Efficacy and Safety of Semaglutide 7.2 mg in Obesity: The STEP UP Trial

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Presenter disclosure

Sean Wharton reports the following:

- Payment or honoraria from AstraZeneca, Bausch Health Canada, Boehringer Ingelheim, Eli Lilly, Metsera, Neurogastrix, Novo Nordisk, and Regeneron Pharmaceuticals for academic talks to colleagues
- Provision of medical writing support from AstraZeneca, Boehringer Ingelheim, Bausch Health Canada, Eli Lilly, and Novo Nordisk
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Introduction

- Once-weekly subcutaneous semaglutide 2.4 mg, a GLP-1RA, was investigated in the global phase 3 Semaglutide Treatment Effect in People with obesity (STEP) program[1]
- Semaglutide 2.4 mg is FDA-approved for weight management in people with overweight/obesity and for risk reduction of MACE in people with overweight/obesity with established CV disease[2]
- In the STEP 1 trial, semaglutide 2.4 mg provided a 14.9% reduction in body weight at week 68, vs 2.4% with placebo, and was well tolerated[3]

- Despite the efficacy of semaglutide 2.4 mg, some individuals do not reach their weight management goals and could potentially benefit from **intensification of treatment**
- An **increased dose** of semaglutide, **7.2 mg**, was therefore assessed in the **STEP UP trial**[4]

CV, cardiovascular; FDA, Food and Drug Administration; GLP-1RA, glucagon-like peptide-1 receptor agonist; MACE, major adverse cardiovascular events.
1. Kushner RF et al. Obesity (Silver Spring) 2020;28:1050–1061; 2. US FDA. Wegovy (semaglutide) Prescribing Information. 2024; 3. Wilding JPH et al. N Engl J Med 2021;384:989; 4. ClinicalTrials.gov NCT05646706. https://clinicaltrials.gov/study/NCT05646706 (accessed April 2025).

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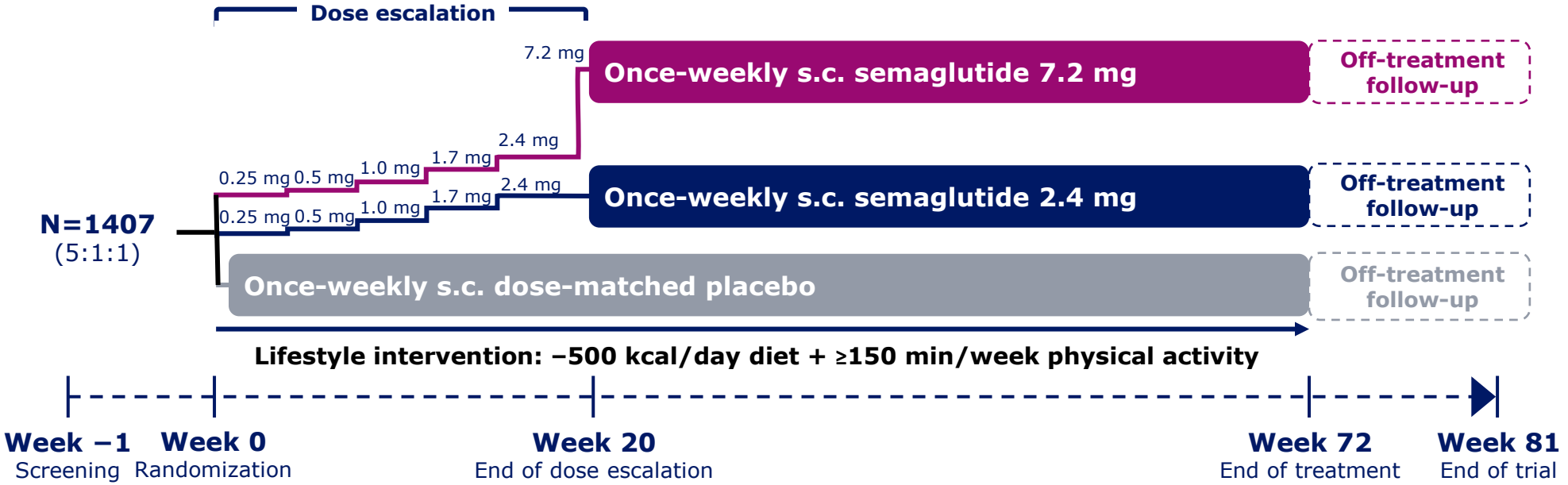
STEP UP trial design

72-week, randomized, double-blind, multicenter, placebo-controlled trial



95 sites in 11 countries (Bulgaria, Canada, Germany, Greece, Hungary, Norway, Poland, Portugal, Slovakia, South Africa, USA)

Key inclusion criteria

- Adults with BMI ≥30 kg/m^2
- Without T2D (HbA_{1c} <6.5%)

Co-primary endpoints*	• Change in body weight (%) • Proportion of participants achieving ≥5% WL
Confirmatory secondary endpoints	• Proportion of participants achieving ≥10%, ≥15%, ≥20%, and ≥25% WL* • Change in waist circumference (cm)* • Change in body weight (%)† • Proportion of participants achieving ≥20% and ≥25% WL†

**Semaglutide 7.2 mg vs placebo; †Semaglutide 7.2 mg vs 2.4 mg. The trial was designed in a double-blind manner with respect to active versus placebo treatment as well as semaglutide dose. BMI, body mass index; HbA_{1c}, glycated hemoglobin; N, number of participants; s.c., subcutaneous; T2D, type 2 diabetes; WL, weight loss.*

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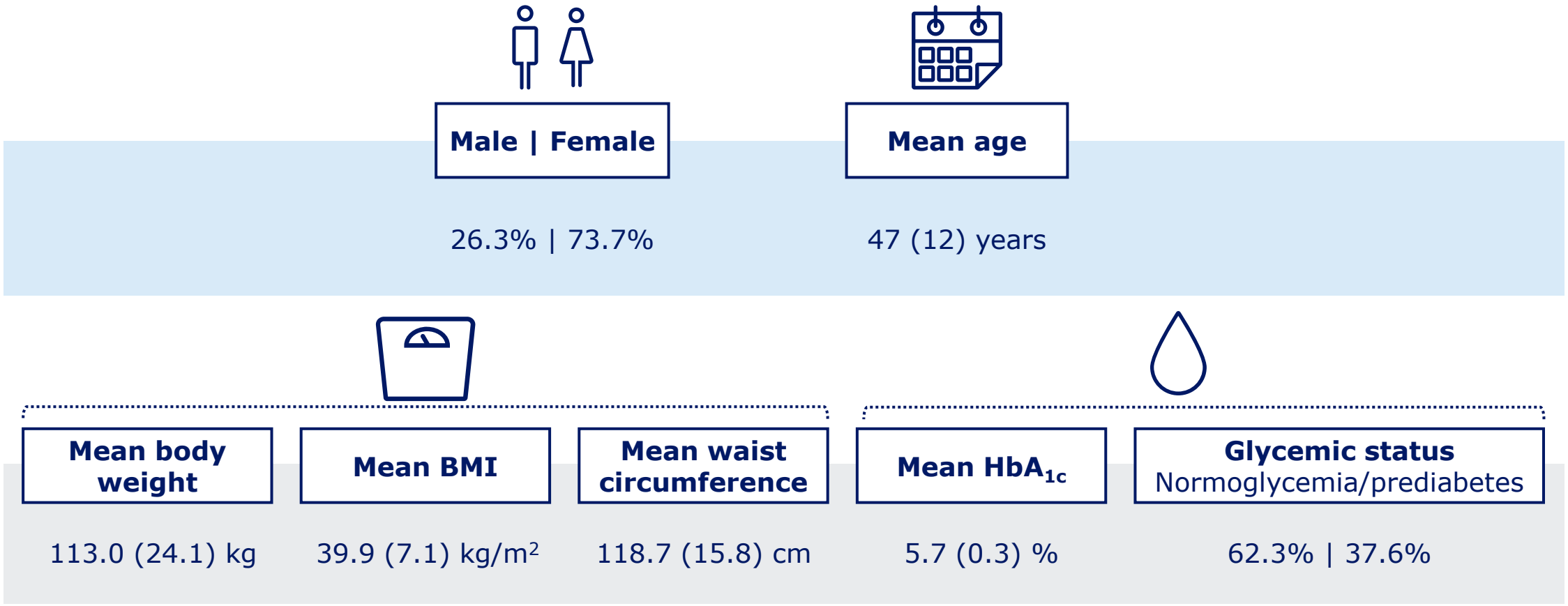
Demographics and baseline characteristics



Data are mean (standard deviation), unless otherwise stated.
BMI, body mass index; HbA_{1c}, glycated hemoglobin.

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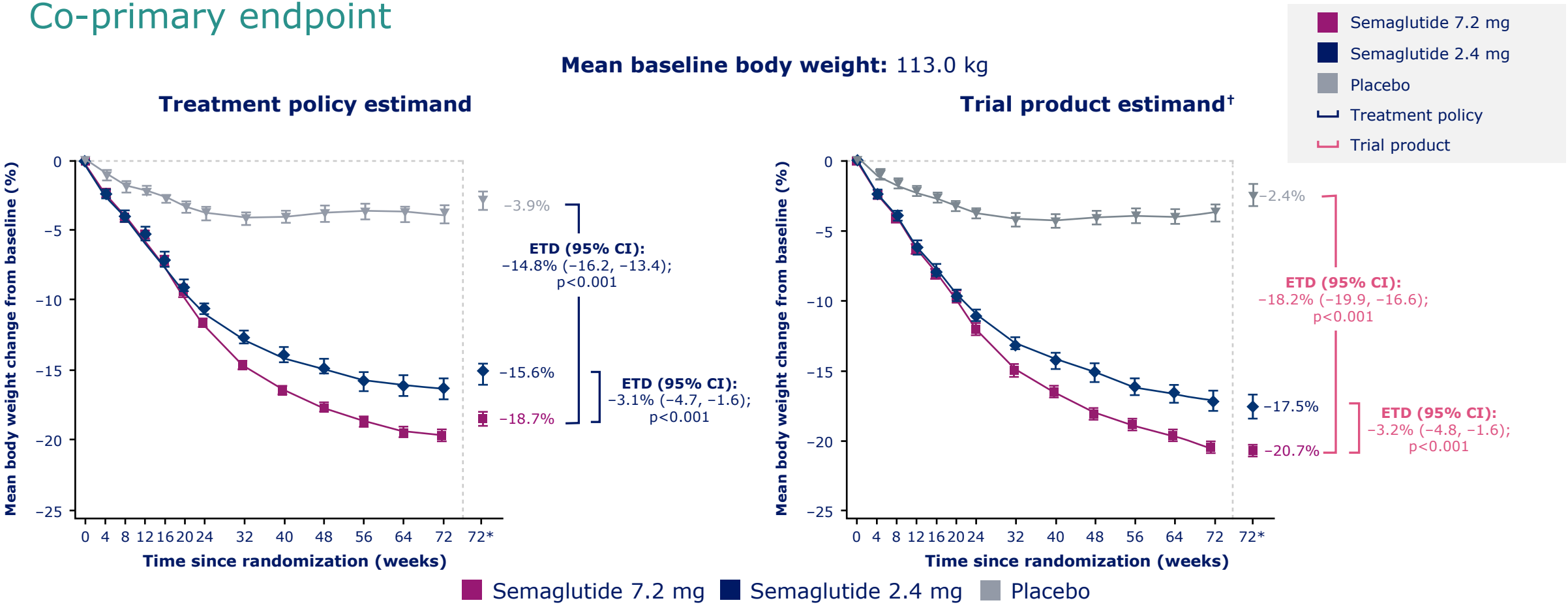
Change in body weight (%)

Co-primary endpoint

Mean baseline body weight: 113.0 kg



Observed data are for the full analysis set for the in-trial observation period (treatment policy estimand) or the on-treatment observation period (trial product estimand). Estimated data are for the treatment policy estimand (primary analysis; effect regardless of treatment discontinuation or rescue medication use) or the trial product estimand (effect in all participants treated as intended). Error bars are ± standard errors. Among those who completed treatment (semaglutide 7.2 mg, n=887; semaglutide 2.4 mg, n=177; placebo, n=142), 75.4% of participants randomized to semaglutide 7.2 mg received the final dose of 7.2 mg, 89.3% randomized to semaglutide 2.4 mg received the final dose of 2.4 mg, and 96.5% randomized to placebo received the equivalent of the final dose of 7.2 mg at week 72.

**Estimated means. †Anti-obesity medication and/or bariatric surgery was received by 1.4% (n=14), 1.5% (n=3), and 9% (n=18) of participants receiving semaglutide 7.2 mg, semaglutide 2.4 mg, and placebo, respectively.*

CI, confidence interval; ETD, estimated treatment difference.

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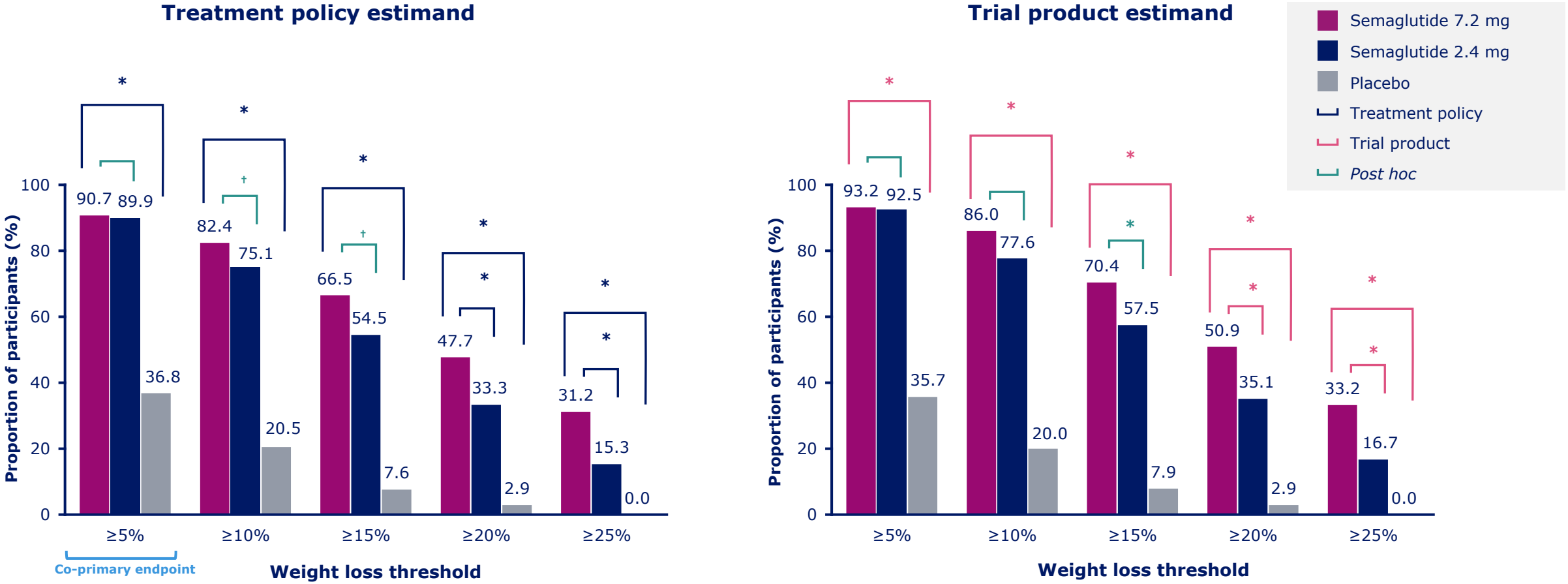
Categorical weight loss at week 72

Co-primary and confirmatory secondary endpoints



Observed data are for the full analysis set for the in-trial observation period (treatment policy estimand) or the on-treatment observation period (trial product estimand). Estimated data are for the treatment policy estimand (primary analysis; effect regardless of treatment discontinuation or rescue medication use) or the trial product estimand (effect in all participants treated as intended). Comparisons of semaglutide 7.2 mg vs 2.4 mg for the ≥5%, ≥10%, and ≥15% weight loss thresholds are post hoc.
**p<0.001 for the odds ratio. †p<0.05 for the odds ratio.*

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Adverse event overview

AE, n (%)	Semaglutide 7.2 mg (n=1004)	Semaglutide 2.4 mg (n=201)	Placebo (n=201)
All AEs	878 (87.5)	169 (84.1)	156 (77.6)
Mild	805 (80.2)	154 (76.6)	136 (67.7)
Moderate	506 (50.4)	97 (48.3)	73 (36.3)
Severe	81 (8.1)	21 (10.4)	9 (4.5)
Serious AEs	68 (6.8)	22 (10.9)	11 (5.5)
AEs leading to dose reduction	186 (18.5)	25 (12.4)	1 (0.5)
AEs leading to permanent discontinuation	54 (5.4)	8 (4.0)	2 (1.0)
Fatal AEs (IT)	0	0	0
Hypoglycemia events	3 (0.3)	2 (1.0)	0
Mild	3 (0.3)	2 (1.0)	0
Gastrointestinal AEs	711 (70.8)	123 (61.2)	86 (42.8)
Skin and subcutaneous tissue disorders	216 (21.5)	31 (15.4)	13 (6.5)
Nervous system disorders	309 (30.8)	39 (19.4)	28 (13.9)
Dysesthesia*	230 (22.9)	12 (6.0)	1 (0.5)

Dysesthesia AE, n (%)*	Semaglutide 7.2 mg (n=1004)	Semaglutide 2.4 mg (n=201)	Placebo (n=201)
All AEs	230 (22.9)	12 (6.0)	1 (0.5)
Mild	177 (77.0)	9 (75.0)	1 (100)
Moderate	67 (29.1)	3 (25.0)	0
Severe	8 (3.5)	0	0
Serious AEs	0	0	0
AEs leading to dose reduction	47 (20.4)	2 (16.7)	0
AEs leading to temporary discontinuation	17 (7.4)	0	0
AEs leading to permanent discontinuation	4 (1.7)	0	0
Recovered	197 (85.7)	10 (83.3)	1 (100)

Data are for the safety analysis set and are from the on-treatment observation period, unless otherwise stated.
**Proportions are expressed in terms of participants who experienced dysesthesia, except for "all events." Dysesthesia AEs were identified by a pre-defined MedDRA search (version 27.1) and included AEs with preferred terms of allodynia, burning sensation, dysesthesia, hyperesthesia, hyperpathia, pain of skin, paresthesia, sensitive skin, skin burning sensation, skin discomfort, and skin sensitization.*
AE, adverse event; IT, in-trial; MedDRA, Medical Dictionary for Regulatory Activities.

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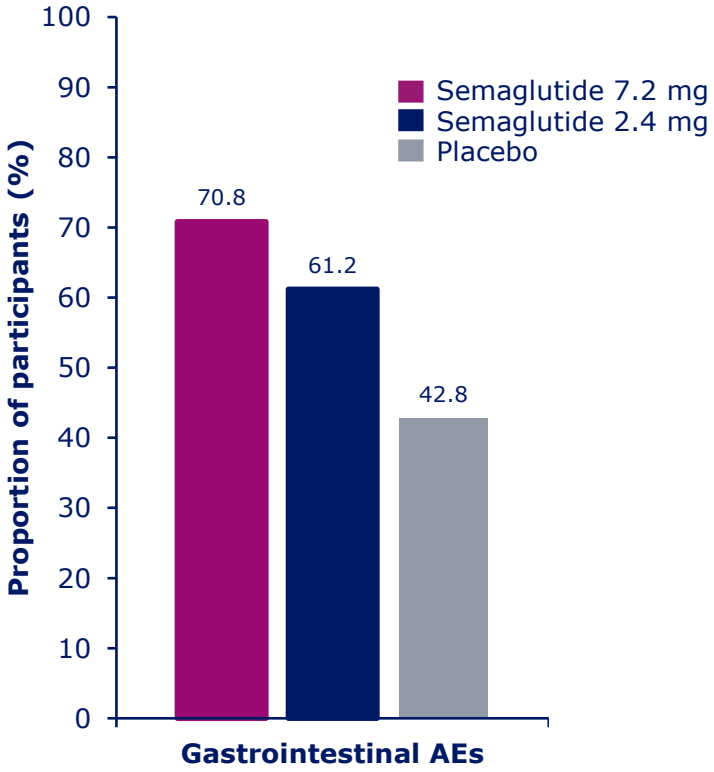
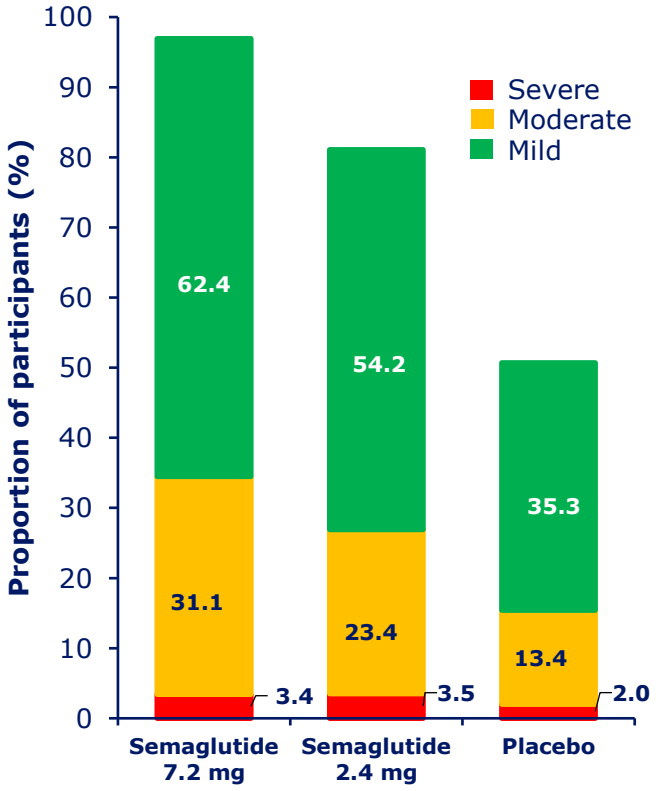
Gastrointestinal adverse events

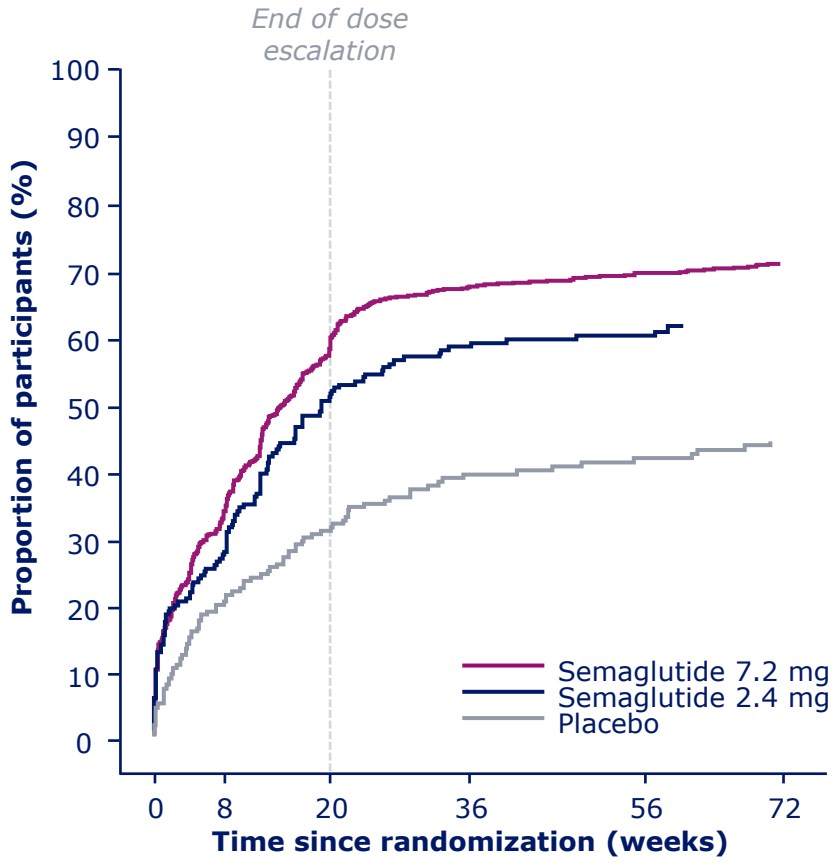
Proportion of participants with GI AEs, %



Proportion of participants with GI AEs by severity, %



Time to onset of first GI AE



Data are for the safety analysis set and are from the on-treatment observation period. Gastrointestinal AEs were identified by a pre-defined MedDRA search (version 27.1) and included AEs with preferred terms encompassing, but not limited to, nausea, vomiting, diarrhea and constipation. The grey line at week 20 indicates the last stage of dose escalation for participants receiving semaglutide 7.2 mg.
AE, adverse event; GI, gastrointestinal; MedDRA, Medical Dictionary for Regulatory Activities.

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Conclusions

In adults with obesity, **semaglutide 7.2 mg was superior to placebo** with respect to change in body weight (treatment policy estimand: −18.7% vs −3.9%; trial product estimand: −20.7% vs −2.4%, respectively), and achievement of body weight reductions up to ≥25%

Semaglutide 7.2 mg was also **superior to semaglutide 2.4 mg** with respect to change in body weight and achievement of higher magnitude body weight reductions of ≥20% and ≥25%

Overall, the **safety and tolerability** profiles of the semaglutide doses were **similar** to the GLP-1RA therapeutic class

The rate of gastrointestinal and dysesthesia AEs were higher with semaglutide 7.2 mg versus 2.4 mg and placebo. Most events were mild to moderate in severity, and most dysesthesia AEs recovered while on treatment

The results from STEP UP support a **favorable benefit–risk profile** of semaglutide 7.2 mg for weight management in individuals with obesity

AE, adverse event; GLP-1RA, glucagon-like peptide-1 receptor agonist.

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