Medications When, Which, and How?

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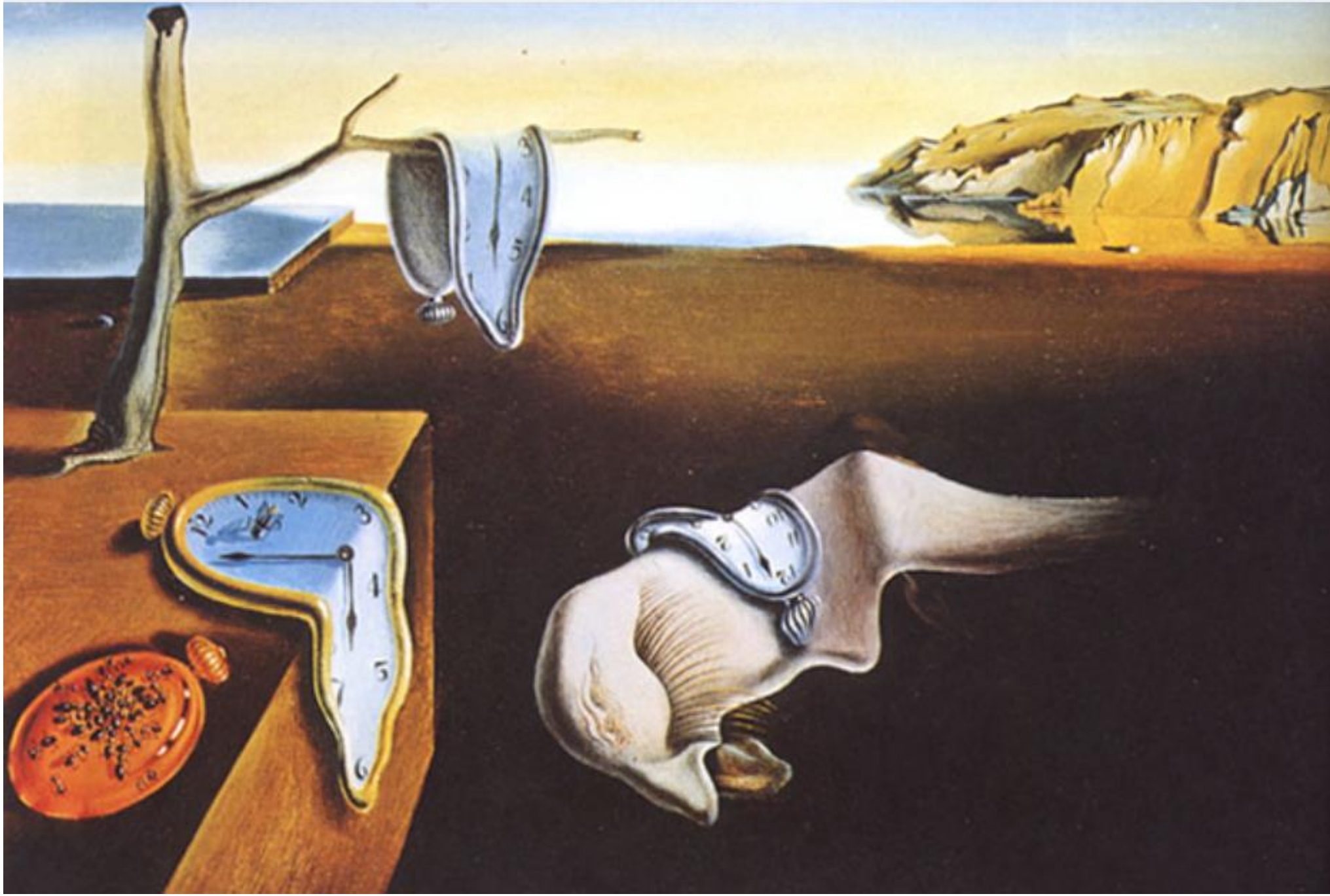


Persistence of Memory, Salvator Dali 1931 hanging in Museum of Modern Art (MoMA) New York

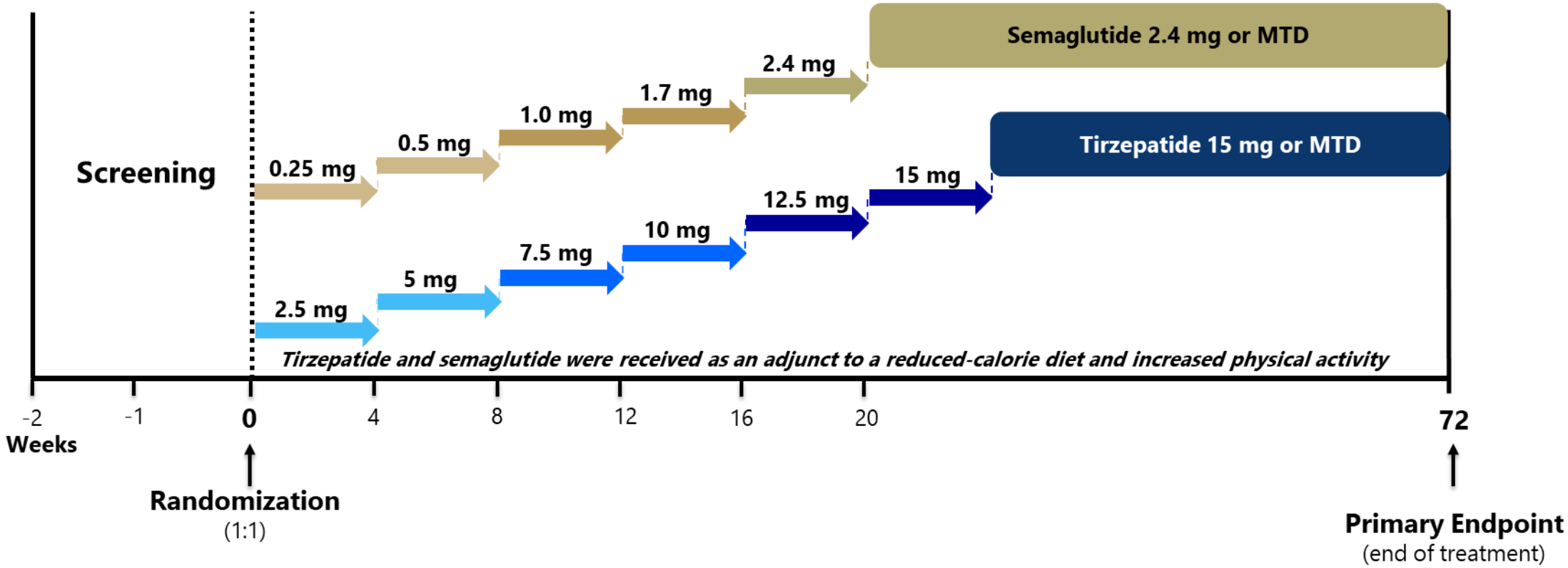
Disclosures

- **Consultant:** Arrowhead Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Currax Pharmaceuticals LLC, Eli Lilly and Company, F. Hoffmann-La Roche AG, Johnson and Johnson, Medtronic, and Novo Nordisk.

SURMOUNT-5: Study Design in People with Obesity

A Phase 3b, 72-Week, Multicenter, Randomized, Controlled, Parallel-Arm, Open-Label Trial.

- Stratification factors: prediabetes status at randomization, sex, and BMI <35 vs ≥35 kg/m^2
- US only to limit risk to semaglutide supply; US semaglutide label update July 2023, 1.7mg added as maintenance dose



MTD=maximum tolerated dose.

Data from Aronne LJ, et al. N Engl J Med 2025; *in press.*

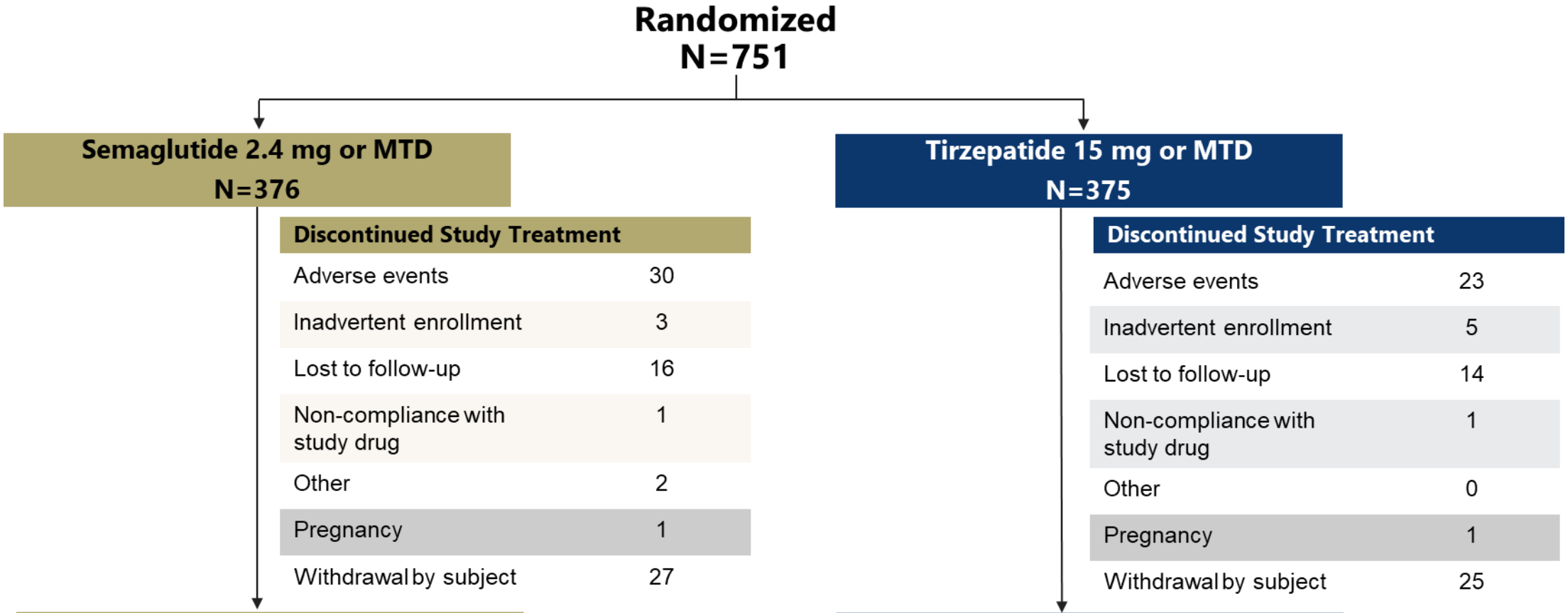
Baseline Clinical Characteristics

Parameter (mean ± SD, unless otherwise specified)	Semaglutide MTD (N=376)	Tirzepatide MTD (N=374)	Total (N=750)
HbA1c (%)	5.6 ± 0.38	5.6 ± 0.35	5.6 ± 0.36
Pre-diabetes at randomization, n (%)	210 (55.9)	215 (57.5)	425 (56.7)
FSG (mg/dL)	94.9 ± 9.83	94.4 ± 10.43	94.6 ± 10.13
Total cholesterol (mg/dL)	190.9 ± 35.30	188.7 ± 37.42	189.8 ± 36.36
Triglycerides (mg/dL)	133.5 ± 105.11	127.0 ± 66.19	130.3 ± 87.99
HDL cholesterol (mg/dL)	49.9 ± 13.53	49.9 ± 13.09	49.9 ± 13.30
LDL cholesterol (mg/dL)	114.6 ± 30.68	113.5 ± 31.71	114.1 ± 31.18
Non-HDL cholesterol (mg/dL)	141.0 ± 35.28	138.9 ± 36.22	140.0 ± 35.74
VLDL cholesterol (mg/dL)	24.9 ± 11.26	25.0 ± 12.22	24.9 ± 11.74
eGFR[a] (mL/min/m^2)	106.0 ± 16.88	104.6 ± 17.43	105.3 ± 17.16

The baseline clinical characteristics were well balanced across the treatment groups.

Note: Data are mean ± SD, unless otherwise indicated.
[a]The value of the eGFR was calculated according to the serum creatinine-based CKD-EPI equation.
CKD-EPI=chronic kidney disease epidemiology collaboration; eGFR=estimated glomerular filtration rate; FSG=fasting serum glucose; HbA1c=glycated hemoglobin; HDL=high-density lipoprotein; LDL=low-density lipoprotein; mITT=modified intent-to-treat; MTD=maximum tolerated dose; SD=standard deviation; VLDL=very-low-density lipoprotein.
Data from Aronne LJ, et al. N Engl J Med 2025; *in press.*

Participant Disposition

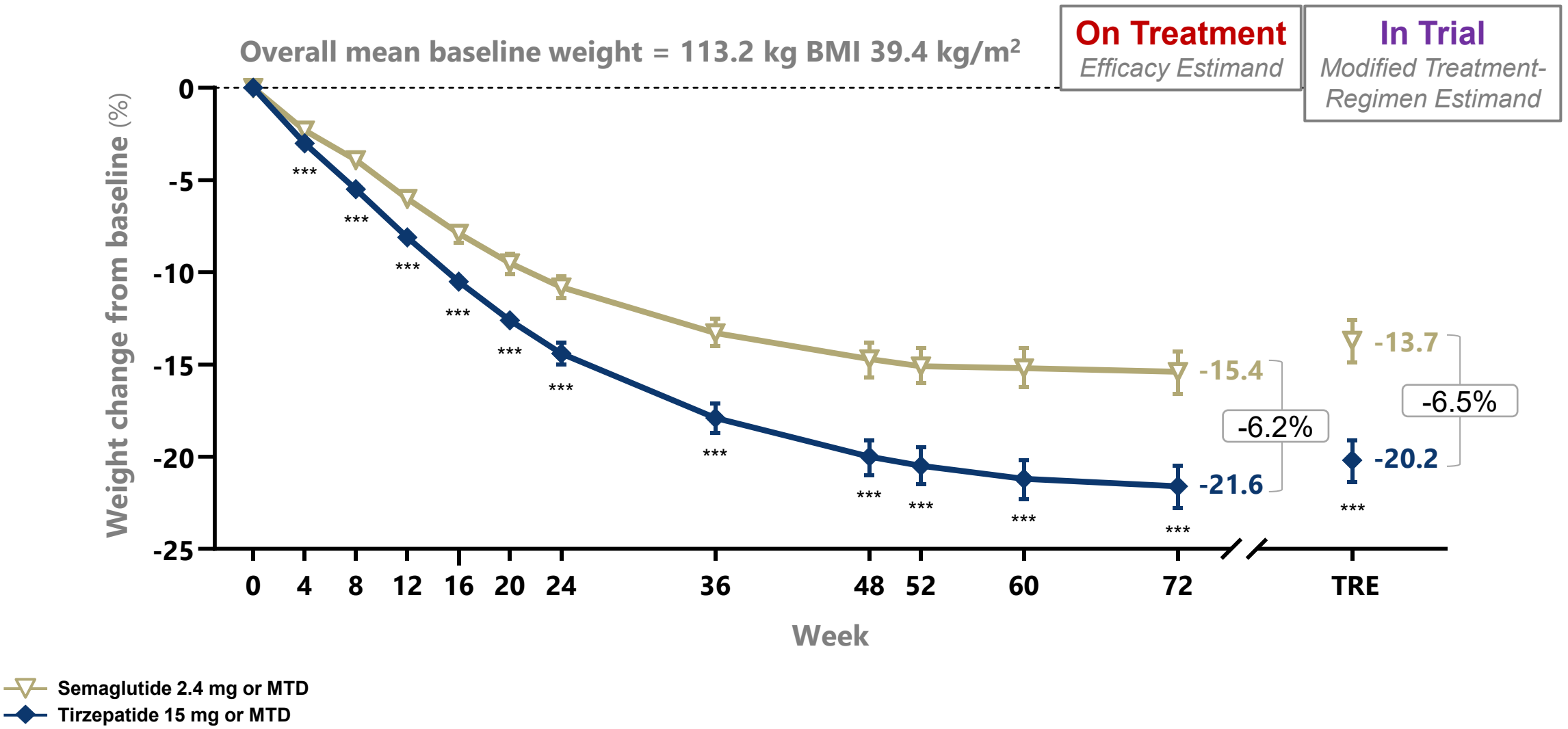


Dose	Received Maximum Dose at Any Time n (%)	Received as Final Dose n (%)
2.4 mg	349 (92.8)	325 (86.4)

Dose	Received Maximum Dose at Any Time n (%)	Received as Final Dose n (%)
15 mg	334 (89.3)	306 (81.8)

Participant disposition from randomization to primary endpoint.
Data from Aronne LJ, et al. N Engl J Med 2025; *in press.*

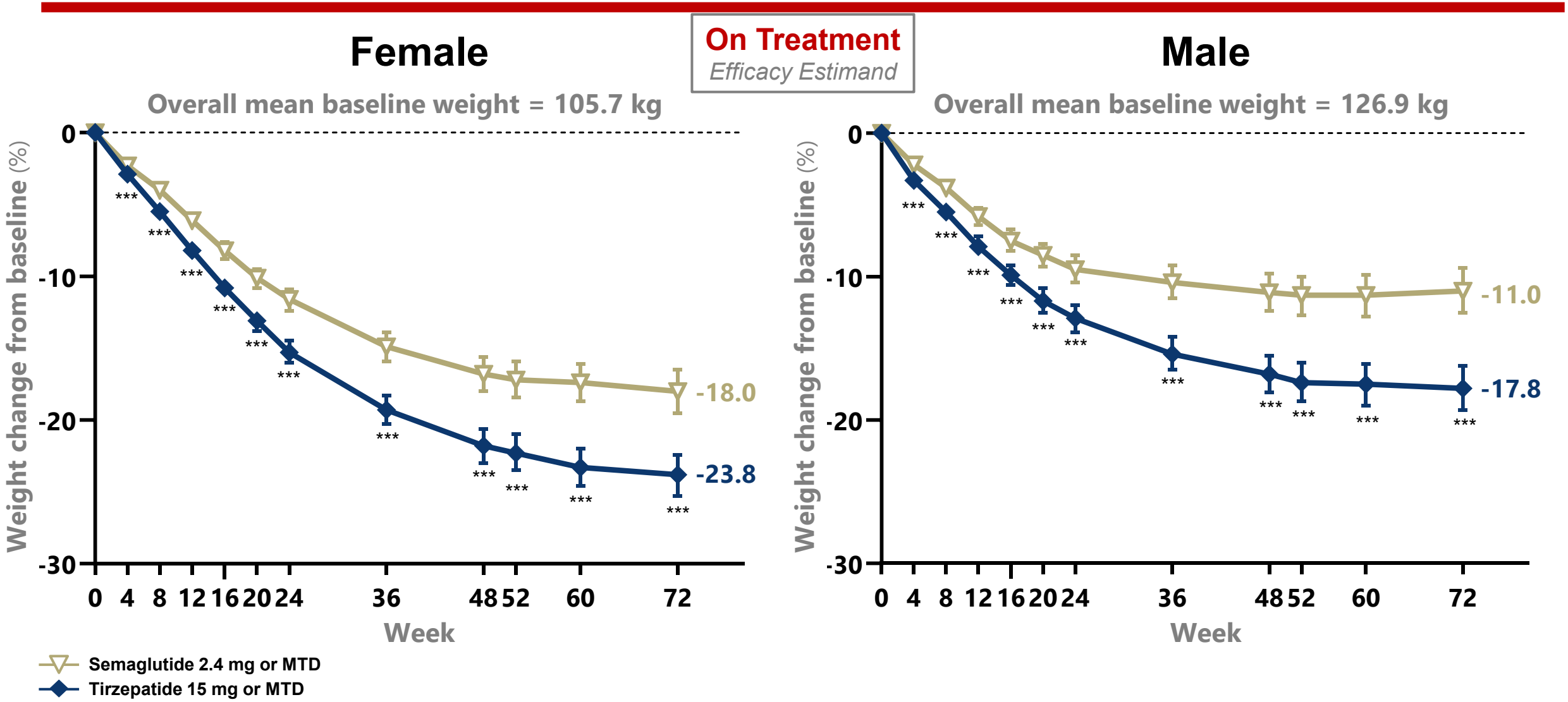
Weight Reduction from Baseline to Week 72: percent change



***p<0.001 vs semaglutide. Data are LSM ± 95% CI. Week 4 through Week 60 data were not controlled for multiplicity.
Data from Aronne LJ, et al. N Engl J Med 2025; *in press.*

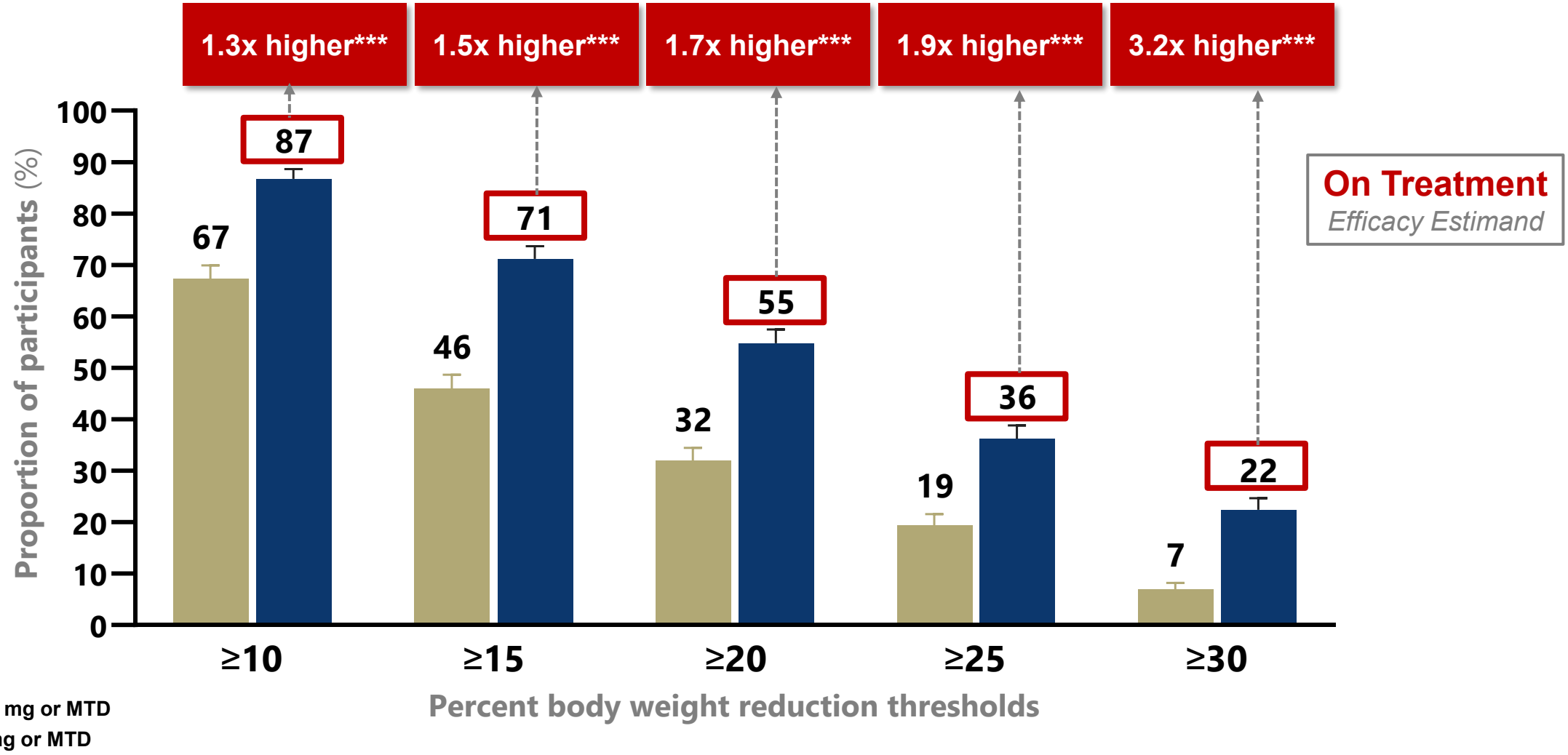
Weight Reduction from Baseline to Week 72: by sex

On Treatment
Efficacy Estimand



***p<0.001 vs semaglutide. Data are LSM ± 95% CI. Weight reduction by sex was not controlled for multiplicity.
Data from Aronne LJ, et al. N Engl J Med 2025; *in press.*

Percent of Participants Reaching Body Weight Reduction Thresholds at Week 72



***p<0.001 vs semaglutide. Error bars indicate standard error (SE). The ≥30% weight reduction threshold was not controlled for multiplicity.
Data from Aronne LJ, et al. N Engl J Med 2025; *in press.*

Treatment Emergent Adverse Events

With ≥5% Frequency in Any Treatment Group *1 of 2*

Parameter	Semaglutide MTD (N=376)	Tirzepatide MTD (N=374)	Total (N=750)
Nausea	167 (44.4)	163 (43.6)	330 (44.0)
Constipation	107 (28.5)	101 (27.0)	208 (27.7)
Diarrhea	88 (23.4)	88 (23.5)	176 (23.5)
Vomiting	80 (21.3)	56 (15.0)	136 (18.1)
COVID-19	47 (12.5)	51 (13.6)	98 (13.1)
Fatigue	46 (12.2)	39 (10.4)	85 (11.3)
Eructation	29 (7.7)	37 (9.9)	66 (8.8)
Injection site reaction	1 (0.3)	32 (8.6)	33 (4.4)
Upper respiratory tract infection	43 (11.4)	32 (8.6)	75 (10.0)
Alopecia	23 (6.1)	31 (8.3)	54 (7.2)

Data are number of participants (%).
Data from Aronne LJ, et al. N Engl J Med 2025; *in press.*

Adverse Events of Special Interest

Parameter	Semaglutide MTD (N=376)	Tirzepatide MTD (N=374)	Total (N=750)
Pancreatitis, adjudication-confirmed	1 (0.3)	0	1 (0.1)
Severe or serious gastrointestinal adverse events	14 (3.7)	17 (4.5)	31 (4.1)
Severe or serious gallbladder diseases	5 (1.3)	4 (1.1)	9 (1.2)
Severe or serious hepatic disorders	0	1 (0.3)	1 (0.1)
Severe or serious arrhythmias and cardiac conductive disorders	1 (0.3)	3 (0.8)	4 (0.5)
Hypoglycemia, blood glucose level <54 mg/dl	1 (0.3)	0	1 (0.1)
Severe or serious acute renal events	0	1 (0.3)	1 (0.1)

In SURMOUNT-5, there were no incidences of:

- Death
- Adjudicated MACE
- Hypoglycemia level 3
- Thyroid malignancies and C-cell hyperplasia
- Severe or serious hypersensitivity events
- Severe or serious injection site reactions
- Severe or serious major depressive disorder, suicidal ideation, or suicidal behaviors

Data are number of participants (%).
Data from Aronne LJ, et al. N Engl J Med 2025; *in press.*

SURMOUNT-5 Key Takeaways

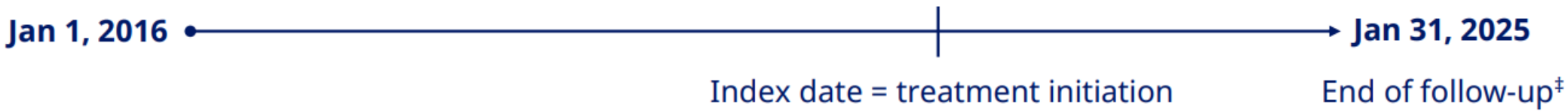
- Over 72 weeks, tirzepatide MTD was statistically and clinically superior to semaglutide MTD for weight reduction
- A higher proportion of participants achieved all weight reduction targets with tirzepatide MTD compared to semaglutide MTD
- Participants on tirzepatide MTD achieved statistically and clinically superior reduction in waist circumference than those on semaglutide MTD
- The overall safety and tolerability profile of tirzepatide and semaglutide in participants with obesity are consistent with the known safety profile of each molecule

STEER Study Design

US Komodo Research Database

Study population

- ≥45 years of age
- Overweight/obesity*
- Established ASCVD†
- Without diabetes
- Initiated semaglutide or tirzepatide on or after May 13, 2022



The propensity score model matched semaglutide and tirzepatide patients 1:1

Primary outcome measures:

- **Revised 3-point MACE:** Myocardial infarction, stroke, and all-cause mortality
- **Revised 5-point MACE:** Myocardial infarction, stroke, hospitalization for heart failure, coronary revascularization, and all-cause mortality

**Defined as body mass index ≥27 kg/m². †Defined as a diagnosis of myocardial infarction or ischemic stroke and/or evidence of peripheral artery disease. ‡End of follow-up for each patient was defined as the earliest of the end of the study period (Jan 31, 2025), end of continuous enrolment, initiation of a non-index GLP-1 or GLP-1/GIP receptor agonist, bariatric surgery, or death.*
ASCVD, atherosclerotic cardiovascular disease; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; MACE, major adverse cardiovascular event.

Wilson L, et al. Presented at the European Society of Cardiology (ESC) Congress together with World Congress of Cardiology; Madrid, Spain; August 29 - September 1, 2025.

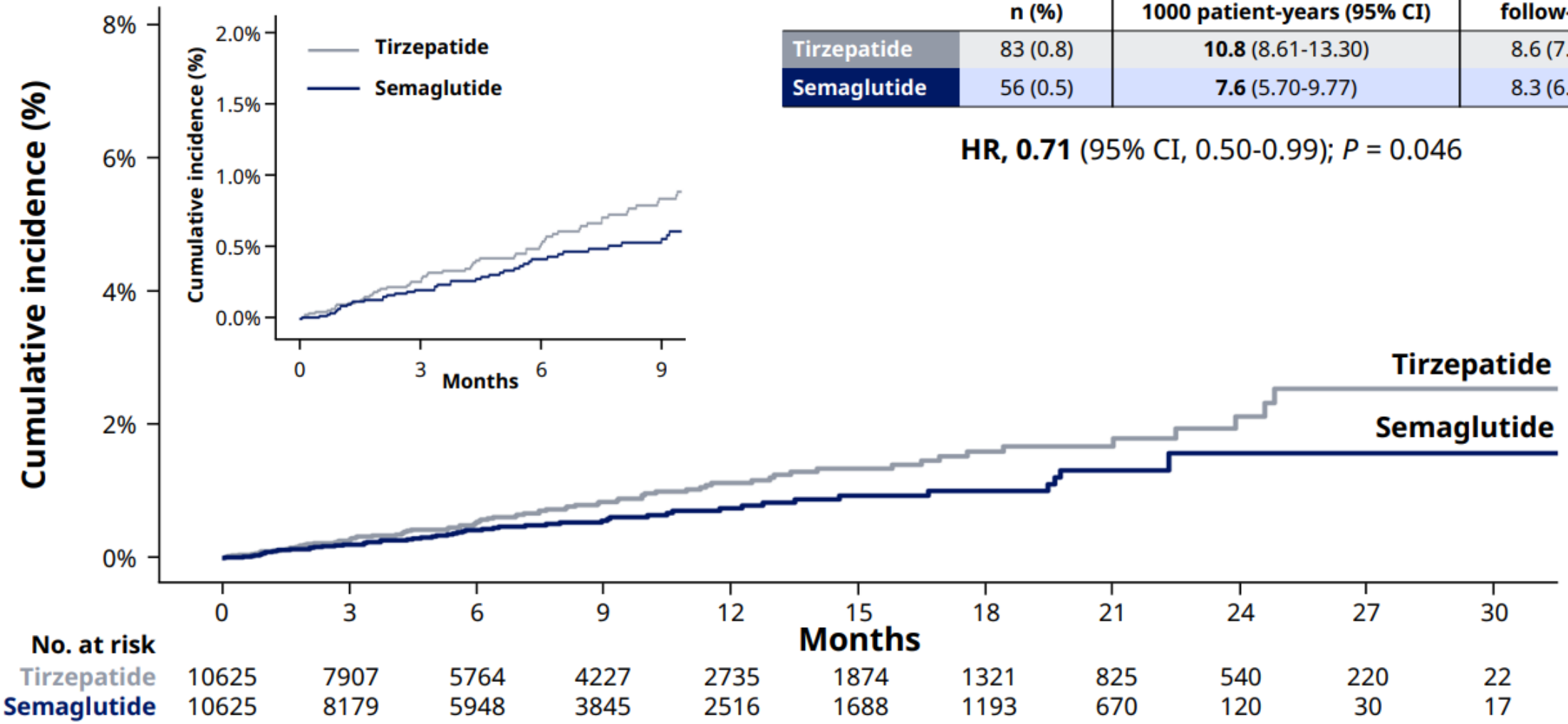
Revised 3-Point MACE*

(ITT Analysis)

The ITT analysis followed patients through the end of follow-up† regardless of persistence on therapy

	Events, n (%)	Incidence rate per 1000 patient-years (95% CI)	Mean (SD) follow-up
Tirzepatide	83 (0.8)	**10.8** (8.61-13.30)	8.6 (7.1)
Semaglutide	56 (0.5)	**7.6** (5.70-9.77)	8.3 (6.4)

HR, 0.71 (95% CI, 0.50-0.99); *P* = 0.046



No. at risk											
Tirzepatide	10625	7907	5764	4227	2735	1874	1321	825	540	220	22
Semaglutide	10625	8179	5948	3845	2516	1688	1193	670	120	30	17

**Revised 3-pont MACE includes myocardial infarction, stroke, and all-cause mortality. †End of follow-up was defined as the earliest of the end of the study period (Jan 31, 2025), end of continuous enrolment, initiation of a non-index GLP-1 or GLP-1/GIP receptor agonist, bariatric surgery, or death.*

CI, confidence interval; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HR, hazard ratio; ITT, intention to treat; MACE, major adverse cardiovascular event; SD, standard deviation.

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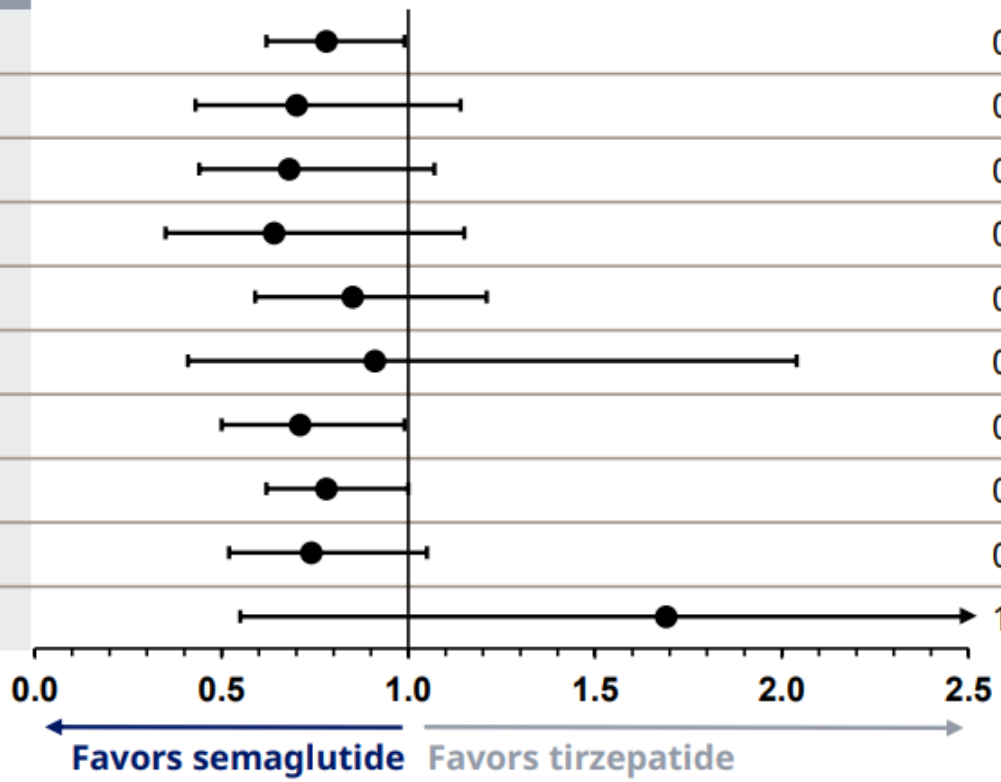
MACE Outcomes

(ITT Analysis)

	Incidence rate per 1000 patient-years		HR (95% CI)	*P* value
	Semaglutide	Tirzepatide		
Revised 5-point MACE*	16.7	21.0	0.78 (0.62-0.99)	**0.040**
Myocardial infarction	3.8	5.4	0.70 (0.43-1.14)	0.149
Heart failure	4.3	6.1	0.68 (0.44-1.07)	0.097
Stroke	2.4	3.9	0.64 (0.35-1.15)	0.135
Coronary revascularization	7.6	8.7	0.85 (0.59-1.21)	0.362
All-cause mortality	1.5	1.7	0.91 (0.41-2.04)	0.820
Revised 3-point MACE†	7.6	10.8	0.71 (0.50-0.99)	**0.046**
5-point MACE‡	16.3	20.4	0.78 (0.62-1.00)	**0.046**
3-point MACE§	7.2	9.8	0.74 (0.52-1.05)	0.091
CV-related mortality	1.1	0.7	1.69 (0.55-5.19)	0.358



**Revised 5-pont MACE includes myocardial infarction, stroke, hospitalization for heart failure, coronary revascularization, and all-cause mortality. †Revised 3-point MACE includes myocardial infarction, stroke, and all-cause mortality. ‡5-point MACE includes myocardial infarction, heart failure, stroke, coronary revascularization, and CV-related mortality. §3-point MACE includes myocardial infarction, stroke, and CV-related mortality.*
CI, confidence interval; CV, cardiovascular; HR, hazard ratio; ITT, intention to treat; MACE, major adverse cardiovascular event.

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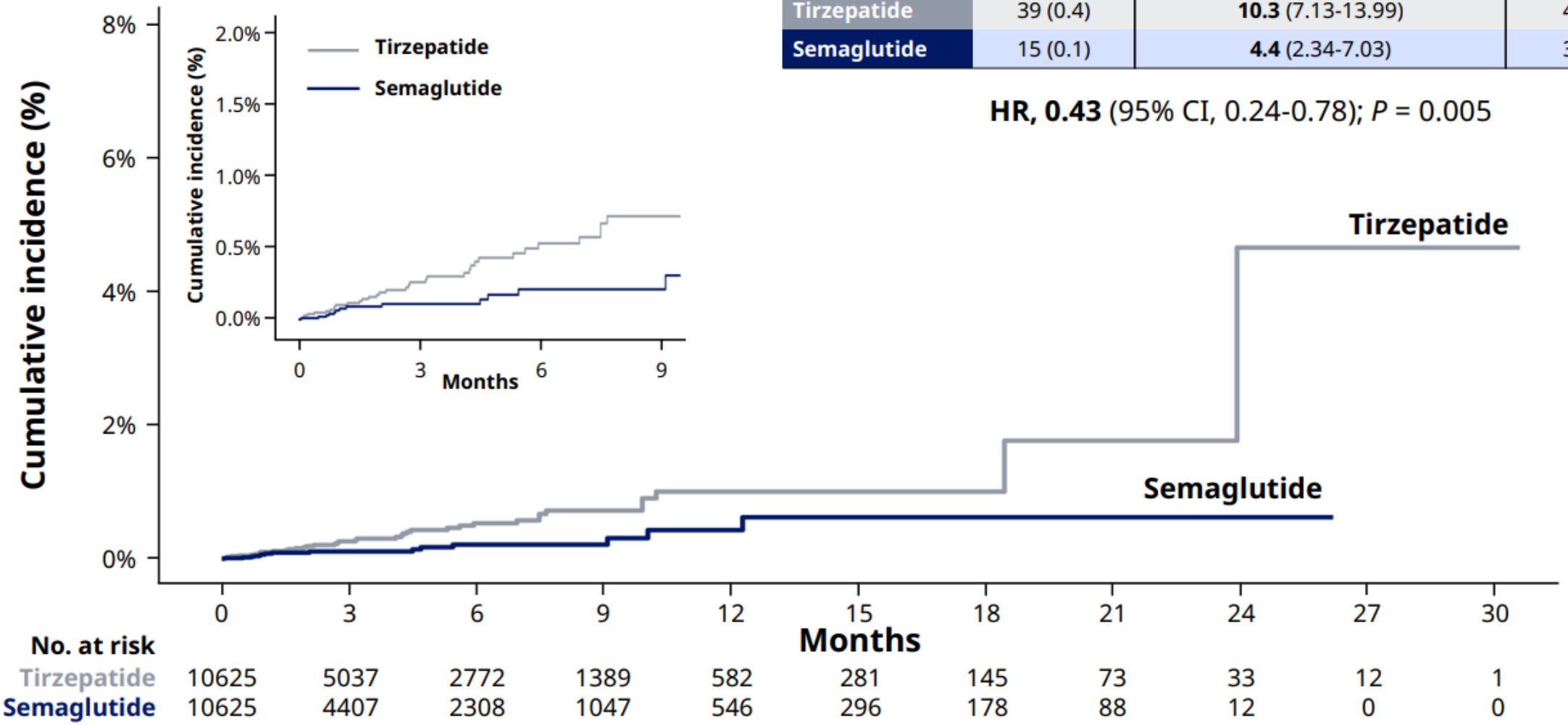
Revised 3-Point MACE*

(Per-Protocol Analysis)

Per-protocol sensitivity analysis censored patients at treatment discontinuation (gap in therapy >30 days)

	Events, n (%)	Incidence rate per 1000 patient-years (95% CI)	Mean (SD) follow-up
Tirzepatide	39 (0.4)	**10.3** (7.13-13.99)	4.3 (4.2)
Semaglutide	15 (0.1)	**4.4** (2.34-7.03)	3.8 (4.1)

HR, 0.43 (95% CI, 0.24-0.78); *P* = 0.005



No. at risk											
Tirzepatide	10625	5037	2772	1389	582	281	145	73	33	12	1
Semaglutide	10625	4407	2308	1047	546	296	178	88	12	0	0

**Revised 3-pont MACE includes myocardial infarction, stroke, and all-cause mortality.*
CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; SD, standard deviation.

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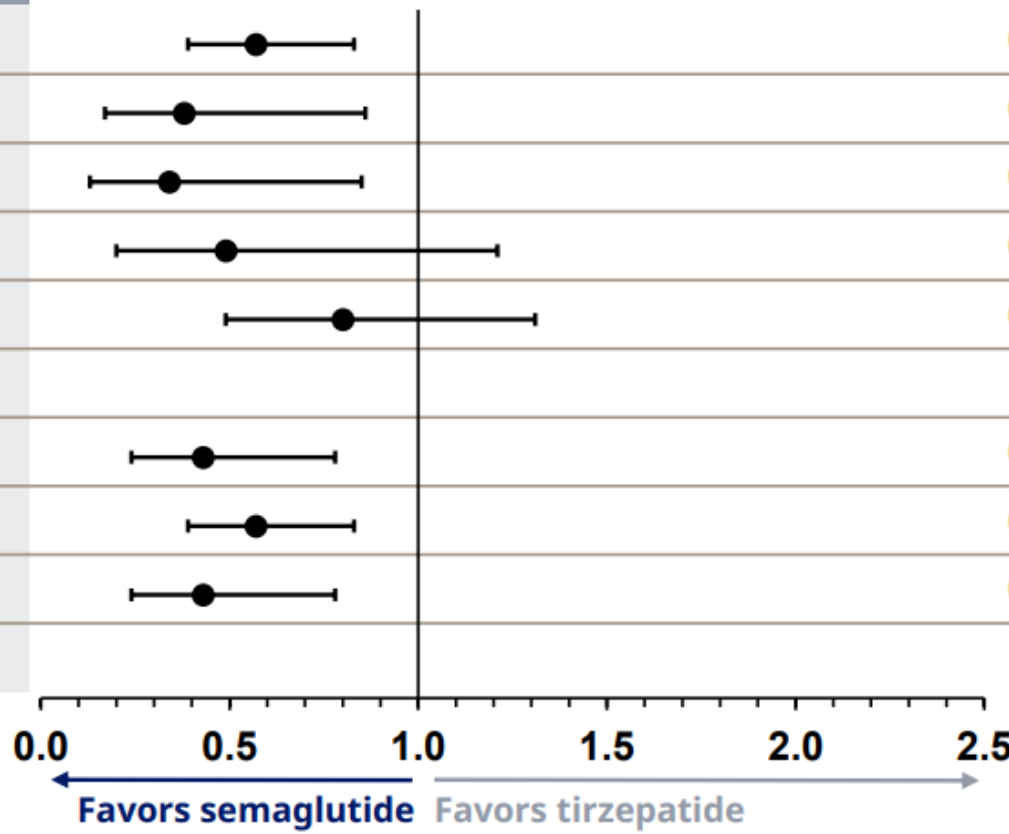
MACE Outcomes

(Per-Protocol Analysis)

0 mortality events were reported, resulting in equivalent traditional MACE (CV-related mortality) and revised MACE (all-cause mortality) outcomes

	Incidence rate per 1000 patient-years		HR (95% CI)	*P* value
	Semaglutide	Tirzepatide		
Revised 5-point MACE*	12.3	21.1	0.57 (0.39-0.83)	**0.003**
Myocardial infarction	2.3	6.1	0.38 (0.17-0.86)	**0.019**
Heart failure	1.8	5.0	0.34 (0.13-0.85)	**0.020**
Stroke	2.1	4.2	0.49 (0.20-1.21)	0.122
Coronary revascularization	7.9	9.8	0.80 (0.49-1.31)	0.374
All-cause mortality†	0	0	–	–
Revised 3-point MACE‡	4.4	10.3	0.43 (0.24-0.78)	**0.005**
5-point MACE§	12.3	21.1	0.57 (0.39-0.83)	**0.003**
3-point MACE‖	4.4	10.3	0.43 (0.24-0.78)	**0.005**
CV-related mortality	0	0	–	–



Revised 5-pont MACE includes myocardial infarction, stroke, hospitalization for heart failure, coronary revascularization, and all-cause mortality. †No mortality was reported in the per-protocol analysis. ‡Revised 3-point MACE includes myocardial infarction, stroke, and all-cause mortality. §5-point MACE includes myocardial infarction, heart failure, stroke, coronary revascularization, and CV-related mortality. ‖3-point MACE includes myocardial infarction, stroke, and CV-related mortality. CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event.

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Conclusions

From the STEER Real-World Study

In this real-world study of US patients with overweight or obesity and ASCVD but without diabetes, the primary endpoint demonstrated **a lower risk of CV events with semaglutide compared with tirzepatide**

Our findings support growing evidence that the established **CV benefit of semaglutide is molecule specific** and cannot be generalized to the GLP-1 or GIP/GLP-1 receptor agonist classes

Significantly lower risk of revised 3-point MACE with semaglutide vs tirzepatide

29%

ITT analysis
7.6 vs 10.8 incidence per 1000 patient-years
HR, 0.71; *P* = 0.046

57%

Per-protocol analysis
4.4 vs 10.3 incidence per 1000 patient-years
HR, 0.43; *P* = 0.005

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HR, hazard ratio; ITT, intention to treat; MACE, major adverse cardiovascular event.

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Conclusion

- Tirzepatide: more weight loss
- Semaglutide: cardiovascular outcome data
- Maximum tolerable dose
- Maximum affordable dose
- Slow and steady wins the race