Supplement 3

Supplemental Online Content

Rubino DM, Greenway FL, Khalid U, et al. Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: the STEP 8 randomized clinical trial. *JAMA*. doi:10.1001/jama.2021.23619

This supplemental material has been provided by the authors to give readers additional information about their work.

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eAppendix 1. Eligibility Criteria

Inclusion Criteria

Participants were eligible to be included in the trial only if all the following criteria applied:

- Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
- Male or female, age ≥18 years at the time of signing informed consent.
- Body mass index (BMI) ≥30.0 kg/m^2 or ≥27.0 kg/m^2 with the presence of at least 1 of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease.
- History of at least 1 self-reported unsuccessful dietary effort to lose body weight.

The criteria were assessed at the investigator's discretion unless otherwise stated.

Exclusion Criteria

Participants were excluded from the trial if any of the following criteria applied:

Glycemia-Related

- Hemoglobin A_{1c} (HbA_{1c}) ≥6.5% (48 mmol/mol) as measured by the central laboratory at screening.
- History of type 1 or type 2 diabetes (T1/2D).
- Treatment with glucose-lowering agent(s) within 90 days before screening.

Obesity-Related

- A self-reported change in body weight >5 kg (11 lb) within 90 days before screening irrespective of medical records.
- Treatment with any medication for the indication of obesity within the past 90 days before screening.
- Previous or planned (during the trial period) obesity treatment with surgery or a weight loss device. However, the following were allowed: (1) liposuction and/or abdominoplasty, if performed >1 year before screening; (2) lap banding, if the band has been removed >1 year before screening; (3) intragastric balloon, if the balloon has been removed >1 year before screening; or (4) duodenal-jejunal bypass sleeve, if the sleeve has been removed >1 year before screening.
- Uncontrolled thyroid disease, defined as thyroid stimulating hormone >6.0 mIU/L or <0.35 mIU/L as measured by the central laboratory at screening.

Mental Health

- History of major depressive disorder within 2 years before screening.
- Diagnosis of other severe psychiatric disorder (eg, schizophrenia, bipolar disorder).
- A Patient Health Questionnaire-9 score ≥15 at screening.
- A lifetime history of suicidal attempt.
- Suicidal behavior within 30 days before screening.
- Suicidal ideation corresponding to type 4 or 5 on the Columbia-Suicide Severity Rating Scale within the past 30 days before screening.

General Safety

- Presence of acute pancreatitis within the past 180 days prior to the day of screening.
- History or presence of chronic pancreatitis.
- Calcitonin ≥100 ng/L as measured by the central laboratory at screening.
- Personal or first-degree relative history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.

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- Renal impairment measured as estimated glomerular filtration rate value of <15 ml/min/1.73 m^2 as defined by Kidney Disease: Improving Global Outcomes 2012[1] by the central laboratory at screening.
- History of malignant neoplasms within the past 5 years prior to screening. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed.
- Any of the following: myocardial infarction, stroke, hospitalization for unstable angina or transient ischemic attack within the past 60 days prior to screening.
- Participant classified as being in New York Heart Association Class IV.
- Surgery scheduled for the duration of the trial, except for minor surgical procedures, in the opinion of the investigator.
- Known or suspected abuse of alcohol or recreational drugs.
- Known or suspected hypersensitivity to trial product(s) or related products.
- Previous participation in this trial. Participation is defined as signed informed consent.
- Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days before screening.
- Other individuals from the same household participating in any semaglutide or liraglutide trial.
- Female who is pregnant, breast-feeding, or intends to become pregnant or is of child-bearing potential and not using a highly effective contraceptive method.
- Any disorder, unwillingness, or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion, might jeopardize the participant's safety or compliance with the protocol.

The criteria were assessed at the investigator's discretion unless otherwise stated.

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eAppendix 2. Supportive Secondary, Exploratory, and *Post Hoc* Efficacy End Points

Supportive Secondary Efficacy End Points

Semaglutide vs Liraglutide
Change from baseline to week 68 in:

- Absolute body weight (in kg)
- Waist circumference
- Systolic and diastolic blood pressure
- Fasting lipid concentrations
- C-reactive protein
- HbA_{1c}
- Fasting plasma glucose
- Fasting serum insulin
- Glycemic status (normo-glycemia, prediabetes, and T2D), defined according to American Diabetes Association 2017 criteria[2]

Proportion of participants who by week 68 had:

- Permanently discontinued trial product

Semaglutide vs Pooled Placebo
Change from baseline to week 68 in:

- Body weight (%)
- Absolute body weight (in kg)

Liraglutide vs Pooled Placebo
Change from baseline to week 68 in:

- Body weight (%)
- Absolute body weight (in kg)

Exploratory Efficacy End Points

Semaglutide vs Liraglutide
Proportion of participants who by week 68 achieved:

- ≥5% weight loss

Post Hoc Efficacy End Points

Semaglutide-Placebo vs Liraglutide-Placebo
Change from baseline to week 68 in:

- Body weight (%)

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eAppendix 3. Estimands

The 2 estimands defined in this trial addressed 2 different scientific questions related to the efficacy objectives by accounting for intercurrent events (in this case, trial product discontinuation and rescue intervention use [initiation of another anti-obesity medication or bariatric surgery]) and missing data differently.

The treatment policy estimand addressed the question, "What is the treatment effect for all randomized participants regardless of trial product discontinuation or use of a rescue intervention?", thus reflecting the intention-to-treat principle. The analysis addressing this estimand used all available data at week 68 from all randomized participants, with data missing at week 68 imputed using multiple imputation (see Methods, Statistical Analyses for further details).

The trial product estimand addressed the question, "What is the treatment effect for all randomized participants assuming they all remain on trial product for the trial duration without use of a rescue intervention?" The analysis addressing this estimand used data obtained during the on-treatment observation period (the time during which treatment with any dose of trial intervention was given within the previous 14 days [after excluding any temporary interruptions in taking trial intervention]) until first discontinuation or initiation of rescue intervention. This, in practice, meant that any data collected 14 days after the last dose before first discontinuation, or right after initiation of rescue intervention, were treated as missing and were imputed using a mixed model for repeated measurements (see eAppendix 4 for further details).

Additional detail on estimands and their application in clinical trials for T2D and obesity can be found in eReferences 3 and 4.

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eAppendix 4. Prespecified Sensitivity Analyses

Prespecified sensitivity analyses performed for the primary end point analysis were: (1) a tipping-point analysis, in which penalties ranging from –30% to 30% were added to the imputed values at week 68 for both the semaglutide and liraglutide arms to explore the effect these would have on the study conclusions; and (2) an analysis using jump-to-reference, in which missing data for participants in the active treatment groups were imputed by sampling from all available data (regardless of treatment completion status) from the pooled placebo group.

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eAppendix 5. Statistical Analysis for the Trial Product Estimand

For the trial product estimand, continuous end points were assessed using a mixed model for repeated measurements, with randomized treatment as a factor and baseline value of the outcome measure of interest as a covariate, all nested within visit, and using an unstructured covariance matrix. For the *post hoc* analysis of the change in pulse at week 68, data were used from the safety analysis set, whereas all other analyses used data from the full analysis set.

For the binary confirmatory secondary end points, the mixed model for repeated measurements was first used to obtain individual predicted percent weight change values for each participant to determine whether they achieved each weight loss threshold. The classification was then analyzed with logistic regression, with treatment as a factor and baseline body weight as a covariate.

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eTable 1. Analysis and Imputation Methods to Address the Treatment Policy and Trial Product Estimands for the Primary and Confirmatory Secondary End Points in the Statistical Testing Hierarchy

Objective	End point	Test order	End point type	Estimand	Analysis set	Statistical model	Imputation approach
Primary end points							
Primary	% weight change	1	Continuous	Treatment policy[a]	FAS	ANCOVA	RD-MI
				Trial product[b]	FAS	MMRM	-
Confirmatory secondary end points							
Primary	10% responders	2	Binary	Treatment policy[a]	FAS	LR	RD-MI
				Trial product[b]	FAS	LR	MMRM
Primary	15% responders	3	Binary	Treatment policy[a]	FAS	LR	RD-MI
				Trial product[b]	FAS	LR	MMRM
Primary	20% responders	4	Binary	Treatment policy[a]	FAS	LR	RD-MI
				Trial product[b]	FAS	LR	MMRM

Abbreviations: ANCOVA, analysis of covariance; FAS, full analysis set; LR, logistic regression; MMRM, mixed model for repeated measurements; RD-MI, multiple imputation using retrieved participants.

Test order refers to the order of the end point in the statistical test hierarchy.

[a]Designated as the primary estimand.

[b]Designated as the secondary estimand.

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eTable 2. Assumptions and Marginal Power Used in the Sample Size Calculation

Hierarchical test order	End point	Expected mean (SD) or proportion		Expected difference or proportion ratio	Marginal power (%)
		Semaglutide 2.4 mg	Liraglutide 3.0 mg		
1	Body weight, % change[a]	12.5 (10)	7.0 (10)	5.5 %-points	99
2	Participants with ≥10% weight loss	61%	37%	1.6	97
3	Participants with ≥15% weight loss	39%	18%	2.2	96
4	Participants with ≥20% weight loss	27%	6%	4.5	99

Based on an anticipated 336 randomized participants. All tests in the hierarchy were based on the treatment policy estimand (assessed the treatment effect at week 68, regardless of treatment discontinuation or rescue intervention use). Since all are tests of superiority of semaglutide 2.4 mg to liraglutide 3.0 mg, power is only shown for this comparison.

[a]Shown as a positive number.

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eTable 3. Participant Disposition by Trial Site

Site	Screened, No.	Randomized, No. (%)[a]	Treatment completers, No. (%)[b,c]	Trial completers, No. (%)[c,d]
801	18	16 (88.9)	11 (68.8)	12 (75.0)
802	25	25 (100)	21 (84.0)	25 (100)
803	21	19 (90.5)	12 (63.2)	16 (84.2)
804	22	17 (77.3)	14 (82.4)	17 (100)
805	21	18 (85.7)	16 (88.9)	18 (100)
806	18	16 (88.9)	12 (75.0)	14 (87.5)
807	19	17 (89.5)	14 (82.4)	17 (100)
808	18	17 (94.4)	12 (70.6)	15 (88.2)
809	21	16 (76.2)	10 (62.5)	12 (75.0)
810	19	17 (89.5)	10 (58.8)	16 (94.1)
811	20	19 (95.0)	17 (89.5)	18 (94.7)
812	25	23 (92.0)	20 (87.0)	22 (95.7)
813	20	17 (85.0)	17 (100)	17 (100)
814	19	15 (78.9)	12 (80.0)	15 (100)
815	21	17 (81.0)	11 (64.7)	17 (100)
816	21	17 (81.0)	14 (82.4)	17 (100)
817	17	15 (88.2)	14 (93.3)	14 (93.3)
818	18	17 (94.4)	15 (88.2)	17 (100)
819	24	20 (83.3)	19 (95.0)	20 (100)

[a]Proportions are based on the number of screened participants at the designated site.

[b]On-treatment (ie, had received any dose of trial product within the prior 14 days) at week 68.

[c]Proportions are based on the number of randomized participants at the designated site.

[d]Attended the end-of-trial visit at week 75.

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eTable 4. Change in Efficacy Outcomes from Baseline to Week 68[a] (Trial Product Estimand[b]; Full Analysis Set)

	Estimated mean change (95% CI) (unless stated otherwise)		Difference for semaglutide 2.4 mg vs liraglutide 3.0 mg (95% CI); *P* value[c]
	Semaglutide 2.4 mg (N=126)	Liraglutide 3.0 mg (N=127)	
Primary end point			
Body weight, % change	–17.1 (–18.7 to –15.4) [95]	–6.6 (–8.3 to –4.9) [90]	–10.5 (–12.8 to –8.1); < .001
Confirmatory secondary end points			
Participants with ≥10% weight loss at week 68, No. (%)[d]	78/106 (73.6)	26/92 (28.3)	Odds ratio: 8.4 (4.7 to 14.9); < .001
Participants with ≥15% weight loss at week 68, No. (%)[d]	60/106 (56.6)	13/92 (14.1)	Odds ratio: 11.7 (6.0 to 22.9); < .001
Participants with ≥20% weight loss at week 68, No. (%)[d]	43/106 (40.6)	6/92 (6.5)	Odds ratio: 12.4 (5.3 to 29.4); < .001
Supportive secondary end points			
Body weight, kg	–16.7 (–18.4 to –14.9) [95]	–6.7 (–8.5 to –4.9) [90]	–10.0 (–12.5 to –7.5)
Waist circumference, cm	–14.7 (–16.3 to –13.1) [93]	–6.8 (–8.5 to –5.2) [88]	–7.9 (–10.2 to –5.6)
Blood pressure, mmHg			
Systolic	–6.6 (–9.0 to –4.2) [93]	–5.4 (–7.9 to –3.0) [87]	–1.2 (–4.6 to 2.2)
Diastolic	–4.2 (–5.9 to –2.6) [93]	–1.3 (–2.9 to 0.4) [87]	–3.0 (–5.3 to –0.7)
Fasting lipid profile, % change[e]			
Total cholesterol	–8.2 (–10.5 to –5.9) [93]	–0.5 (–3.1 to 2.0) [87]	–7.7 (–11.0 to –4.4)
HDL cholesterol	–1.2 (–3.9 to 1.5) [92]	1.6 (–1.2 to 4.5) [87]	–2.8 (–6.5 to 1.1)
LDL cholesterol	–7.8 (–11.3 to –4.2) [92]	0.6 (–3.3 to 4.6) [87]	–8.4 (–13.3 to –3.2)
VLDL cholesterol	–21.0 (–25.6 to –16.2) [92]	–12.4 (–17.5 to –6.9) [87]	–9.8 (–17.2 to –1.9)
Free fatty acids	–11.7 (–21.5 to –0.8) [89]	–9.4 (–19.4 to 2.0) [88]	–2.6 (–17.6 to 15.0)
Triglycerides	–20.8 (–25.5 to –15.8) [92]	–12.5 (–17.7 to –6.9) [87]	–9.5 (–17.0 to –1.3)
CRP, % change[e]	–57.5 (–64.4 to –49.4) [93]	–33.7 (–44.6 to –20.6) [88]	–36.0 (–50.2 to –17.7)

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	Estimated mean change (95% CI) (unless stated otherwise)		Difference for semaglutide 2.4 mg vs liraglutide 3.0 mg (95% CI); *P* value[c]
	Semaglutide 2.4 mg (N=126)	Liraglutide 3.0 mg (N=127)	
HbA_{1c}, %	–0.3 (–0.3 to –0.2) [93]	–0.1 (–0.2 to –0.1) [87]	–0.2 (–0.2 to –0.1)
Fasting plasma glucose, mg/dL	–9.8 (–11.7 to –7.9) [92]	–6.5 (–8.5 to –4.6) [86]	–3.3 (–6.0 to –0.5)
Fasting serum insulin, % change[e]	–28.1 (–35.4 to –20.0) [89]	–17.5 (–26.0 to –8.0) [88]	–12.8 (–25.2 to 1.5)
Exploratory end point			
Participants with ≥5% weight loss at week 68, No. (%)[d]	96/106 (90.6)	57/92 (62.0)	N/A

Abbreviations: CRP, C-reactive protein; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; LDL, low-density lipoprotein; [n], number of participants with a week 68 observation; N/A, not applicable; VLDL, very low-density lipoprotein.

Numbers of participants with an observation at week 68 are denoted by [n] for each end point. The number of participants with imputed data can be calculated by subtracting n from the number in the full analysis set (N), provided in the column headers.

[a]Data are only presented for the active treatment groups. Data for the placebo groups are presented in eTable 5 (Supplement 1).

[b]The trial product estimand assessed the treatment effect at week 68 assuming participants continued taking randomized treatment for the planned study duration without rescue intervention. The analyses were based on data from the on-treatment period (the time during which treatment with any dose of trial intervention was given within the previous 14 days [after excluding any temporary interruptions in taking trial intervention]). Continuous end points were assessed using a mixed model for repeated measurements, with randomized treatment as a factor and baseline value of the outcome measure of interest as a covariate, all nested within visit, and using an unstructured covariance matrix. For the binary confirmatory secondary end points, the mixed model for repeated measurements was first used to obtain individual predicted percent weight change values for each participant to determine whether they achieved each weight loss threshold. The classification was then analyzed with logistic regression, with treatment as a factor and baseline body weight as a covariate.

[c]Data are absolute differences between estimated mean changes unless stated otherwise. The differences between mean percent changes in body weight and mean changes in HbA_{1c} are expressed in percentage points. *P* values are only shown for primary and confirmatory secondary end points.

[d]Data are observed (ie, as-measured) numbers and proportions of participants at week 68 from the on-treatment period (the time during which treatment with any dose of trial intervention was given within the previous 14 days [after excluding any temporary interruptions in taking trial intervention]), and where applicable, estimated odds ratios for semaglutide vs liraglutide for the trial product estimand (achievement of ≥5% weight loss was an exploratory end point and not analyzed statistically).

[e]These parameters were initially analyzed on a log scale as estimated ratio to baseline (within treatment groups) and estimated treatment ratios (between treatment groups). For interpretation, these data are expressed as relative percent change and estimated relative percent difference between groups, respectively, and were calculated using the formula (estimated ratio − 1) × 100.

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eTable 5. Change in Efficacy Outcomes from Baseline to Week 68 for the Placebo Group (Treatment Policy[a] and Trial Product[b] Estimands; Full Analysis Set)

	Estimated mean change (95% CI) [unless stated otherwise] for the treatment policy estimand[a]		Estimated mean change (95% CI) [unless stated otherwise] for the trial product estimand[b]	
	Placebo (N=85)[c]		Placebo (N=85)[c]	
Supportive secondary end points				
Body weight, % change	–1.9 (–4.0 to 0.2) [78]		–1.8 (–3.8 to 0.2) [66]	
Difference for active treatment vs placebo (95% CI)[d]	**Semaglutide 2.4 mg vs placebo[c]** –13.9 (–16.7 to –11.0)	**Liraglutide 3.0 mg vs placebo[c]** –4.5 (–7.3 to –1.7)	**Semaglutide 2.4 mg vs placebo[c]** –15.3 (–17.9 to –12.7)	**Liraglutide 3.0 mg vs placebo[c]** –4.8 (–7.4 to –2.2)
Participants with ≥10% weight loss at week 68, No. (%)	12/78 (15.4)[e]		11/69 (15.9)[f]	
Participants with ≥15% weight loss at week 68, No. (%)	5/78 (6.4)[e]		4/69 (5.8)[f]	
Participants with ≥20% weight loss at week 68, No. (%)	2/78 (2.6)[e]		2/69 (2.9)[f]	
Body weight, kg	–1.6 (–3.9 to 0.8) [78]		–1.4 (–3.5 to 0.8) [66]	
Difference for active treatment vs placebo (95% CI)[d]	**Semaglutide 2.4 mg vs placebo[c]** –13.8 (–16.8 to –10.7)	**Liraglutide 3.0 mg vs placebo[c]** –5.3 (–8.3 to –2.3)	**Semaglutide 2.4 mg vs placebo[c]** –15.3 (–18.1 to –12.5)	**Liraglutide 3.0 mg vs placebo[c]** –5.3 (–8.1 to –2.5)
Waist circumference, cm	–2.0 (–4.0 to 0.1) [76]		–1.7 (–3.7 to 0.3) [65]	
Blood pressure, mmHg				
Systolic	3.2 (0.3 to 6.1) [77]		4.5 (1.6 to 7.3) [66]	
Diastolic	0.7 (–1.5 to 2.9) [77]		0.3 (–1.6 to 2.3) [66]	
Fasting lipid profile, % change[g]				
Total cholesterol	–3.3 (–7.9 to 1.5) [75]		–0.2 (–3.2 to 2.9) [64]	
HDL cholesterol	–0.9 (–4.5 to 2.9) [74]		–0.5 (–3.8 to 2.8) [63]	

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	Estimated mean change (95% CI) [unless stated otherwise] for the treatment policy estimand[a]		Estimated mean change (95% CI) [unless stated otherwise] for the trial product estimand[b]
	Placebo (N=85)[c]		Placebo (N=85)[c]
LDL cholesterol	–1.1 (–11.4 to 10.4) [74]		0.8 (–3.9 to 5.6) [63]
VLDL cholesterol	–4.1 (–12.1 to 4.6) [74]		–3.1 (–9.8 to 4.1) [63]
Free fatty acids	2.6 (–10.5 to 17.5) [73]		9.7 (–4.7 to 26.3) [62]
Triglycerides	–3.2 (–11.4 to 5.8) [74]		–1.7 (–8.7 to 5.9) [63]
CRP, % change[g]	–20.1 (–34.7 to –2.3) [75]		–20.6 (–35.8 to –1.9) [64]
HbA_{1c}, %	0.1 (0.1 to 0.2) [76]		0.1 (0.1 to 0.2) [65]
Fasting plasma glucose, mg/dL	3.3 (0.6 to 6.0) [74]		2.9 (0.6 to 5.2) [63]
Fasting serum insulin, % change[g]	–3.5 (–14.9 to 9.4) [72]		–2.4 (–14.3 to 11.0) [61]
Exploratory end point			
Participants with ≥5% weight loss at week 68, No. (%)	23/78 (29.5)[e]		21/69 (30.4)[f]
***Post hoc* end point**	**Semaglutide-placebo (N=43)**	**Liraglutide-placebo (N=42)**	
Body weight, % change[h]	–0.5 (–3.1 to 2.2) [42]	–3.2 (–5.9 to –0.5) [36]	N/A

Abbreviations: CRP, C-reactive protein; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; LDL, low-density lipoprotein; [n], number of participants with a week 68 observation; N/A, not applicable; VLDL, very low-density lipoprotein.

Numbers of participants with an observation at week 68 are denoted by [n] for each end point. The number of participants with imputed data can be calculated by subtracting n from the number in the full analysis set (N), provided in the column headers.

[a]The treatment policy estimand assessed the treatment effect at week 68, regardless of treatment discontinuation or rescue intervention use. The analyses were based on data from the in-trial observation period (the time from randomization to last contact with the trial site). Continuous end points were assessed using analysis of covariance, with randomized treatment as a factor and baseline value of the outcome measure of interest as a covariate, and a multiple imputation approach for missing data. Analyses were not controlled for multiple comparisons.

[b]The trial product estimand assessed the treatment effect at week 68 assuming participants continued taking randomized treatment for the planned study duration without rescue intervention. The analyses were based on data from for the on-treatment period (the time during which treatment with any dose of trial intervention was given within the previous 14 days [after excluding any temporary interruptions in taking trial intervention]). Continuous end points were assessed using a mixed model for repeated measurements, with randomized treatment as a factor and baseline value of the outcome measure of interest as a covariate, all nested within visit, and using an unstructured covariance matrix.

[c]Pooled placebo data unless stated otherwise.

[d]Data are absolute differences between estimated mean changes. The differences between mean percent changes in body weight are expressed in percentage points.

[e]Data are observed (ie, as-measured) numbers and proportions of participants at week 68 from the in-trial period (the time from randomization to last contact with trial site, irrespective of treatment discontinuation or rescue intervention).

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[f]Data are observed numbers and proportions of participants at week 68 from the on-treatment period (the time during which treatment with any dose of trial intervention was given within the previous 14 days [after excluding any temporary interruptions in taking trial intervention]).

[g]These parameters were initially analyzed on a log scale as estimated ratio to baseline. For interpretation, these data are expressed as relative percent change, and were calculated using the formula (estimated ratio – 1) × 100.

[h]Estimates were obtained using a similar approach as for the primary end point (percent change in body weight), but with imputation within each treatment group, regardless of treatment completion status. This was due to the low number of retrieved data for participants who had discontinued treatment.

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eTable 6. Other Reasons for Premature Treatment Discontinuation Among Trial Completers

Participant ID	Primary reason
Semaglutide 2.4 mg (n=5)	
807009	Participant moved out of the country for the remainder of the trial to attend medical school
808013	Participant's decision
809019	Participant was unable to complete visit 22 (end of treatment) due to work schedule
810004	Participant had multiple life stressors and decided to stop taking medication
818010	Participant had personal issues at home that took up their time
Liraglutide 3.0 mg (n=7)	
803007	Participant forgot to dose for a few days and then decided not to resume treatment
803008	Participant felt treatment was not a priority as they were caring for ill relatives
803021	Participant felt too overworked and stressed to continue
808016	Participant decided to stop study treatment but remain in the trial
810009	Participant decided to have weight loss surgery, and was then unresponsive to trial site until receipt of letter from trial site
815015	Participant was focused on personal issues and chose not to take study treatment; site was not informed until visit 22 (end of treatment)
816007	Participant was too busy to complete the last study visit due to moving house, job change, and illness
Placebo (n=5)	
802014	Treatment not completed due to COVID-19 concerns
806011	Participant moved out of state and agreed to continue in the trial without taking trial medication
807017	Participant discontinued study drug as they thought they were on placebo
808012	Participant did not want to continue due to stress about the COVID-19 pandemic
810003	Participant was a nurse and felt unable to complete the study as they were so busy with the COVID-19 pandemic

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eTable 7. Participants Who Were Below the Target Dose

Group	Time frame, No./total (%)			
	End of dose escalation	Week 20	Week 68	Last dose
Semaglutide, 2.4 mg	67/121 (55.4%)	16/119 (13.4%)	15/109 (13.8%)	15/109 (13.8%)
Liraglutide, 3.0 mg	77/123 (62.6%)	6/115 (5.2%)	3/92 (3.3%)	3/91 (3.3%)

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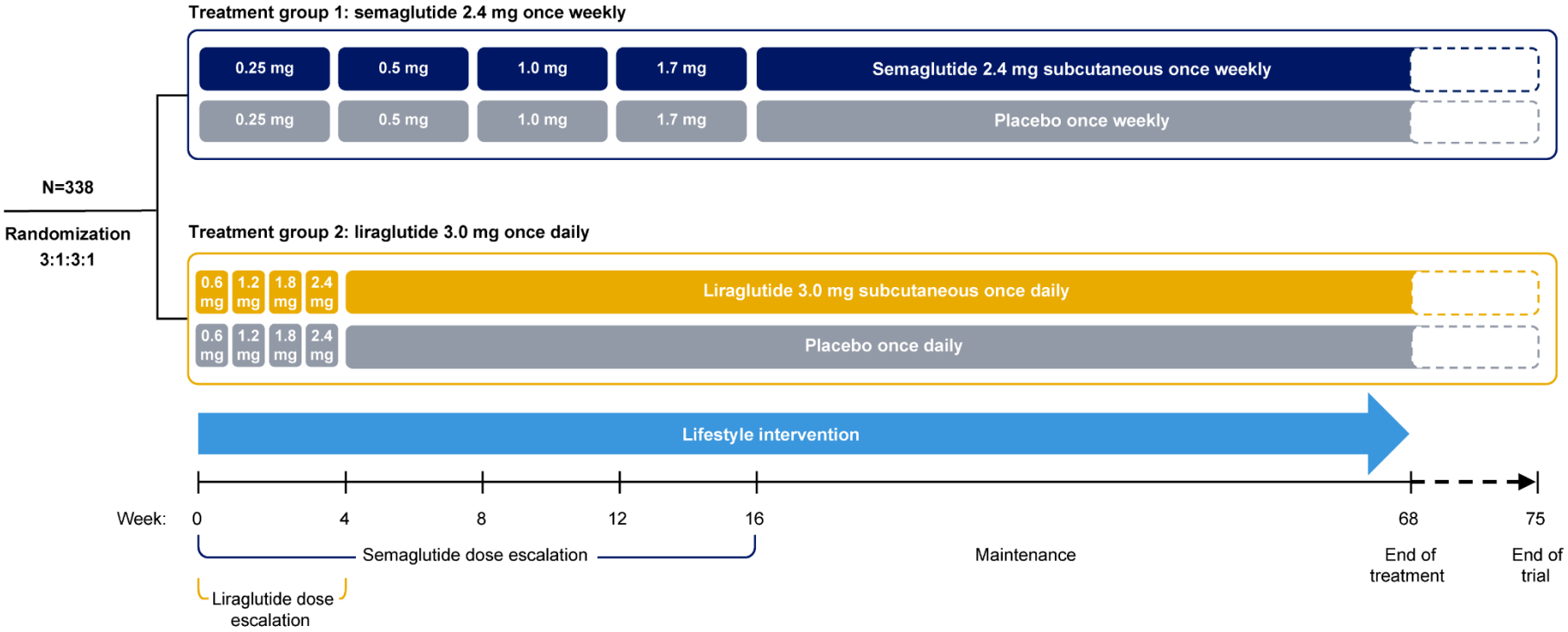
eFigure 1. Trial Design



All study treatments were given as adjunct to lifestyle intervention, which included counseling (by a dietician or similarly qualified healthcare professional, every 4–6 weeks, via visits or phone contact) on diet (500 kcal deficit per day relative to baseline estimated total daily energy expenditure) and physical activity (minimum of 150 minutes of physical activity per week encouraged).

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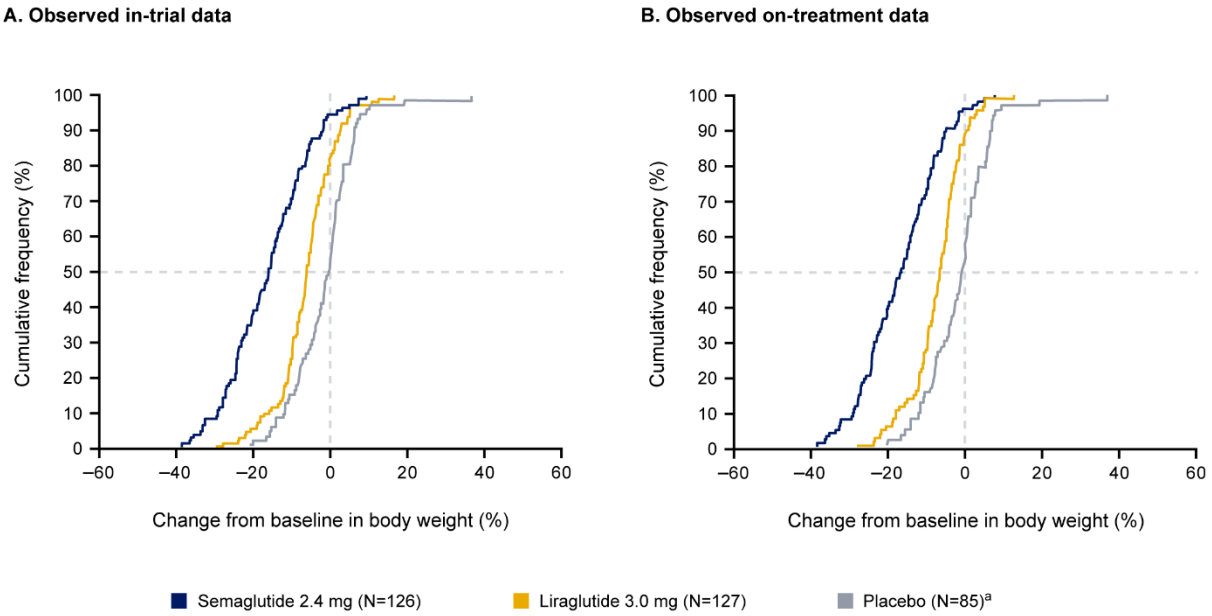
eFigure 2. Cumulative Distribution Plot of Percent Change in Body Weight from Baseline to Week 68 (Observed In-Trial and On-Treatment Data; Full Analysis Set)



Panel A presents observed (ie, as-measured) percent change in body weight from baseline to week 68 for the full analysis set from the in-trial period (the time from randomization to the date of last contact with trial site).

Panel B presents percent change in body weight from baseline to week 68 for the full analysis set from the on-treatment period (the time during which treatment with any dose of trial intervention was given within the previous 14 days [after excluding any temporary interruptions in taking trial intervention]).

Participant numbers in the legend are for the full analysis set.

[a]Pooled placebo data.

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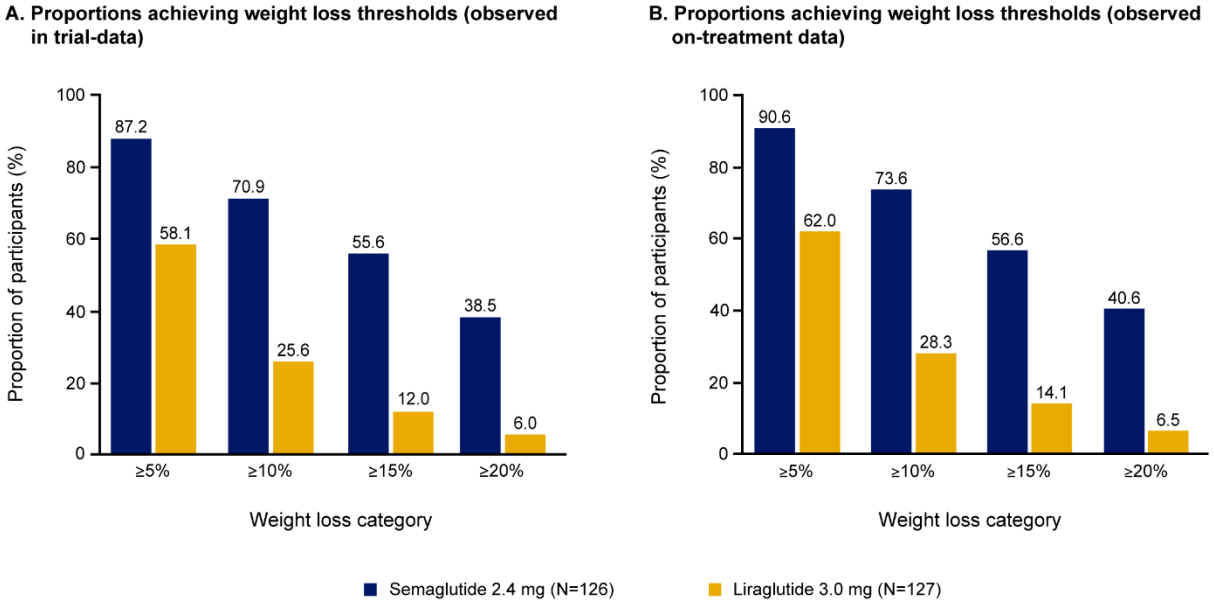
eFigure 3. Proportions of Participants Achieving Weight Loss Thresholds at Week 68 (Observed In-Trial and On-Treatment Data; Full Analysis Set)



Panel A presents observed (ie, as-measured) data for the full analysis set from the in-trial period (the time from randomization to the date of last contact with trial site).

Panel B presents observed data for the full analysis set from the on-treatment period (the time during which treatment with any dose of trial intervention was given within the previous 14 days [after excluding any temporary interruptions in taking trial intervention]).

In both panels, data are from all randomized participants with a week 68 assessment (Panel A: semaglutide n=117, liraglutide n=117; Panel B: semaglutide n=106; liraglutide n=92). Participant numbers in the legend are for the full analysis set. Data are only presented for the active treatment groups.

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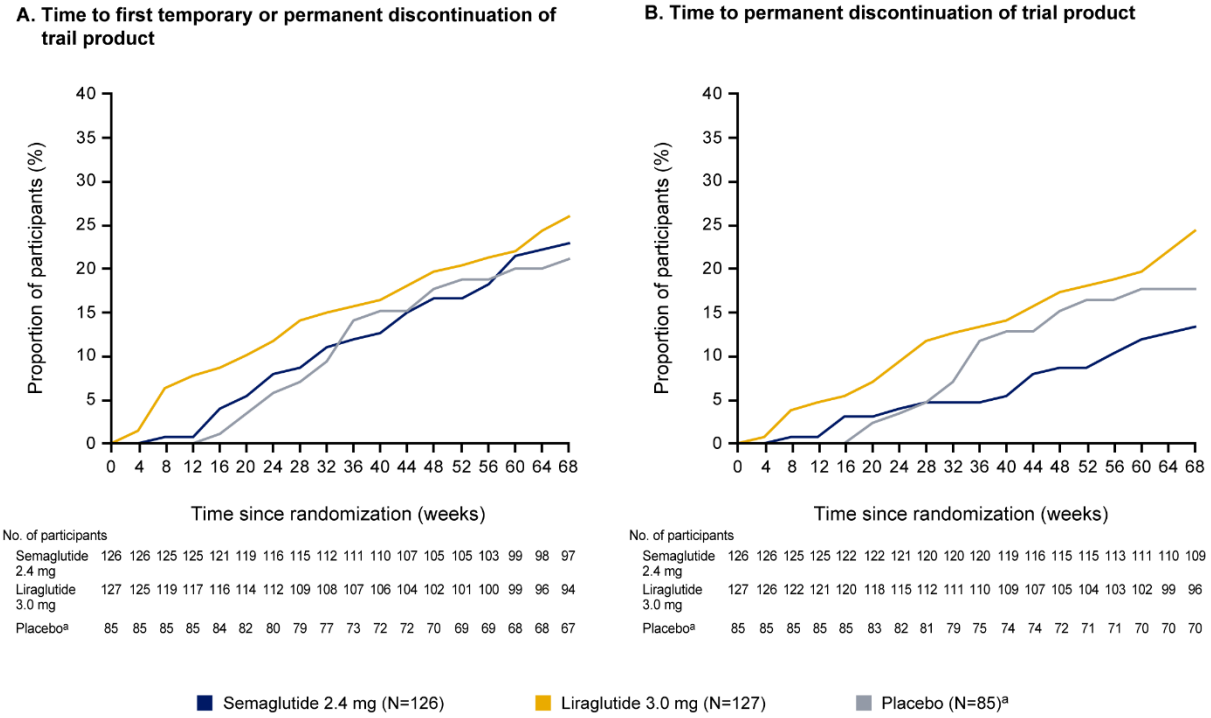
eFigure 4. Time to First Discontinuation and Time to Permanent Discontinuation of Trial Product (Observed Data; Full Analysis Set)



Panel A presents the time from randomization to first temporary interruption or permanent discontinuation of trial product (whichever occurred first).

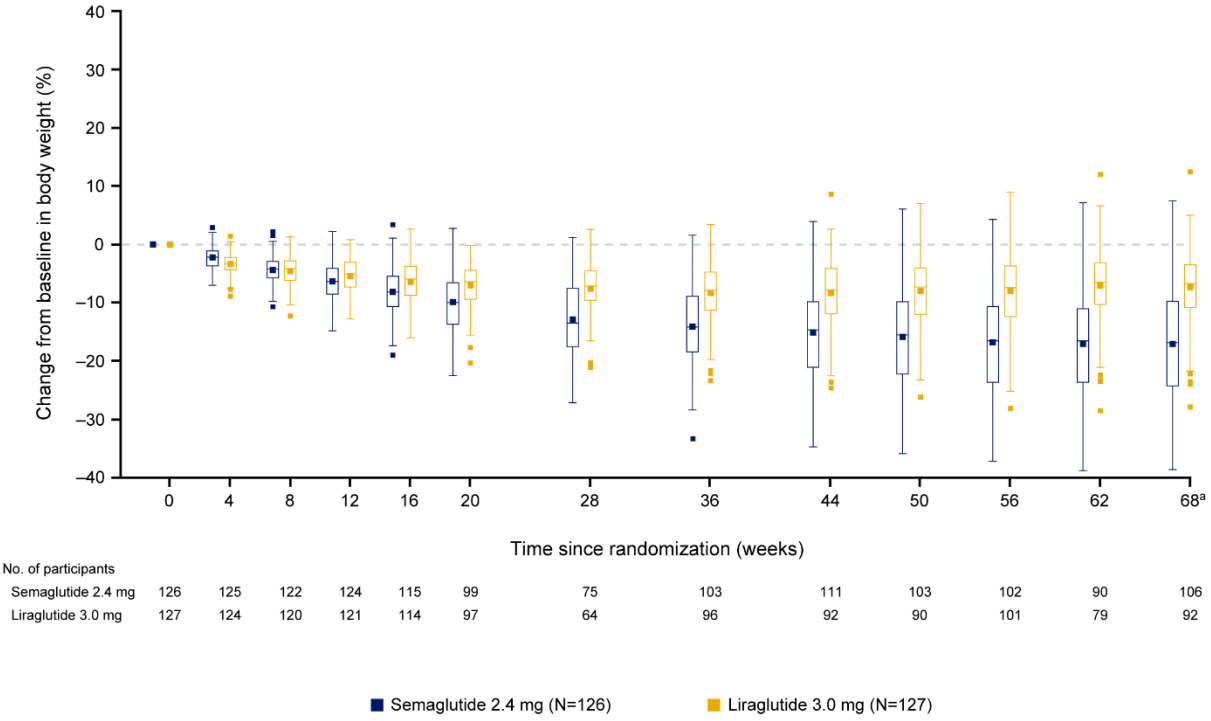
Panel B presents the time from randomization to permanent discontinuation of trial product.

Numbers shown below each panel are participants who have not yet discontinued the trial product (temporarily or permanently for Panel A, and permanently for Panel B). Permanent discontinuation was defined as when a participant stopped taking trial product, did not resume treatment, and was not considered to be 'on-treatment' at week 68. A timepoint was considered as 'on-treatment' if any dose of trial product had been administered within the prior 14 days. Temporary interruption was defined as a participant missing at least 2 consecutive doses of trial product and resuming treatment before the end of the treatment period (week 68). Participant numbers in the legend are for the full analysis set.

[a]Pooled placebo data.

Supplement 3

eFigure 5. Percent Change in Body Weight from Baseline to Week 68 (Observed On-Treatment Data; Full Analysis Set)



Data presented are observed (ie, as-measured) changes during the on-treatment period (the time during which treatment with any dose of trial intervention was given within the previous 14 days [after excluding any temporary interruptions in taking trial intervention]) for the full analysis set .

The middle lines within each box represent the median observed changes from baseline; the symbols in the boxes represent the mean observed percent change; the box tops and bottoms represent the interquartile range; the whiskers extend to the most extreme observed values with 1.5 times the interquartile range of the nearer quartile; and the symbols beyond these points represent the observed values outside that range. More negative values indicate greater reductions. Numbers shown below the graph are the number of participants with observed data at each timepoint. Participant numbers in the legend are for the full analysis set. Data are only presented for the active treatment groups.

[a]The observed mean (95% CI) changes from baseline to week 68 for treatment completers (on-treatment at week 68) were –17.1% (–19.0 to –15.2) for semaglutide, –7.5% (–8.9 to –6.0) for liraglutide, and –1.7% (–3.8 to 0.4) for placebo.

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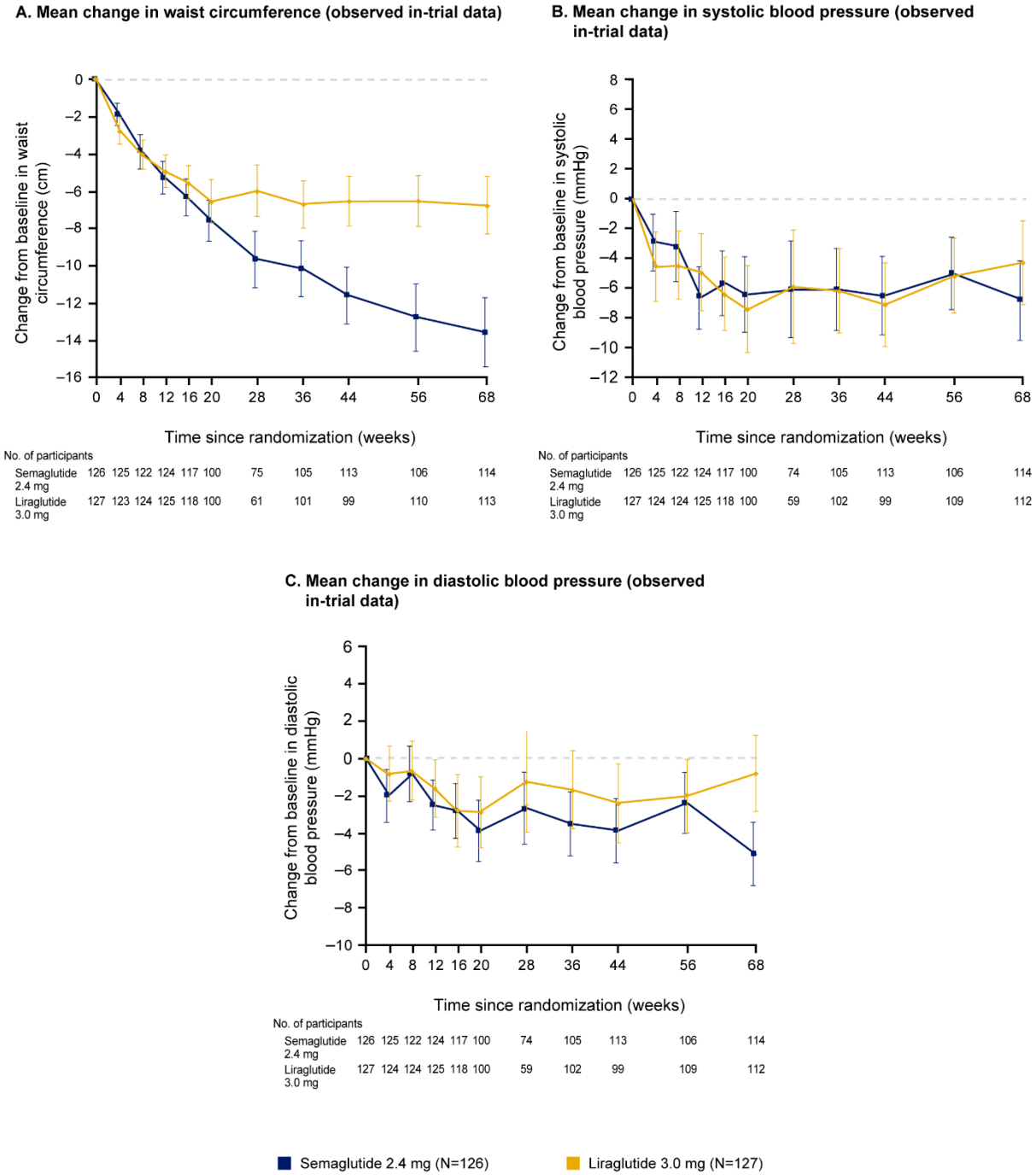
eFigure 6. Change in Selected Cardiovascular-Related Efficacy Outcomes from Baseline to Week 68 (Observed In-Trial Data; Full Analysis Set)



Data presented are observed (ie, as-measured) changes during the in-trial period (the time from randomization to last contact with trial site, irrespective of treatment discontinuation or rescue intervention) for the full analysis set. Error bars are 95% CI. Numbers shown below each panel are the number of participants contributing to the mean. Participant numbers in the legend are for the full analysis set. Data are only presented for the active treatment groups.

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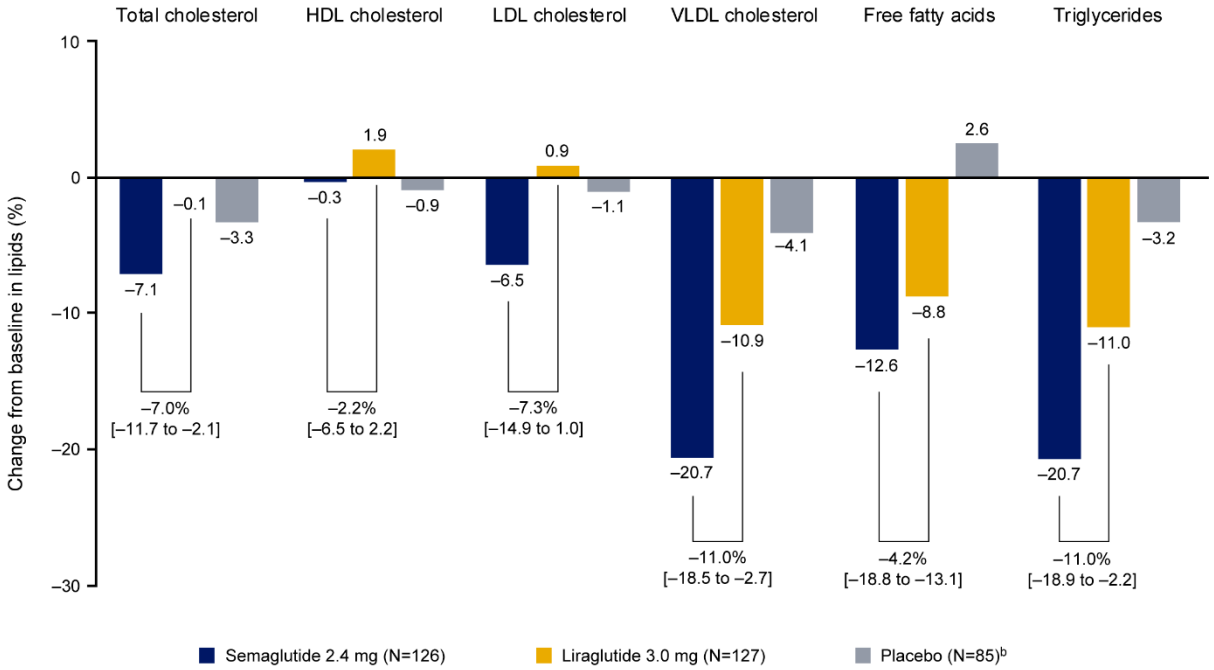
eFigure 7. Change in Fasting Lipid Profile from Baseline to Week 68 (Treatment Policy Estimand[a]; Full Analysis Set)



Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

Values spanning the bars represent the relative percent differences and 95% CI for semaglutide vs liraglutide. Participant numbers in the legend are for the full analysis set.

[a]The treatment policy estimand assessed the treatment effect at week 68, regardless of treatment discontinuation or rescue intervention use. The analyses were based on data from the in-trial observation period (from randomization to last contact with the trial site). Analyses were conducted using analysis of covariance, with randomized treatment as a factor and baseline lipid value as a covariate. The ratio to baseline and the corresponding baseline value were log-transformed prior to analysis. A multiple imputation approach was used for missing data. These parameters were initially analyzed on a log scale as estimated ratio to baseline (within treatment groups) and estimated treatment ratios (between treatment groups). For interpretation, these data are expressed as relative percent change and estimated relative percent difference between groups, respectively, and were calculated using the formula (estimated ratio − 1) × 100.

[b]Pooled placebo data.

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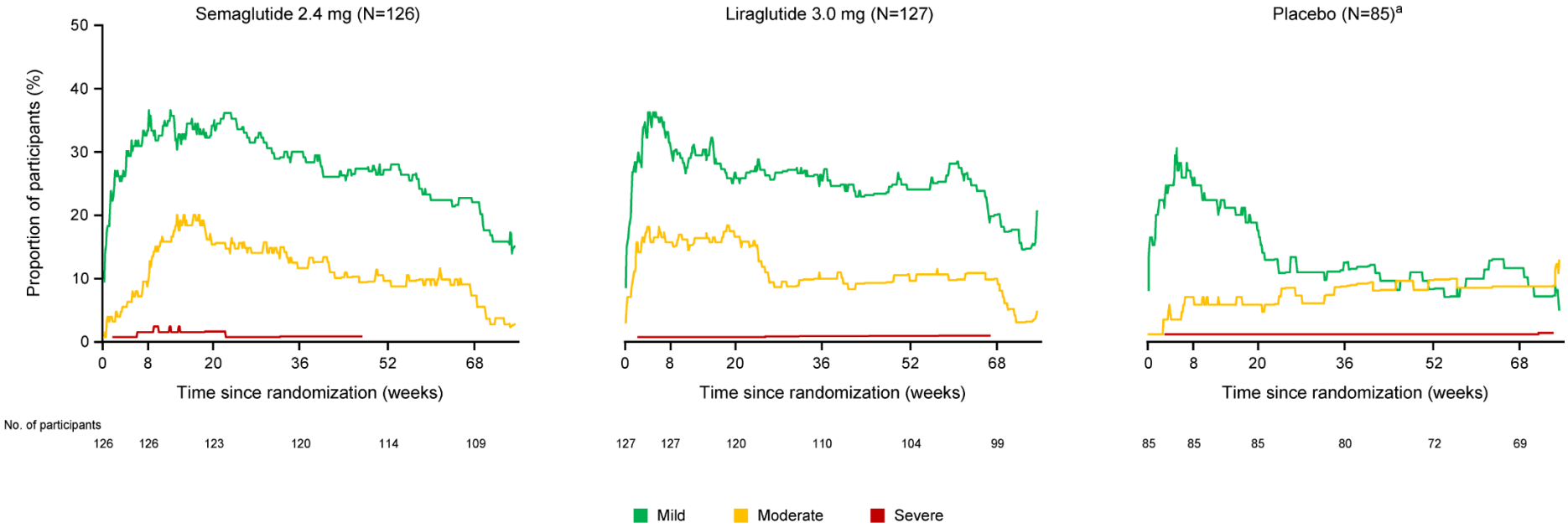
eFigure 8. Prevalence of Gastrointestinal Events by Severity (Observed On-Treatment Data; Safety Analysis Set)



Data presented are for adverse events with onset during the on-treatment period (the time during which treatment with any dose of trial intervention was given within the previous 49 days [after excluding any temporary interruptions in taking trial intervention]). Gastrointestinal adverse events were identified based on a pre-defined Medical Dictionary for Regulatory Activities (MedDRA) search (MedDRA version 23.1). Severity of adverse events was assessed by investigators and classified as mild (an event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities), moderate (an event that causes sufficient discomfort and interferes with normal everyday activities), or severe (an event that prevents normal everyday activities). Numbers shown below the figure are the numbers of participants at risk. Participant numbers in the figure headings are for the safety analysis set.

[a]Pooled placebo data.

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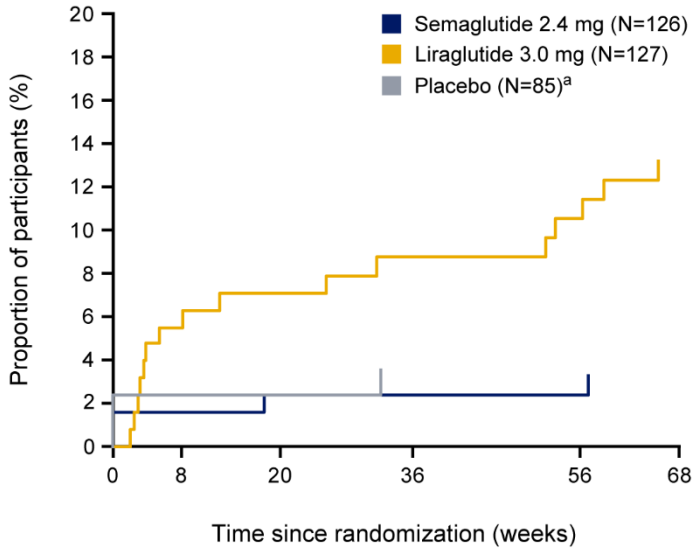
eFigure 9. Time to Onset of First Adverse Event Leading to Permanent Trial Product Discontinuation (Observed On-Treatment Data; Safety Analysis Set)



No. of participants

Semaglutide 2.4 mg	126	124	120	117	112	108
Liraglutide 3.0 mg	127	120	117	108	101	96
Placebo[a]	85	83	83	78	69	68

Data presented are for adverse events with onset during the on-treatment period (the time during which treatment with any dose of trial intervention was given within the previous 49 days [after excluding any temporary interruptions in taking trial intervention]). Numbers shown below the figure are the numbers of participants at risk. Participant numbers in the legend are for the safety analysis set.

[a]Pooled placebo data.

Supplement 3

eReferences

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2013;3(1):1-150.
2. American Diabetes Association. 2. Classification and Diagnosis of Diabetes. *Diabetes Care*. 2017;40(Suppl 1):S11-S24.
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4. Wharton S, Astrup A, Endahl L, et al. Estimating and reporting treatment effects in clinical trials for weight management: using estimands to interpret effects of intercurrent events and missing data. *Int J Obes (Lond)*. 2021;45(5):923-933.