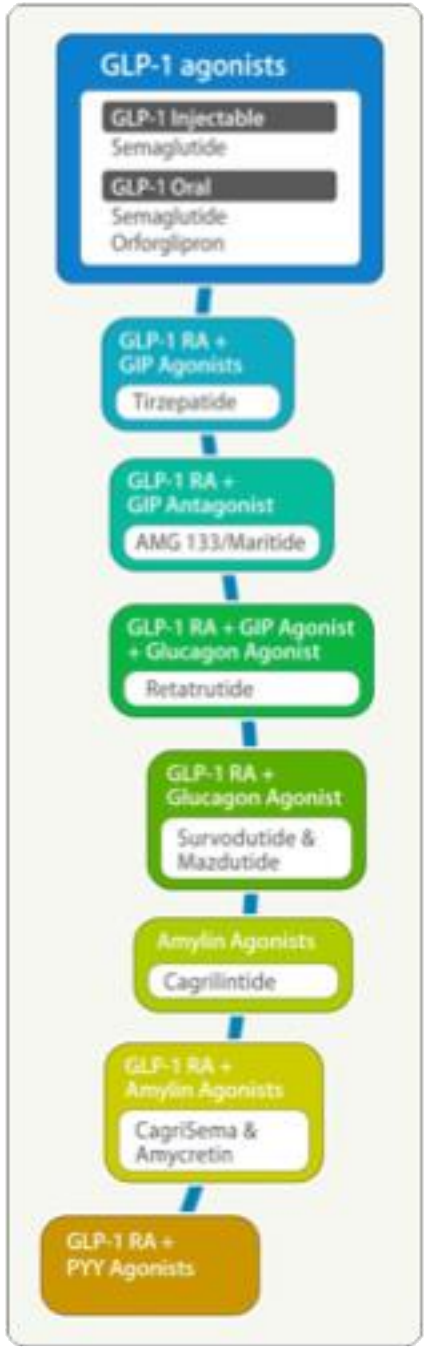
Cumulative incidence estimates are based on time from randomization to first MACE with non-CV death modelled as competing risk using the Aalen-Johansen estimator. Time from randomization to first MACE was analysed using a Cox proportional hazards model with treatment as categorical fixed factor. Adjustment for group sequential design was done using likelihood ratio ordering.
CI, confidence interval; CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction; NNT, number needed to treat.

CagriSema demonstrates superior weight loss in adults with obesity or overweight in the REDEFINE 1 trial

When evaluating the effects of treatment if all people adhered to treatment[1], people treated with CagriSema achieved a superior weight loss of 22.7% after 68 weeks compared to a reduction of 11.8% with cagrilintide 2.4 mg, 16.1% with semaglutide 2.4 mg and 2.3% with placebo alone. In addition, 40.4% of patients who received CagriSema reached a weight loss of 25% or more after 68 weeks, compared to 6.0% with cagrilintide 2.4 mg, 16.2% with semaglutide 2.4 mg, and 0.9% with placebo.

AMGEN ANNOUNCES ROBUST WEIGHT LOSS WITH MARITIDE IN PEOPLE LIVING WITH OBESITY OR OVERWEIGHT AT 52 WEEKS IN A PHASE 2 STUDY

MariTide Demonstrated up to ~20% Average Weight Loss at 52 Weeks Without a Weight Loss Plateau in People Living With Obesity or Overweight
MariTide is the First Obesity Treatment With Monthly or Less Frequent Dosing to Demonstrate Safe and Effective Weight Loss in a Phase 2 Study
In People With Type 2 Diabetes Living With Obesity or Overweight MariTide Demonstrated up to ~17% Average Weight Loss Without a Weight Loss Plateau and Lowered Average HbA1c by up to 2.2 Percentage Points at 52 Weeks



S/c Semaglutide: Wegovy

1 INDICATIONS

Wegovy® (semaglutide injection) is indicated as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in:

- Adult patients with an initial body mass index (BMI) of
  - 30 kg/m^2 or greater (obesity), or
  - 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus, dyslipidemia, or obstructive sleep apnea.
- Pediatric patients aged 12 to less than 18 years:
  - with an initial BMI at the 95th percentile or greater for age and sex (obesity; see Table 1), and
  - a body weight above 60 kg (132 lbs), and
  - an inadequate response to reduced calorie diet and physical activity alone.

Health Canada approves Wegovy® (semaglutide injection) to reduce the risk of non-fatal myocardial infarction

- *Wegovy® is the first-and-only medication indicated for both chronic weight management and to reduce the risk of non-fatal myocardial infarction (MI) in Canada.*[1]
- *Close to one in three Canadian adults are living with obesity, which is a risk factor for heart disease.*[2,3]

MOUNJARO (tirzepatide injection) is indicated for once-weekly administration as an adjunct to diet and exercise to improve glycemic control for the treatment of adult patients with type 2 diabetes mellitus.

- As **monotherapy** when metformin is inappropriate due to contraindication or intolerance.
- In **combination with**:
  - metformin, or
  - metformin and a sulfonylurea (see 4.1 Dosing Considerations and 7 WARNINGS AND PRECAUTIONS), or
  - metformin and a sodium-glucose cotransporter 2 inhibitor (SGLT2i), or
  - basal insulin with or without metformin (see 4.1 Dosing Considerations and 7 WARNINGS AND PRECAUTIONS).

Thank you