Semaglutide Treatment Effect in People with Obesity: STEP Program

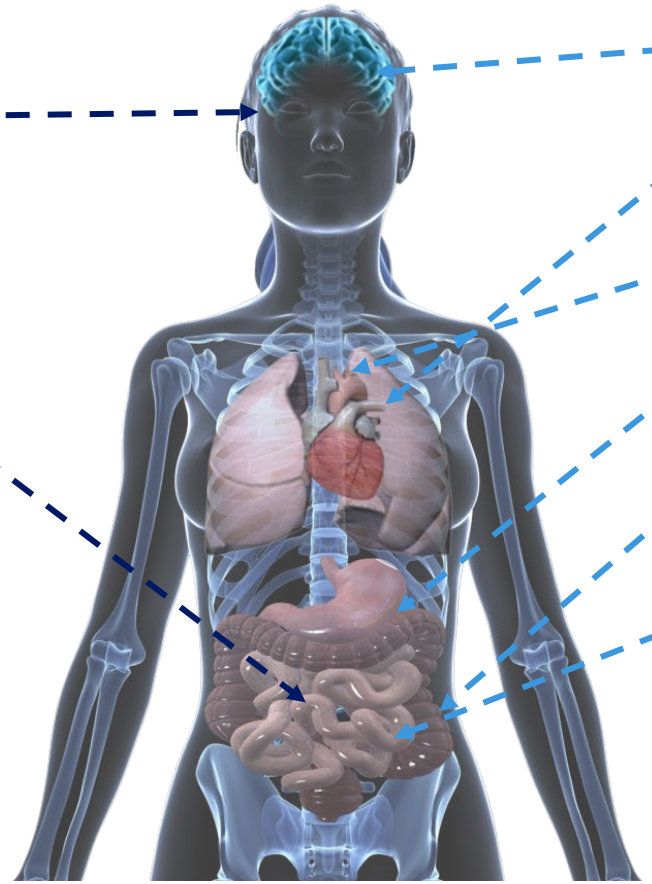
Phase 3 program overview: Chronic Weight Management Studies

GLP-1 secretion and receptor expression

GLP-1 is synthesized and secreted by:

Neurons in hindbrain[1]

L-cells of the gut[3]



GLP-1R is expressed in:

- Brain[2]
- Lungs[3]
- Heart (AV node) [3,4]
- Pancreas[3]
- Kidney[3]
- GI tract[3]

GLP-1R is **not expressed** in the liver[7]

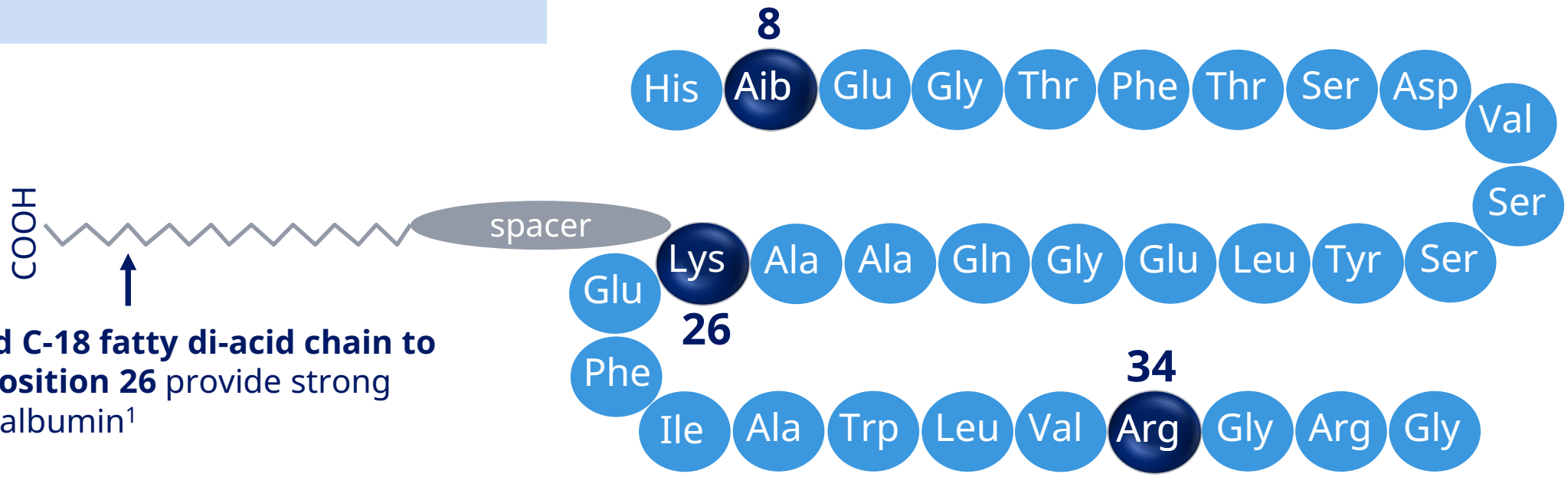
AV, atrioventricular; GI, gastrointestinal; GLP-1R, glucagon-like peptide-1 receptor.

1. Trapp S et al Curr Opin Pharmacol. 2013 Dec;13(6):964-9; 2. Farr OM et al Diabetologia. 2016 May;59(5):954-65; 3. Baggio LL and Drucker D. Gastroenterology. 2007; 132(6): 2131–57; 4. Baggio LL et al Endocrinology. 2018 Apr 1;159(4):1570-1584; 5. Asmar A et al J Clin Endocrinol Metab. 2019 Jul 1;104(7):2509-2519; 6. Drucker DJ et al Cell Metab. 2016 Jul 12;24(1):15-30; 7. Newsome PN et al J Hepatol. 2023 Dec;79(6):1557-1565

Semaglutide is a human GLP-1 analog

- **94%** homology to human GLP-1[1]
- $t_{½}$ of approximately **1 week**[2]

Amino acid substitution at position 8
(alanine to alpha-aminoisobutyric acid)
protects against DPP-4 degradation[1]



Spacer and C-18 fatty di-acid chain to lysine in position 26 provide strong binding to albumin[1]

Amino acid substitution at position 34
(lysine to arginine) prevents C-18 fatty di-acid binding at the wrong site[1]

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; t½, half-life.
1.Kapitza C et al. J Clin Pharmacol. 2015; 55(5): 497–504; 2.Lau J et al. J Med Chem. 2015; 58(18): 7370–80

Phase 3 program

The primary endpoint for the following STEP trials was **weight reduction**

STEP was the phase 3a/3b clinical development program for subcutaneous semaglutide 2.4 mg weekly for obesity management

STEP 1–4
Phase 3a

Semaglutide 2.4 mg

68 weeks + 7 week follow-up

The treatment period in the following STEP trials was followed by a 7-week period off treatment to account for the long half-life of semaglutide

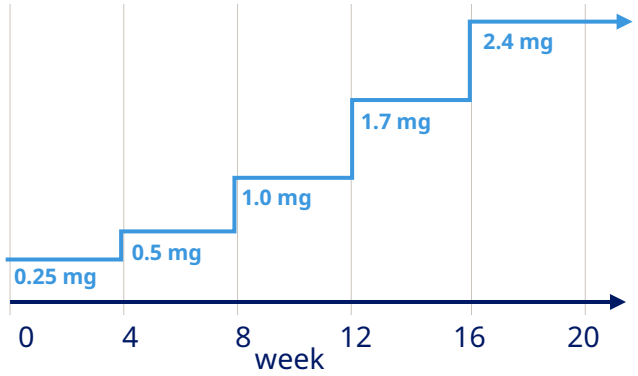
STEP 5
Phase 3b

Semaglutide 2.4 mg

104 weeks + 7 week follow-up

Dose escalation

Semaglutide 2.4 mg OW treatment is initiated at 0.25 mg, followed by increments every 4 weeks to 0.5, 1.0, 1.7, and 2.4 mg OW



Across the STEP program

Treatment with semaglutide 2.4 mg OW was compared to placebo, as an adjunct to lifestyle intervention

STEP 3

In STEP 3 only, lifestyle intervention consisted of IBT, an initial 8-week low-energy diet and higher target for physical activity

STEP 6 Evaluation of Semaglutide 2.4 and 1.7 mg in East Asian Adults with Obesity or Overweight with/without T2D

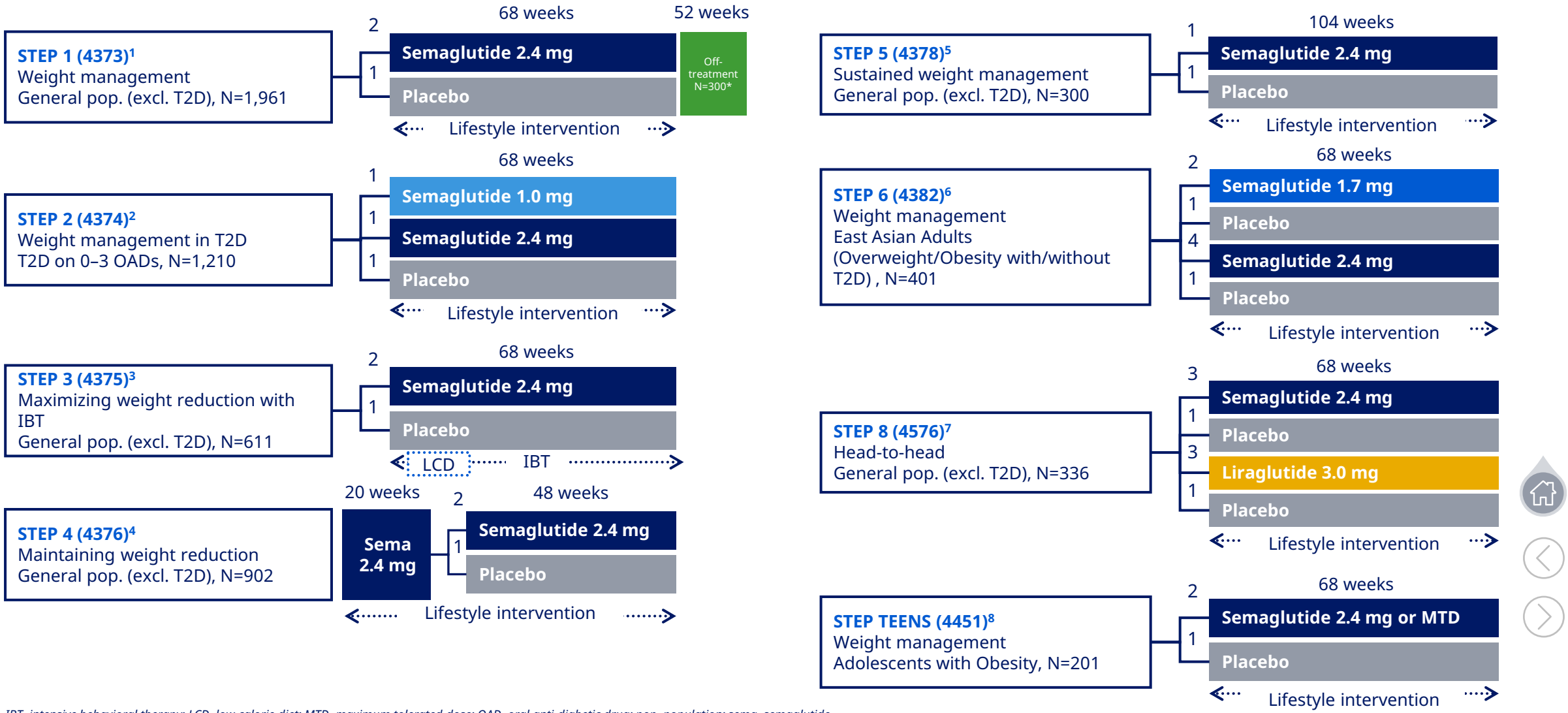
STEP 8 Head-to-head vs liraglutide

STEP TEENS Weight Management in Adolescents with Obesity

CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction; IBT, intensive behavioral therapy; MRCT, multiregional clinical trial; OA, osteoarthritis; OW, once-weekly.

1. Novo Nordisk. Data on file.

STEP program at a glance: Chronic Weight Management Trials



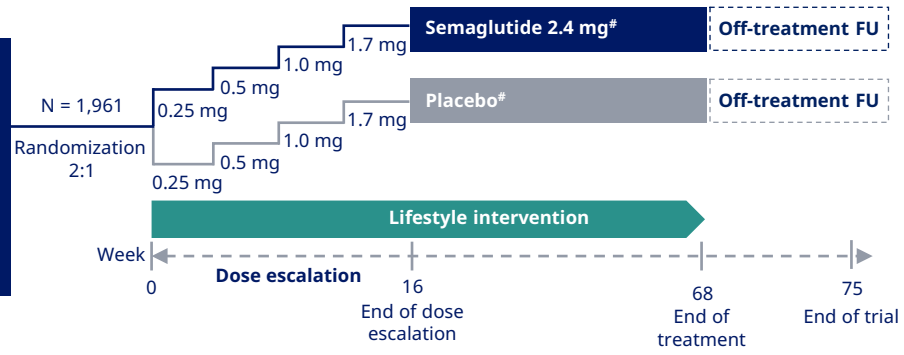
IBT, intensive behavioral therapy; LCD, low-calorie diet; MTD, maximum tolerated dose; OAD, oral anti-diabetic drug; pop, population; sema, semaglutide.

1. Wilding JPH et al. New Engl J Med. 2021 384:989–1002 2. Davies M et al. Lancet. 2021; 397:971–84; 3. Wadden TA et al. JAMA. 2021;325:1403–13; 4. Rubino D et al. JAMA. 2021; 325:1414–25; 5. Garvey et al. Nat Med 28, 2083–2091 (2022); 6. Kadowaki T et al. Lancet Diabetes Endocrinol 2022; 20(3):193–206; 7. Rubino et al. JAMA. 2022; 327:138–150; 8. Weghuber et al. N Engl J Med 2022;387:2245–2257

STEP 1

Trial Design

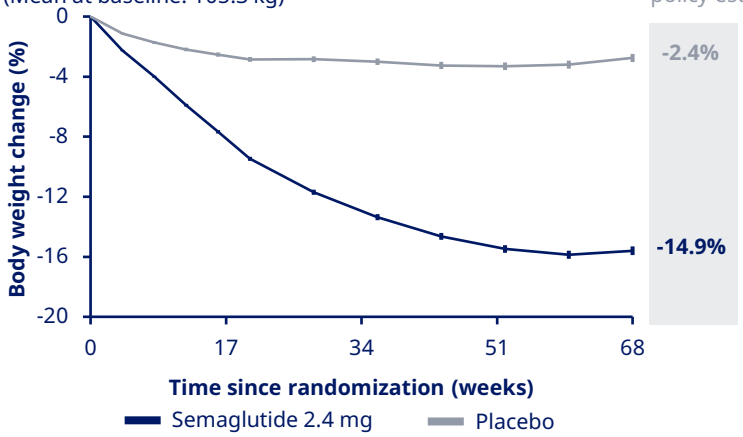
- BMI ≥30 or ≥27 kg/m² and ≥1 comorbidity
- ≥1 prior weight reduction attempt via D&E
- HbA_{1c} ≤ 6.5%



Co-Primary Endpoint

Observed body weight change over time*

(Mean at baseline: 105.3 kg)



Treatment policy estimand

-2.4%

-14.9%

86.4% achieved **≥5% weight reduction** in Semaglutide 2.4 mg arm

31.5% achieved **≥5% weight reduction** in Placebo arm

Objective

To evaluate the efficacy and safety of once-weekly subcutaneous semaglutide 2.4 mg versus placebo for body weight management in adults with overweight or obesity over 68 weeks

Key Secondary Efficacy Endpoints†

	Semaglutide 2.4 mg vs Placebo (68 weeks)	Treatment comparison Semaglutide 2.4 mg vs Placebo (68 weeks)
≥10% weight reduction	69.1% vs 12.0%	**OR 14.7** [11.1 to 19.4], P<0.001
≥15% weight reduction	50.5% vs 4.9%	**OR 19.3** [12.9 to 28.8], P<0.001
Waist Circumference (cm)	-13.54 cm vs -4.13 cm	**ETD -9.42 cm** [-10.30 to -8.53], P<0.001
Systolic blood pressure (mm Hg)	-6.16 mm Hg vs -1.06 mm Hg	**ETD -5.10 mm Hg** [–6.34 to –3.87], P<0.001
SF-36 physical functioning	2.21 vs 0.41	**ETD 1.80** [1.18 to 2.42], P<0.001
C-reactive protein	0.47 vs 0.85	**ETD 0.56** [0.51 to 0.61]

Safety

	Semaglutide 2.4 mg n=1306 (68 weeks)	Placebo n=655 (68 weeks)
Total AEs	89.7% (n=1171)	86.4% (n=566)
GI AEs	74.2% (n=969)	47.9% (n=314)
Serious AEs	9.8% (n=128)	6.4% (n=42)
Discontinuations d/t AEs	7.0% (n=92)	3.1% (n=20)
Discontinuations d/t GI AEs	4.5% (n=59)	0.8% (n=5)
AEs in ≥10% of patients	Nausea, Diarrhea, Vomiting, Constipation, Nasopharyngitis, Headache, Dyspepsia, Abdominal pain, and Upper Respiratory tract infection	

- The most common AEs were gastrointestinal in nature, including nausea, diarrhea, and vomiting
- Majority of the GI AEs were mild to moderate in severity & transient

Conclusion

Semaglutide 2.4 mg, as an adjunct to diet and exercise counselling, resulted in a mean weight reduction of 14.9%, compared to 2.4% with placebo, in participants with obesity or overweight and without diabetes. Safety AE profile consistent with the GLP-1 RA class.

*#Subcutaneous and once weekly, as an adjunct to lifestyle intervention (-500 kcal/day diet + 150 min/week physical activity); *In-trial; †95% CI; Error bars are +/- standard error of the mean; AEs, adverse events; BMI, body mass index; BW, body weight; CI, confidence interval; D&E, diet and exercise; ETD, estimated treatment difference (for the treatment policy estimand); ETR, estimated treatment ratio; FU, follow-up; GI, gastrointestinal; GLP1-RA, glucagon like peptide1 receptor agonist; HbA_{1c}, glycated haemoglobin; OW, once-weekly; OR, odds ratio; SF-36, short form 36-item health survey*

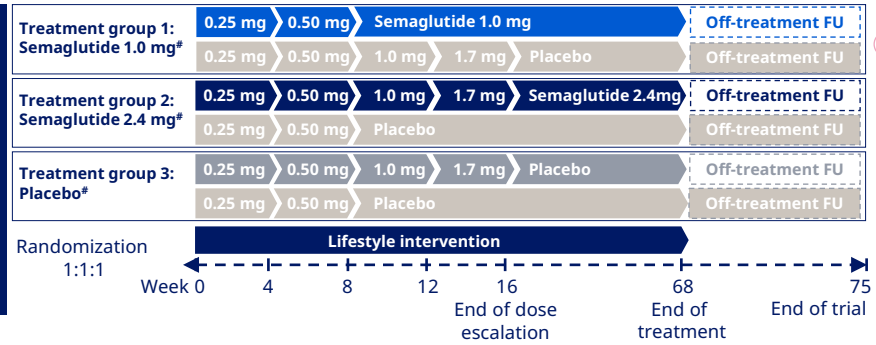
Wilding et al. N Engl J Med 2021;384:989-1002

STEP 2

Trial Design

Key inclusion criteria

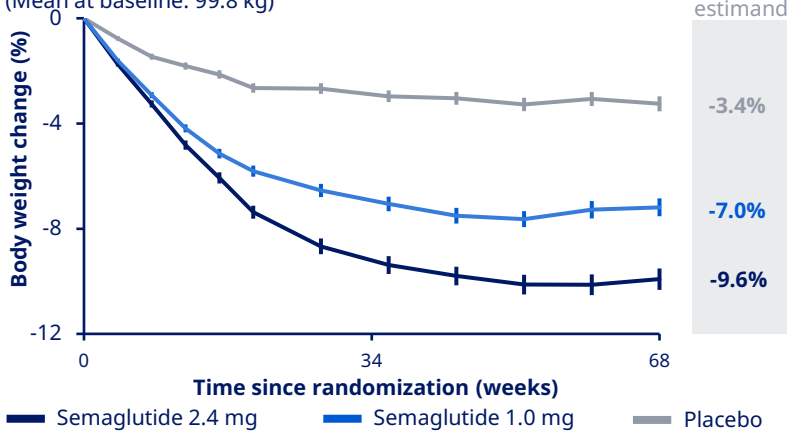
- BMI ≥27 kg/m² and ≥1 comorbidity
- D&E alone or up to 3 OADs
- Presence of T2D with HbA_{1c} 7-10%



Co-Primary Endpoint

Observed body weight change over time*

(Mean at baseline: 99.8 kg)



Treatment policy estimand

-3.4%

-7.0%

-9.6%

68.8% achieved **≥5% weight reduction** in Semaglutide 2.4 mg arm

57.1% achieved **≥5% weight reduction** in Semaglutide 1.0 mg arm

28.5% achieved **≥5% weight reduction** in Placebo arm

Objective

To evaluate the efficacy and safety of once-weekly subcutaneous semaglutide 2.4 mg versus semaglutide 1.0 mg and placebo for body weight management in adults with overweight or obesity and type 2 diabetes over 68 weeks

Key Secondary Efficacy Endpoints†

	Semaglutide 2.4 mg vs Semaglutide 1.0 mg vs Placebo	Treatment comparison Semaglutide 2.4 mg vs Placebo (68 weeks)
≥10% weight reduction	45.6% vs 28.7% vs 8.2%	**OR 7.41** [4.89 to 11.24], P<0.0001
≥15% weight reduction	25.8% vs 13.7% vs 3.2%	**OR 7.65** [4.11 to 14.22], P<0.0001
Waist Circumference (cm)	-9.4 cm vs -6.7 cm vs -4.5 cm	**ETD -4.9** [-6.0 to -3. 8], P<0.0001
HbA_{1c}	-1.6% vs -1.5% vs -0.4%	**ETD -1.2** [-1.4 to -1], P<0.0001
Systolic blood pressure (mm Hg)	-3.9 mm Hg vs -2.9 mm Hg vs -0.5 mm Hg	**ETD -3.4** [-5.6 to -1.3] P=0.0016
C-reactive protein	0.51 vs 0.58 vs 0.83	**ETR 0.61** [0.54 to 0.70)

Safety

	Semaglutide 2.4 mg n=403 (68 weeks)	Semaglutide 1.0 mg n=402 (68 weeks)	Placebo n=402 (68 weeks)
Total AEs	87.6% (n=353)	81.8% (n=329)	76.9% (n=309)
GI AEs	63.5% (n=256)	57.5% (n=231)	34.3% (n=138)
Serious AEs	9.9% (n=40)	7.7% (n=31)	9.2% (n=37)
Discontinuations d/t AEs	6.2% (n=25)	5.0% (n=20)	3.5% (n=14)
Discontinuations d/t GI AEs	4.2% (n=17)	3.5% (n=14)	1.0% (n=4)
AEs in ≥10% of patients	Nausea, Diarrhoea, Vomiting, Constipation, Nasopharyngitis, and Upper Respiratory tract infection		

- Majority of the GI AEs were mild to moderate in severity & transient

Conclusion

Semaglutide 2.4 mg, as an adjunct to diet and exercise counselling, resulted in a mean weight reduction of 9.6% over 68 weeks in participants with diabetes and obesity or overweight. Safety AE profile consistent with the GLP-1 RA class.

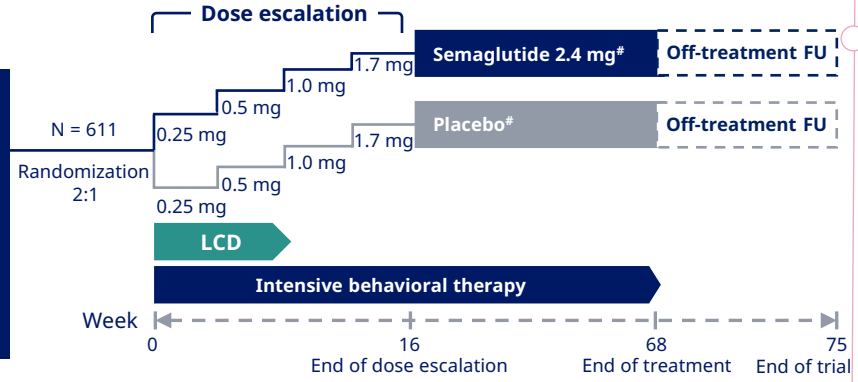
*#Subcutaneous and once weekly, as an adjunct to lifestyle intervention (-500 kcal/day diet + 150 min/week physical activity); *In-trial; †95% CI; Error bars are +/- standard error of the mean; AEs, adverse events; AOM, anti-obesity medication; BMI, body mass index BW, body weight; CI, confidence interval; ETD, estimated treatment difference (for the treatment policy estimand); ETR, estimated treatment ratio; FU, follow-up; GI, gastrointestinal; GLP1-RA, glucagon like peptide 1 receptor agonist; HbA_{1c}, glycated haemoglobin; OAD, oral anti-diabetic drug; OR; odds ratio; OW, once-weekly; SF-36, short form 36-item health survey; T2D, Type 2 diabetes. Davies et al. Lancet 2021;397:971-84.*

STEP 3

Trial Design

Key inclusion criteria

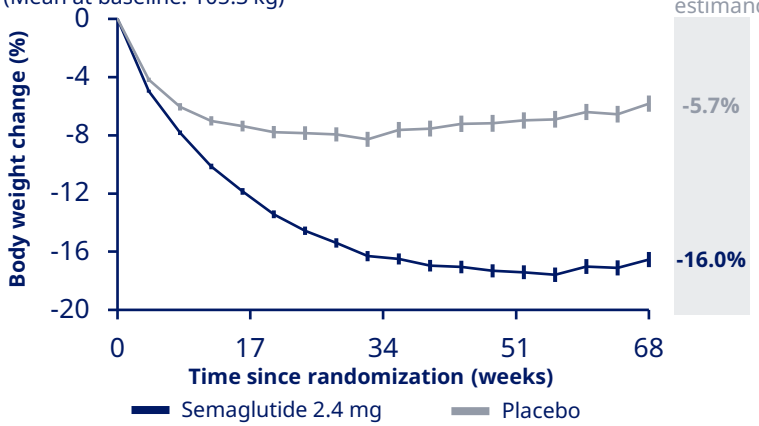
- BMI ≥30kg/m² or ≥27 kg/m² and ≥1 comorbidity
- Stable body weight ≥90 days
- HbA_{1c} ≤6.5%



Co-Primary Endpoint

Observed body weight change over time*

(Mean at baseline: 105.3 kg)



86.6% achieved **≥5% weight reduction** in Semaglutide 2.4 mg arm

47.6% achieved **≥5% weight reduction** in Placebo arm

Objective

To evaluate the efficacy and safety of once-weekly subcutaneous semaglutide 2.4 mg versus placebo as an adjunct to IBT with initial LCD for body weight management

Key Secondary Efficacy Endpoints†

	Semaglutide 2.4 mg vs Placebo (68 weeks)	Treatment comparison Semaglutide 2.4 mg vs Placebo (68 weeks)
≥10% weight reduction	75.3% vs 27.0%	OR 7.4 [4.9 to 11] P<0.001
≥15% weight reduction	55.8% vs 13.2%	OR 7.9 [4.9 to 12.6] P<0.001
Waist Circumference (cm)	-14.6 cm vs -6.3 cm	ETD -8.3 [–10.1 to –6.6] P<0.001
Systolic blood pressure (mmHg)	-5.6 mmHg vs -1.6 mmHg	ETD -3.9 [-6.4 to -1.5] P=0.001
C-reactive protein	-59.6% vs -22.9%	ETD -47.6 [–55 to –39] P<0.001
What is IBT?	**IBT** is **Intensive behavioral Therapy** that includes **increased physical activity and reduced calorie intake** with 30 behavioral counselling sessions	

Safety

	Semaglutide 2.4mg n=407 (68 weeks)	Placebo n=204 (68 weeks)
Total AEs	95.8% (n=390)	96.1% (n=196)
GI AEs	82.8% (n=337)	63.2% (n=129)
Serious AEs	9.1% (n=37)	2.9% (n=6)
Discontinuations d/t AEs	5.9% (n=24)	2.9% (n=6)
Discontinuations d/t GI AEs	3.4% (n=14)	0% (n=0)
AEs in ≥10% of patients	Nausea, Constipation, Diarrhea, Vomiting, Nasopharyngitis, Upper Respiratory tract infection, Headache, Abdominal pain, Back pain, Dizziness, Fatigue, Flatulence, Gastroenteritis viral, Urinary tract infection, Abdominal distension, and Sinusitis	

- The most common AEs were gastrointestinal in nature, including nausea, diarrhea, constipation and vomiting
- Majority of the GI AEs were mild to moderate in severity & transient

Conclusion

STEP 3 showed that participants treated with semaglutide 2.4 mg for obesity or overweight, on top of intensive behavioral therapy, achieved 16.0% body weight reduction. Safety AE profile consistent with the GLP-1 RA class.

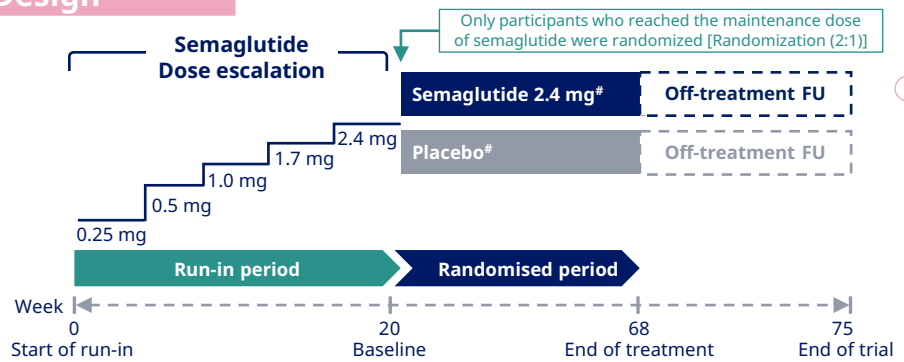
*#Subcutaneous and once weekly; *In-trial; † 95% CI; Error bars are +/- standard error of the mean; AEs, adverse events; BMI, body mass index; BW, body weight; CI, confidence interval; ETD, estimated treatment difference (for the treatment policy Estimand; FU, Follow-up; GI, gastrointestinal; IBT, Intensive behavioral therapy; LCD, Low Calorie Diet (meal replacement 1000-1200 kcal); OR, odds ratio; Wadden et al. JAMA 2021;325:1403-13.*

STEP 4

Trial Design

Key inclusion criteria

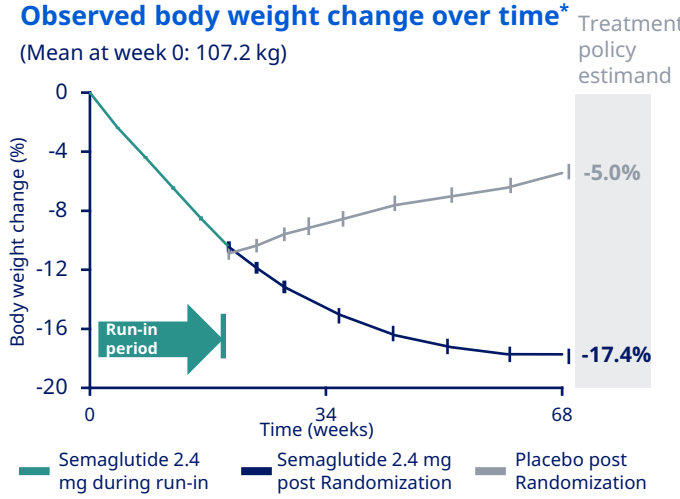
- BMI ≥30kg/m² or ≥27 kg/m² and ≥1 comorbidity
- Stable body weight ≥90 days
- HbA_{1c} ≤6.5%



Co-Primary Endpoint

Observed body weight change over time*

(Mean at week 0: 107.2 kg)



Subjects who persisted with semaglutide 2.4 mg continued to lose weight, while placebo-treated participants regained approx. half of their weight reduction

weight reduction during run-in period (all subjects)
(Week 0-20)

−10.6%

weight reduction post-randomization
(Week 20-68)

Continued semaglutide 2.4 mg	Switched to placebo
-7.9%	**+6.9%**

Objective

To evaluate the efficacy and safety of continued once-weekly subcutaneous semaglutide 2.4 mg versus a switch to placebo for body weight management in adults with overweight or obesity over 68 weeks

Key Secondary Efficacy Endpoints†

	Semaglutide 2.4 mg vs Placebo (68 weeks)	Treatment comparison Semaglutide 2.4 mg vs Placebo (68 weeks)
Waist Circumference (cm)	-6.4 cm vs +3.3 cm	**-9.7 cm** [-10.9 to -8.5] P<0.001
Systolic blood pressure (mm Hg)	+0.5 mm Hg vs +4.4 mm Hg	**-3.9 mm Hg** [-5.8 to -2.0] P<0.001
Triglycerides (% change)	-6% vs +15%	**-18%** [-24 to -11] P<0.001
SF-36 physical functioning score	1.0 vs -1.5	**2.5** [1.6 to 3.3] P<0.001

Safety

	Continued Semaglutide 2.4mg n=535 (20-68 weeks)	Switched to Placebo n=268 (20-68 weeks)
Total AEs	81.3% (n=435)	75.0% (n=201)
GI AEs	41.9% (n=224)	26.1% (n=70)
Serious AEs	7.7% (n=41)	5.6% (n=15)
Discontinuations d/t AEs	2.4% (n=13)	2.2% (n=6)
AEs in ≥5% of patients	Diarrhea, Nausea, Constipation, Nasopharyngitis, Vomiting, Headache, Influenza, Abdominal pain, Back pain, and Arthralgia	

- The most common AEs were gastrointestinal in nature, including nausea, diarrhea, constipation and vomiting
- Majority of the GI AEs were mild to moderate in severity & transient

Conclusion

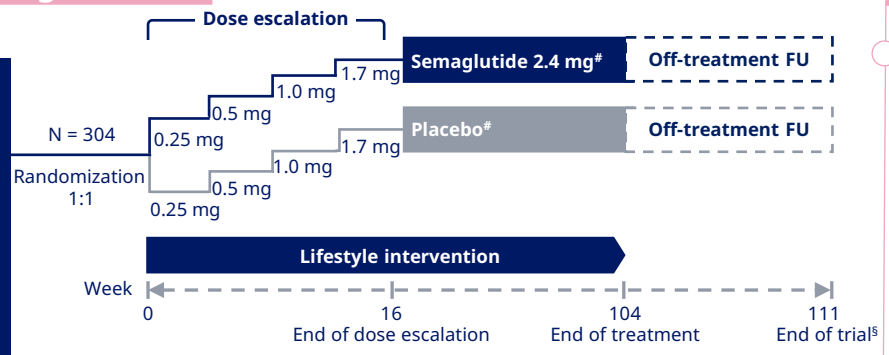
Results from STEP 4 highlight that obesity must be treated as a chronic disease, and that discontinuation of treatment can lead to weight regain and reversal of improvement in cardiometabolic parameters. Continued treatment enabled further weight reduction and reduction in waist circumference with a safety AE profile consistent with the GLP-1 RA class.

*#Subcutaneous and once weekly, as an adjunct to lifestyle intervention (-500 kcal/day diet + 150 min/week physical activity); *In-trial; † 95% CI; Error bars are +/- standard error of the mean; AEs, adverse events; AOMs, anti-obesity medications; BMI, body mass index; BW, body weight; CI, confidence interval; ETD, estimated treatment difference (for the treatment policy Estimand); GI, gastrointestinal; SF-36, Short Form 36-item Health Survey; T2D, type 2 diabetes; Rubino et al. JAMA. 2021;325:1414-25.*

STEP 5

Trial Design

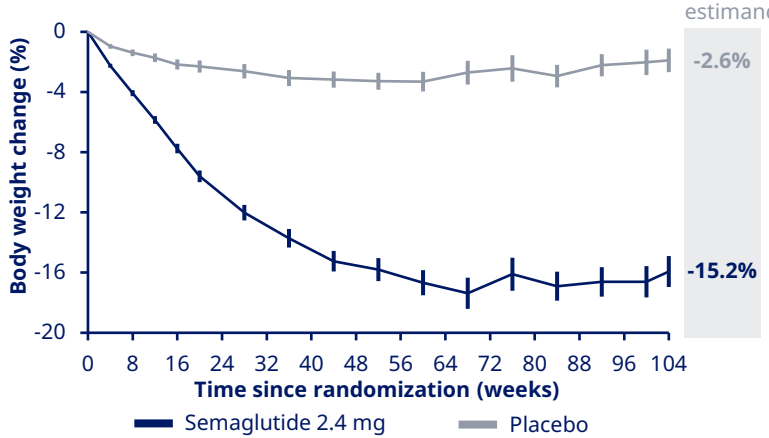
Key inclusion criteria
- BMI ≥30 kg/m² or ≥27 kg/m² and ≥1 weight-related comorbidity
- ≥1 prior weight reduction attempt via D&E
- Without T2D



Co-Primary Endpoint

Observed mean change over time**

(Mean at baseline: 106.0 kg)



Treatment policy estimand

-2.6%

-15.2%

77.1% achieved **≥5% weight reduction** in Semaglutide 2.4mg arm

34.4% achieved **≥5% weight reduction** in Placebo arm

Objective

To evaluate the efficacy and safety of once-weekly subcutaneous semaglutide 2.4 mg versus placebo for body weight management in adults with overweight or obesity over 2 years

Key Secondary Efficacy Endpoints†

	Semaglutide 2.4mg vs Placebo (68 weeks)	ETD Semaglutide 2.4mg vs Placebo (68 weeks)
≥10% weight reduction	61.8% vs 13.3%	OR 7.2 [4.0 to 13.2] P<0.0001
≥15% weight reduction	52.1% vs 7.0%	OR 9.4 [4.4 to 20.0] P<0.0001
Waist Circumference (cm)	-14.4 cm vs -5.2 cm	ETD -9.2 [-12.2 to -6.2] P<0.001
Systolic blood pressure (mmHg)	-5.7 mmHg vs -1.6 mmHg	ETD -4.2 [–7.3 to –1.0] P=0.0102
C-reactive protein	-56.7% vs -7.8%	ERPD –53.1 [–63.2 to –40.0]
HbA_{1c}	-0.4% vs -0.1%	ETD –0.3 [–0.4 to –0.3]

Safety

	Semaglutide 2.4mg n=152 (104 weeks)	Placebo n=152 (104 weeks)
Total AEs	96.1% (n=146)	89.5% (n=136)
GI AEs	82.2% (n=125)	53.9% (n=82)
Serious AEs	7.9% (n=12)	11.8% (n=18)
Discontinuations d/t AEs	5.9% (n=9)	4.6% (n=7)
Discontinuations d/t GI AEs	3.9% (n=6)	0.7% (n=1)
AEs in ≥10% of patients	Nausea, Diarrhea, Constipation, Vomiting, Nasopharyngitis, Abdominal pain upper, Abdominal pain, Dyspepsia, Flatulence, Gastroenteritis, Influenza, Upper respiratory tract infection, Decreased appetite, Eructation, Headache, and Back pain	

- The most common AEs were gastrointestinal in nature, including nausea, vomiting, diarrhea, and constipation
- Majority of the GI AEs were mild to moderate in severity & transient

Conclusion

STEP 5 demonstrated that participants with obesity or overweight treated with semaglutide 2.4 mg were able to sustain a mean body weight reduction of 15.2% over a period of 2 years. No new safety signals were identified in this 2-year trial.

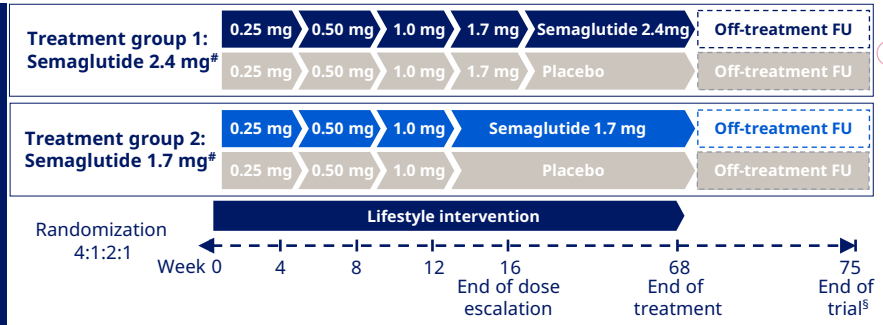
*#Subcutaneous and once weekly; *In-trial; §End of trial for the main phase; †95% CI; Error bars are +/- standard error of the mean; AEs, adverse events; BMI, body mass index; CI, confidence interval; D&E, diet and exercise; ETD, estimated treatment difference (for the treatment policy Estimand); FU, Follow-up; GI, gastrointestinal; ERPD, estimated relative percentage difference; OR, odds ratio; T2D, type 2 diabetes; Garvey et al. Nat Med 28, 2083–2091 (2022).*

STEP 6

Trial Design

Key inclusion criteria

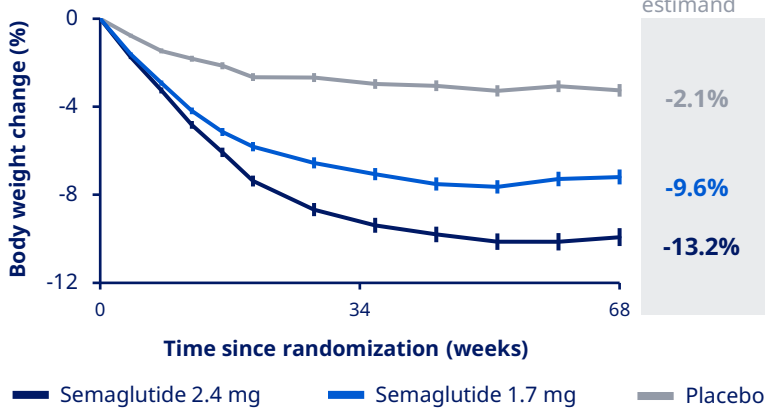
- BMI ≥27 kg/m² and ≥2 comorbidity or BMI ≥35.0 kg/m² and ≥2 comorbidity
- At least one comorbidity should be hypertension, dyslipidemia or T2D.



Co-Primary Endpoint

Observed body weight change over time*

(Mean at baseline: 87.5 kg)



Treatment policy estimand

-2.1%

-9.6%

-13.2%

83% achieved **≥5% weight reduction** in Semaglutide 2.4 mg arm

72% achieved **≥5% weight reduction** in Semaglutide 1.7 mg arm

21% achieved **≥5% weight reduction** in Placebo arm

Objective

To evaluate the efficacy and safety of once-weekly subcutaneous semaglutide 2.4 mg versus semaglutide 1.7 mg and placebo for body weight management in East Asian adults with overweight or obesity with or without type 2 diabetes over 68 weeks

Key Secondary Efficacy Endpoints†

	Semaglutide 2.4 mg vs 1.7 mg vs Placebo (68 weeks)	ETD Semaglutide 2.4 mg vs Placebo, Semaglutide 1.7 mg vs Placebo (68 weeks)
≥10% weight reduction	61% vs 42% vs 5%	**OR 32** [12 to 83] P<0.0001, **OR 14** [5 to 37] P<0.0001
≥15% weight reduction	41% vs 24% vs 3%	**OR 24** [7 to 78] P<0.0001, **OR 10** [3 to 35] P<0.0001
Waist Circumference (cm)	-11.1 cm vs -7.7 cm vs -1.8 cm	**ETD -9 cm** [-11 to -8] P<0.0001, **ETD -6 cm** [-8 to -4] P<0.0001
Systolic blood pressure (mmHg)	-10.8 mmHg vs -10.8 mmHg vs -5.3 mmHg	**ETD -5.5** [-8.5 to -2.5], **ETD -5.4** [-8.9 to -2.0]
C-reactive protein	0.42 vs 0.62 vs 0.89	**ETR 0.5** [0.4 to 0.6], **ETR 0.7** [0.5 to 0.9]
HbA_{1c}	-0.93% vs -0.89% vs -0.03	**ETD -0.90** [-1.05 to -0.74], **ETD -0.86** [-1.04 to -0.68]

Safety

	Semaglutide 2.4mg n=199 (68 weeks)	Semaglutide 1.7mg n=100 (68 weeks)	Placebo n=101 (68 weeks)
Total AEs	86% (n=171)	82% (n=82)	79% (n=80)
GI AEs	59% (n=118)	64% (n=64)	30% (n=30)
Serious AEs	5% (n=10)	7% (n=7)	7% (n=7)
Discontinuations d/t AEs	3% (n=5)	3% (n=3)	1% (n=1)
Discontinuations d/t GI AEs	2% (n=4)	2% (n=2)	0% (n=0)
AEs in ≥10% of patients	Nasopharyngitis, Constipation, Nausea, Diarrhea, Vomiting, and Abdominal discomfort		

- Majority of the GI AEs were mild to moderate in severity & transient

Conclusion

Treatment with semaglutide 2.4 mg and 1.7 mg as adjunct to lifestyle intervention resulted in mean reductions in body weight of 13.2% and 9.6%, respectively, in East Asian adults with overweight or obesity, with or without T2D. Safety AE profile consistent with the GLP-1 RA class.

*#Subcutaneous and once weekly, as an adjunct to lifestyle intervention (-500 kcal/day diet + 150 min/week physical activity); §End of trial for the main phase; *In-trial; †95% CI; Error bars are +/- standard error of the mean;.AEs, adverse events; BMI, body mass index BW, body weight; CI, confidence interval; ETD, estimated treatment difference (for the treatment policy estimand); ETR, estimated treatment ration; OR, odds ratio; GI, gastrointestinal; HbA1c, glycated haemoglobin; OW, once-weekly; SF-36, short form 36-item health survey; T2D, Type 2 diabetes.; Kadowaki T et al. Lancet Diabetes Endocrinol 2022; 20(3):193–206.*

STEP 8

Trial Design

Key inclusion criteria

- ≥1 self-reported unsuccessful dietary effort to lose weight
- BMI ≥30kg/m² or ≥27 kg/m² and ≥1 treated or untreated weight-related comorbidity
- HbA_{1c} ≤6.5%

N = 338

Randomization (3:1:3:1)

Treatment group 1: Semaglutide 2.4 mg once-weekly

0.25 mg → 0.50 mg → 1.0 mg → 1.7 mg → Semaglutide 2.4 mg#† → Off-treatment FU

0.25 mg → 0.50 mg → 1.0 mg → 1.7 mg → Placebo#† → Off-treatment FU

Treatment group 2: Liraglutide 3.0 mg once-daily

0.6 mg → 1.2 mg → 1.8 mg → 2.4 mg → Liraglutide 3.0 mg$† → Off-treatment FU

0.6 mg → 1.2 mg → 1.8 mg → 2.4 mg → Placebo$† → Off-treatment FU

Lifestyle intervention

Week 0 — 4 — 16 — 68 — 75

Semaglutide dose escalation (Week 0 to 16)

Liraglutide dose escalation (Week 0 to 4)

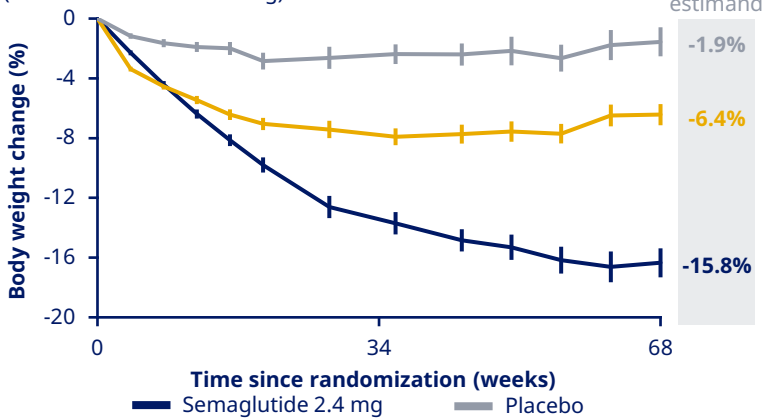
End of treatment (Week 68)

End of trial§ (Week 75)

Co-Primary Endpoint

Observed body weight change over time*

(Mean at baseline: 104.5 kg)



87.2% achieved **≥5% weight reduction** in Semaglutide 2.4 mg arm

58.1% achieved **≥5% weight reduction** in Liraglutide 3.0 mg arm

29.5% achieved **≥5% weight reduction** in Placebo arm

Objective

To compare the effect of once-weekly semaglutide 2.4 mg versus once-daily liraglutide 3.0 mg as an adjunct to lifestyle interventions on body weight, cardiovascular risk factors and glucose metabolism and the safety and tolerability

Key Secondary Efficacy Endpoints‡

	Semaglutide 2.4 mg vs Liraglutide 3.0 mg (68 weeks)	ETD Semaglutide 2.4 mg vs Liraglutide 3.0 mg (68 weeks)
≥10% weight reduction	70.9% vs 25.6%	**OR 6.3** [3.5 to 11.2], P<0.001
≥15% weight reduction	55.6% vs 12%	**OR 7.9** [4.1 to 15.4], P<0.001
Waist Circumference (cm)	-13.2 cm vs -6.6 cm	**-6.6 cm** [-9.1 to -4.2]
Systolic blood pressure (mmHg)	-5.7 mm Hg vs -2.9 mm Hg	**–2.8 mm Hg** [–6.1 to 0.6]
HbA_{1c}	-0.2% vs -0.1%	**–0.2%** [–0.2 to –0.1]
C-reactive protein	-52.6% vs -24.5%	**–37.2%** [–51.7 to –18.5]

Safety

	Semaglutide 2.4mg n=126 (68 weeks)	Liraglutide 3.0mg n=127 (68 weeks)	Placebo n=85 (68 weeks)
Total AEs	95.2% (n=120)	96.1% (n=122)	95.3% (n=81)
GI AEs	84.1% (n=106)	82.7% (n=105)	55.3% (n=47)
Serious AEs	7.9% (n=10)	11% (n=14)	7.1% (n=6)
Discontinuations d/t AEs	3.2% (n=4)	12.6% (n=16)	3.5% (n=3)
Discontinuations d/t GI AEs	0.8% (n=1)	6.3% (n=8)	1.2% (n=1)
AEs in ≥10% of patients	Nausea, Constipation, Diarrhea, Vomiting, Headache, Eructation, Decreased appetite, Fatigue, Dyspepsia, Nasopharyngitis, Upper respiratory tract infection, Arthralgia, Sinusitis, Back pain, and Influenza		

- Majority of the GI AEs were mild to moderate in severity & transient

Conclusion

Semaglutide 2.4 mg achieved significantly greater weight reduction compared to liraglutide 3.0 mg and placebo. No new safety findings of concern, reflecting a safety profile consistent with the GLP-1RA class.

*#Subcutaneous and once weekly; $Subcutaneous and once daily; †As an adjunct to lifestyle intervention (individual counselling sessions every 4–6 weeks; 500 kcal deficit/day relative to the energy expenditure estimated at Randomization; physical activity such as walking); *In-trial; §End of trial for the main phase; ‡95% CI; Error bars are +/- standard error of the mean; AEs, adverse events; BMI, body mass index; CI, confidence interval; ETD, estimated treatment difference (for the treatment policy Estimand); FU, follow-up; GI, gastrointestinal; GLP-1RA, Glucagon-like peptide-1 receptor agonists; HbA1c, glycated hemoglobin; OR, odds ratio.*

Rubino et al. JAMA 2022; 327(2): 138-150

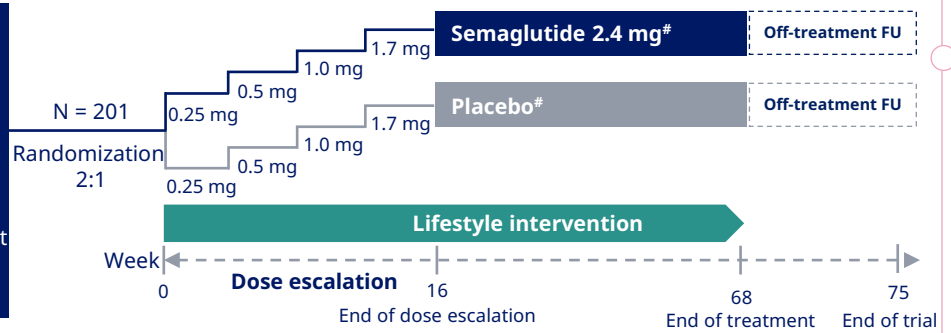
STEP TEENS

Trial Design

BMI ≥95th percentile or ≥85th percentile and ≥1 comorbidity

≥1 unsuccessful dietary weight reduction attempt

HbA_{1c} ≤ 10.0%



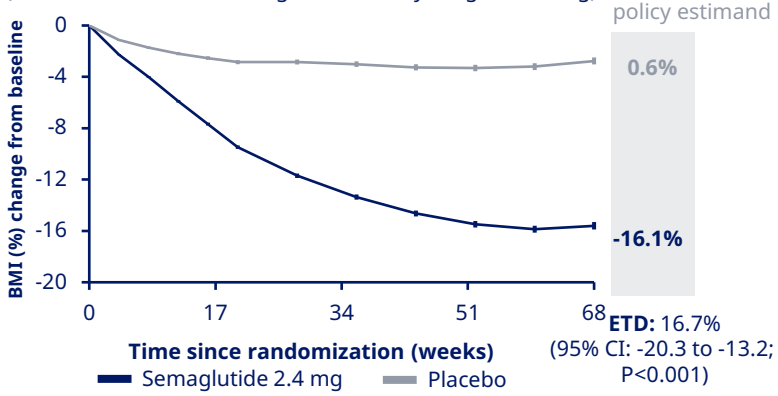
Objective

To evaluate the efficacy and safety of once-weekly subcutaneous semaglutide 2.4 mg versus placebo for body weight management in adolescents with overweight or obesity over 68 weeks

Key Efficacy Results

Primary Endpoint: Change in BMI (%) from Baseline*

(Mean baseline BMI: 37.0 kg/m² and body weight: 107.5kg)



Treatment policy estimand

0.6%

-16.1%

ETD: 16.7% (95% CI: -20.3 to -13.2; P<0.001)

Confirmatory secondary endpoint:

73% achieved **≥5% weight reduction** in Semaglutide 2.4 mg arm

18% achieved **≥5% weight reduction** in Placebo arm

Estimated Odds Ratio: 14.0 (95% CI: 6.3 to 31.0; P<0.001)

Key Secondary Endpoints

	Semaglutide 2.4mg vs placebo (68 weeks)	Treatment difference Semaglutide 2.4 mg vs placebo (68 weeks)
Waist circumference (cm)	-12.7 cm vs -0.6 cm	-12.1 cm [-15.6 to -8.7]
Systolic blood pressure (mm Hg)	-2.7 mm Hg vs -0.8 mm Hg	-1.9 mm Hg [–5.0 to 1.1]
Percentage change in ALT level	-18.3 vs -4.9	-14.1 [-25.2 to -1.4]
IWQOL-Kids questionnaire scores	5.3 vs 1.0	4.3 [0.2 to 8.3]

Conclusion

Semaglutide 2.4 mg, as an adjunct to diet and exercise counselling, resulted in a mean weight reduction of 16.1% over 68 weeks in adolescents with obesity or overweight with a co-morbidity. Safety AE profile consistent with the GLP-1 RA class.

Safety

Total AEs:
79% vs 82%
Semaglutide 2.4 mg vs placebo

GI AEs prevelence:
62% vs 42%
Semaglutide 2.4mg vs placebo
Majority of the GI AEs were mild to moderate & transient.

Discontinuations d/t AEs:
5% vs 4%
Semaglutide 2.4 mg vs placebo

Discontinuations d/t GI AEs:
2% vs 1%
Semaglutide 2.4 mg vs placebo

*#Subcutaneous and once weekly, as an adjunct to lifestyle intervention (-500 kcal/day diet + 150 min/week physical activity); *In-trial; AEs, adverse events; ALT, alanine aminotransferase; BMI, body mass index; BW, body weight; CI, confidence interval; ETD, estimated treatment difference; GI, gastrointestinal; GLP1-RA, glucagon like peptide 1 receptor agonist; HbA_{1c}, glycated hemoglobin; IWQOL-Kids, Impact of Weight on Quality of Life–Kids questionnaire; OW, once-weekly; Weghuber et al. N Engl J Med 2022;387:2245–2257.*