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# Supplemental methods

## Full eligibility criteria

### Inclusion and exclusion criteria

**Inclusion criteria**

Patients are eligible to be included in the trial only if all of the following criteria apply:

1. 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.

2. Male or female; age ≥18 years at the time of signing informed consent.

3. Body mass index (BMI) ≥27 kg/m2.

4. History of at least one self-reported unsuccessful dietary effort to lose body weight.

5. Diagnosed with type 2 diabetes ≥180 days prior to the day of screening.

6. Patient treated with either:

* Diet and exercise alone or stable treatment with metformin, sulfonylurea (SU), sodium–glucose co-transporter-2 inhibitors (SGLT2is), or glitazone as single-agent therapy; or
* Up to 3 oral glucose-lowering drugs (metformin, SU, SGLT2i, or glitazone) according to local label.

Any approved and marketed metformin, glitazone, SGLT2i, or SU product, or combination products are allowed. Treatment with oral agents should be stable (same drug[s], dose, and dosing frequency) for at least 90 days prior to screening.

7. Glycated haemoglobin (HbA1c) 7–10% (53–86 mmol/mol) (both inclusive).

The criteria are assessed at the investigator’s discretion unless otherwise stated.

**Exclusion criteria**

Patients are excluded from the trial if any of the following criteria apply:

*Diabetes-related:*

1. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within the past 90 days before screening.

2. Receipt of any other glucose-lowering investigational drug within 90 days prior to screening for this trial, or receipt of any investigational drugs not affecting diabetes within 30 days before screening for this trial.

3. Treatment with a glucagon-like peptide-1 receptor agonist within 180 days prior to screening.

4. Renal impairment measured as estimated glomerular filtration rate value of <30 mL/min/1·73 m2 (<60 mL/min/1·73 m2 in patients treated with SGLT2i) according to Chronic Kidney Disease Epidemiology Collaboration creatinine equation as defined by Kidney Disease: Improving Global Outcomes 2012 by the central laboratory at screening.

5. Uncontrolled and potentially unstable diabetic retinopathy or maculopathy, verified by a pharmacologically pupil-dilated fundus examination performed by an ophthalmologist or an equally qualified healthcare provider (e.g. optometrist) within the past 90 days before screening or in the period between screening and randomisation.

*Obesity-related:*

6. A self-reported change in body weight of >5 kg (11 lbs) within 90 days before screening, irrespective of medical records.

7. Previous or planned (during the trial period) obesity treatment with surgery or a weight-loss device. However, the following are 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.

8. Uncontrolled thyroid disease, defined as thyroid-stimulating hormone >6·0 mIU/L or <0·4 mIU/L as measured by central laboratory at screening.

*Mental health:*

9. History of major depressive disorder within 2 years before screening.

10. Diagnosis of other severe psychiatric disorder (e.g. schizophrenia, bipolar disorder).

11. A score of ≥15 on the Patient Health Questionnaire-9 at screening.

12. A lifetime history of a suicidal attempt.

13. Suicidal behavior within 30 days before screening.

14. Suicidal ideation corresponding to type 4 or 5 on the Columbia-Suicide Severity Rating Scale within the past 30 days before screening.

*General safety:*

15. Use of non-herbal Chinese medicine or other non-herbal local medicine with unknown/unspecified content within 90 days before screening.

16. Presence of acute pancreatitis within the past 180 days prior to the day of screening.

17. History or presence of chronic pancreatitis.

18. Calcitonin ≥100 ng/L as measured by the central laboratory at screening.

19. Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.

20. 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.

21. Any of the following: myocardial infarction, stroke, hospitalisation for unstable angina, or transient ischemic attack within the past 60 days prior to screening.

22. Patient presently classified as being in New York Heart Association Class IV.

23. Surgery scheduled for the duration of the trial, except for minor surgical procedures, in the opinion of the investigator.

24. Known or suspected abuse of alcohol or recreational drugs.

25. Known or suspected hypersensitivity to trial product(s) or related products.

26. Previous participation in this trial. Participation is defined as signed informed consent.

27. Participation in another clinical trial within 90 days before screening.

28. Other patient(s) from the same household participating in any semaglutide trial.

29. Woman who is pregnant, breast-feeding, or intends to become pregnant, or is of child-bearing potential and not using a highly effective contraceptive method.

30. Any disorder, unwillingness, or inability, not covered by any of the other exclusion criteria, which in the investigator’s opinion, might jeopardise the patient’s safety or compliance with the protocol.

The criteria are assessed at the investigator’s discretion unless otherwise stated.

## Patient-reported outcome assessments

### Short Form36v2® Health Survey, Acute Version (SF-36)

The SF-36 is a generic patient-reported outcome (PRO) instrument measuring health-related quality of life and general health status across disease areas. It consists of 36 questions (items) across eight domains (physical functioning, role limitations due to physical health problems, body pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health). The SF-36 also provides two aggregated scores, the physical component summary (PCS), and mental component summary (MCS), created by aggregating the eight domains according to the scoring algorithm.1 SF-36 scores are norm-based scores, i.e. transformed to a scale on which the 2009 US general population has a mean of 50 and a standard deviation of 10. The lowest to highest scores are 19·03 to 57·60 for the physical functioning domain, 6·11 to 79·67 for the PCS, and −3·83 to 78·75 for the MCS, reported as norm-based scores. An increase in score represents an improvement in health status.

### Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite-CT)

The IWQOL-Lite-CT is a 20-item PRO instrument used to assess weight-related physical and psychosocial functioning in three composite scores (physical, physical function, and psychosocial) and a total score. The range of possible scores for the IWQOL-Lite-CT is 0–100. Larger values on composite scores as well as total scores of the IWQOL-Lite-CT indicate better patient functioning.2

## Endpoints

Primary endpoints are used to compare the effect of subcutaneous semaglutide 2·4 mg once weekly versus placebo.

### Co-primary endpoints

* Change from baseline (week 0) to week 68 in body weight (%).
* Patients who after 68 weeks achieved (yes/no) body weight reduction ≥5% from baseline (week 0).

### Confirmatory secondary endpoints

Confirmatory secondary endpoints are used to compare the effect of subcutaneous semaglutide 2·4 mg once weekly versus placebo unless otherwise stated.

* Subjects who after 68 weeks achieved (yes/no):
  + Body weight reduction ≥10% from baseline (week 0).
  + Body weight reduction ≥15% from baseline (week 0).
* Change from baseline (week 0) to week 68 in:
  + Waist circumference (cm).
  + Body weight (%) (semaglutide subcutaneous 2·4 mg once weekly versus semaglutide subcutaneous 1·0 mg once weekly).
  + Glycated haemoglobin (%, mmol/mol).
  + Systolic blood pressure (mmHg).
  + SF-36 physical functioning score.
  + IWQOL-Lite-CT physical function (5 items) score.

### Exploratory secondary endpoints

The exploratory secondary endpoints are used to compare the effect of subcutaneous semaglutide 2·4 mg once weekly versus placebo, and subcutaneous semaglutide 2·4 mg once weekly versus subcutaneous semaglutide 1·0 mg once weekly, unless otherwise stated.

* Change from baseline (week 0) to week 68 in:
  + Body weight (kg) and BMI (kg/m2).
  + HbA1c (%, mmol/mol) (semaglutide subcutaneous 1·0 mg once weekly *vs* semaglutide placebo), fasting plasma glucose (mg/dL) and fasting serum insulin (mIU/L).
  + Diastolic blood pressure (mmHg).
  + Lipids (mg/dL): total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, free fatty acids, triglycerides.
  + High-sensitivity C-reactive protein (mg/L).
  + Plasminogen activator inhibitor-1 activity (AU/mL).
  + SF-36 scores: role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health, PCS, MCS.
  + IWQOL-Lite-CT: physical function score, psychosocial score, and total score.
* Patients who after 68 weeks achieved (yes/no):
  + Responder definition value for SF-36 physical functioning score.
  + Responder definition value for IWQOL-Lite-CT physical function (5 items) score.
  + HbA1c <7·0% (53 mmol/mol).
  + HbA1c ≤6·5% (48 mmol/mol).

### Exploratory secondary safety endpoints

* Number of treatment-emergent adverse events from baseline (week 0) to week 75.
* Number of serious adverse events from baseline (week 0) to week 75.
* Number of treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemia episodes from baseline (week 0) to week 75.
* Change from baseline (week 0) to week 68 in:
  + Pulse (bpm).
  + Amylase (U/L).
  + Lipase (U/L).
  + Calcitonin (ng/L).

### Exploratory endpoints

The exploratory endpoints reflect the comparison of subcutaneous semaglutide 2·4 mg once weekly versus placebo.

* Patients who after 68 weeks achieved (yes/no) the following in:
  + New onset of micro-albuminuria (urine albumin-to-creatinine ratio [UACR] ≥30 and ≤300 mg/g) in patients without albuminuria (UACR <30 mg/g) at randomisation (week 0).
  + New onset of macro albuminuria (UACR >300 mg/g) in patients without macro-albuminuria at randomisation (week 0).
  + Regression of micro-/macro-albuminuria to normal (in patients with either micro- (UACR ≥30 and ≤300 mg/g) or macro-albuminuria (UACR >300 mg/g) at baseline [week 0]).
* Change from baseline (week 0) to week 68 in:
  + Antihypertensive medication (decrease, no change, increase).
  + Lipid-lowering medication (decrease, no change, increase).
  + Concomitant glucose-lowering medication (decrease, no change, increase).
  + 6 metre walk test (only for patients with a BMI ≥35 kg/m2).
  + Fatty liver index score category (<30, ≥30–<60, ≥60).
  + Work Productivity and Activity Impairment Questionnaire - Specific Health Problem V2.0 (WPAI-SHP).
    - Work time missed due to weight (%).
    - Impairment while working due to weight (%).
    - Overall work impairment due to weight (%).
    - Activity impairment due to weight (%).
* Patients who, from randomisation (week 0) to week 68, permanently discontinued randomised trial product (yes/no).
* Time to permanent discontinuation of randomised trial product (weeks).

# Supplementary figures and tables

## Table S1: Analysis and imputation methods to address the treatment policy and trial product estimands for the primary and confirmatory secondary endpoints in the statistical testing hierarchy

| **Endpoint** | **Test order** | **Estimand** | **Comparison. Semaglutide 2·4 mg *vs*** | **Statistical model** | **Imputation approach** |
| --- | --- | --- | --- | --- | --- |
| **Primary endpoints** | | | | | |
| Body weight change — % | 1 | Treatment policy | Placebo | ANCOVA | RD-MI |
|  | Trial product | Placebo | MMRM | ·· |
| Body weight reduction ≥5% | 2 | Treatment policy | Placebo | Logistic regression | RD-MI |
|  | Trial product | Placebo | Logistic regression | MMRM |
| **Confirmatory secondary endpoints** | | | | | |
| Body weight reduction ≥10% | 3 | Treatment policy | Placebo | Logistic regression | RD-MI |
|  | Trial product | Placebo | Logistic regression | MMRM |
| Body weight reduction ≥15% | 4 | Treatment policy | Placebo | Logistic regression | RD-MI |
|  | Trial product | Placebo | Logistic regression | MMRM |
| Waist circumference change — cm | 5 | Treatment policy | Placebo | ANCOVA | RD-MI |
|  | Trial product | Placebo | MMRM | ·· |
| Body weight change — % | 6 | Treatment policy | Semaglutide 1·0 mg | ANCOVA | RD-MI |
| HbA1c change — %, mmol/mol | 7 | Treatment policy | Placebo | ANCOVA | RD-MI |
|  | Trial product | Placebo | MMRM | ·· |
| Systolic blood pressure change — mmHg | 8 | Treatment policy | Placebo | ANCOVA | RD-MI |
|  | Trial product | Placebo | MMRM | ·· |
| SF-36 physical functioning score change | 9 | Treatment policy | Placebo | ANCOVA | RD-MI |
|  | Trial product | Placebo | MMRM | ·· |
| IWQOL-Lite-CT physical function score change | 10 | Treatment policy | Placebo | ANCOVA | RD-MI |
|  | Trial product | Placebo | MMRM | ·· |

Test order refers to the order of the endpoint in the statistical test hierarchy. ·· denotes missing data.

ANCOVA=analysis of covariance. FAS=full analysis set. HbA1c=glycated hemoglobin. IWQOL-Lite-CT=Impact of Weight on Quality of Life-Lite Clinical Trials Version. LR=logistic regression. MMRM=mixed model for repeated measurements. RD-MI=multiple imputation using retrieved patients. sBP=systolic blood pressure. SF-36=Short Form36v2® Health Survey, Acute Version.

## Table S2: Co-primary, secondary, and selected exploratory trial endpoints (trial product estimand\*)

| **Endpoint** | **Semaglutide 2·4 mg (N=404)** | **Semaglutide 1·0 mg (N=403)** | **Placebo (N=403)** | **Treatment comparison (95% CI)** |
| --- | --- | --- | --- | --- |
| **Primary endpoints** | | | | |
| Body weight — % |  |  |  |  |
| n | 351 | 353 | 340 |  |
| Change from baseline to week 68 — % (SE) | −10·64 (0·4) | −7·55 (0·4) | −3·07 (0·4) | Semaglutide 2·4 mg – placebo (percentage points); ETD: −7·57 (−8·56 to −6·58) |
|  |  |  |  | Semaglutide 2·4 mg – semaglutide 1·0 mg (percentage points); ETD: −3·09 (−4·08 to −2·10) |
| Body weight reduction ≥5% |  |  |  |  |
| n | 351 | 353 | 340 |  |
| Proportion of patients at week 68 — n (%) | 257 (73·2) | 209 (59·2) | 94 (27·6) | Semaglutide 2·4 mg / placebo; OR: 8·69 (6·31 to 11·97) |
|  |  |  |  | Semaglutide 2·4 mg / semaglutide 1·0 mg; OR: 1·91 (1·41 to 2·59) |
| **Secondary endpoints** | | | | |
| Body weight reduction ≥10% |  |  |  |  |
| n | 351 | 353 | 340 |  |
| Proportion of patients at week 68 — n (%) | 175 (49·9) | 105 (29·7) | 24 (7·1) | Semaglutide 2·4 mg / placebo; OR: 14·60 (9·44 to 22·57) |
|  |  |  |  | Semaglutide 2·4 mg / semaglutide 1·0 mg; OR: 2·71 (2·01 to 3·65) |
| Body weight reduction ≥15% |  |  |  |  |
| n | 351 | 353 | 340 |  |
| Proportion of patients at week 68 — n (%) | 99 (28·2) | 51 (14·4) | 9 (2·6) | Semaglutide 2·4 mg / placebo; OR: 12·35 (6·50 to 23·47) |
|  |  |  |  | Semaglutide 2·4 mg / semaglutide 1·0 mg; OR: 2·28 (1·57 to 3·29) |
| Waist circumference — cm |  |  |  |  |
| n | 351 | 353 | 340 |  |
| Week 68 mean ± SD | 103·6 ±14·7 | 106·9 ±14·7 | 110·7 ±13·5 | Semaglutide 2·4 mg – placebo (cm); ETD: −6·6 (−7·6 to −5·6) |
| Change from baseline — cm to week 68 (SE) | −10·7 (0·4) | −7·3 (0·4) | −4·1 (0·4) | Semaglutide 2·4 mg – semaglutide 1·0 mg (cm); ETD: −3·3 (−4·4 to −2·3) |
| HbA1c — % |  |  |  |  |
| n | 350 | 350 | 337 |  |
| Week 68 mean ± SD | 6·3 ± 1·1 | 6·5 ± 1·0 | 7·8 ± 1·3 | Semaglutide 2·4 mg – placebo (percentage points); ETD: −1·5 (−1·7 to −1·4) |
| Change from baseline to week 68 — % points (SE) | −1·9 (0·1) | −1·7 (0·1) | −0·3 (0·1) | Semaglutide 2·4 mg – semaglutide 1·0 mg (percentage points); ETD: −0·2 (−0·3 to 0·0) |
| HbA1c — mmol/mol |  |  |  |  |
| n | 350 | 350 | 337 |  |
| Week 68 mean ± SD | 45·5 ± 11·8 | 47·3 ± 10·7 | 61·7 ± 13·9 | Semaglutide 2·4 mg – placebo (mmol/mol); ETD: −16·8 (−18·5 to −15·1) |
| Change from baseline to week 68 — mmol/mol (SE) | −20·3 (0·6) | −18·3 (0·6) | −3·5 (0·6) | Semaglutide 2·4 mg – semaglutide 1·0 mg (mmol/mol); ETD: −2·0 (−3·7 to −0·3) |
| Systolic blood pressure — mmHg |  |  |  |  |
| n | 351 | 353 | 340 |  |
| Week 68 mean ± SD | 126 ± 14 | 127 ± 15 | 130 ± 14 | Semaglutide 2·4 mg – placebo (mmHg); ETD: −4·8 (−6·7 to −2·9) |
| Change from baseline to week 68 — mmHg (SE) | −4·5 (0·7) | −3·3 (0·7) | 0·3 (0·7) | Semaglutide 2·4 mg – semaglutide 1·0 mg (mmHg); ETD: −1·2 (−3·1 to 0·6) |
| SF-36 physical functioning score |  |  |  |  |
| n | 347 | 346 | 338 |  |
| Week 68 mean ± SD | 52·4 ± 7·7 | 52·9 ± 6·9 | 50·6 ± 8·9 | Semaglutide 2·4 mg – placebo; ETD: 2·0 (1·0 to 2·9) |
| Change from baseline to week 68 (SE) | 2·7 (0·3) | 2·7 (0·3) | 0·7 (0·3) | Semaglutide 2·4 mg – semaglutide 1·0 mg; ETD: 0·0 (−0·9 to 0·9) |
| IWQOL-Lite-CT physical function score |  |  |  |  |
| n | 347 | 346 | 338 |  |
| Week 68 mean ± SD | 79·8 ± 22·6 | 80·3 ± 20·6 | 75·3 ± 24·1 | Semaglutide 2·4 mg – placebo; ETD: 6·3 (3·7 to 8·9) |
| Change from baseline to week 68 (SE) | 11·3 (0·9) | 9·7 (0·9) | 5·1 (0·9) | Semaglutide 2·4 mg – semaglutide 1·0 mg; ETD: 1·6 (−1·0 to 4·2) |
| **Exploratory secondary endpoints** | | | | |
| Body weight — kg |  |  |  |  |
| n | 351 | 353 | 340 |  |
| Week 68 mean ± SD | 89·1 ± 21·3 | 92·2 ± 21·0 | 96·3 ± 19·9 | Semaglutide 2·4 mg – placebo (kg); ETD: −7·5 (−8·5 to −6·5) |
| Change from baseline to week 68 — kg (SE) | −10·6 (0·4) | −7·5 (0·4) | −3·1 (0·4) | Semaglutide 2·4 mg – semaglutide 1·0 mg (kg); ETD: −3·1 (−4·2 to −2·1) |
| BMI — kg/m2 |  |  |  |  |
| n | 351 | 353 | 340 |  |
| Week 68 mean ± SD | 32·1 ± 6·1 | 32·9 ± 6·0 | 34·6 ± 6·3 | Semaglutide 2·4 mg – placebo (kg/m2); ETD: −2·7 (−3·1 to −2·4) |
| Change from baseline to week 68 — kg/m2 (SE) | −3·8 (0·1) | −2·7 (0·1) | −1·1 (0·1) | Semaglutide 2·4 mg – semaglutide 1·0 mg (kg/m2); ETD: −1·1 (−1·5 to −0·8) |
| HbA1c ≤6·5% |  |  |  |  |
| n | 350 | 350 | 337 |  |
| Proportion of patients at week 68 — n (%) | 252 (72·0) | 221 (63·1) | 48 (14·2) | Semaglutide 2·4 mg / placebo; OR: 28·06 (18·67 to 42·17) |
|  |  |  |  | Semaglutide 2·4 mg / semaglutide 1·0 mg; OR: 1·64 (1·19 to 2·27) |
| HbA1c <7·0% |  |  |  |  |
| n | 350 | 350 | 337 |  |
| Proportion of patients at week 68 — n (%) | 288 (82·3) | 266 (76·0) | 87 (25·8) | Semaglutide 2·4 mg / placebo; OR: 28·19 (18·84 to 42·17) |
|  |  |  |  | Semaglutide 2·4 mg / semaglutide 1·0 mg; OR: 1·70 (1·17 to 2·48) |
| Fasting plasma glucose — mmol/L |  |  |  |  |
| n | 350 | 350 | 337 |  |
| Week 68 mean ± SD | 6·2 ± 1·9 | 6·5 ± 1·9 | 8·5 ± 2·6 | Semaglutide 2·4 mg – placebo (mmol/L); ETD: –2·27 (−2·58 to −1·96 ) |
| Change from baseline to week 68 — mmol/L (SE) | −2·4 (0·1) | −2·1 (0·1) | −0·2 (0·1) | Semaglutide 2·4 mg – semaglutide 1·0 mg (mmol/L); ETD: −0·33 (−0·63 to −0·02) |
| Fasting serum insulin — pmol/L |  |  |  |  |
| n | 342 | 339 | 327 |  |
| Week 68 geometric mean (CV) | 83·3 (73·7) | 91·4 (72·8) | 91·8 (72·4) | Semaglutide 2·4 mg / placebo; ETR: 0·94 (0·87 to 1·01) |
| Ratio to baseline | 0·87 | 0·96 | 0·93 | Semaglutide 2·4 mg / semaglutide 1·0 mg; ETR: 0·91 (0·84 to 0·98) |
| Diastolic blood pressure change — mmHg |  |  |  |  |
| n | 351 | 353 | 340 |  |
| Week 68 ± SD | 78 ± 9 | 79 ± 9 | 79 ± 9 | Semaglutide 2·4 mg – placebo (mmHg); ETD: −1·2 (−2·4 to 0·0) |
| Change from baseline to week 68 (SE) | −1·8 (0·4) | −0·8 (0·4) | −0·6 (0·4) | Semaglutide 2·4 mg – semaglutide 1·0 mg (mmHg); ETD: −0·9 (−2·1 to 0·2) |
| Lipids |  |  |  |  |
| Total cholesterol — mmol/L |  |  |  |  |
| n | 350 | 350 | 338 |  |
| Week 68 geometric mean (CV) | 4·3 (23·2) | 4·3 (25·8) | 4·5 (24·6) | Semaglutide 2·4 mg / placebo; ETR: 0·98 (0·95 to 1·00) |
| Ratio to baseline† | 0·98 | 0·97 | 1·00 | Semaglutide 2·4 mg / semaglutide 1·0 mg; ETR: 1·01 (0·98 to 1·04) |
| HDL cholesterol — mmol/L |  |  |  |  |
| n | 347 | 350 | 334 |  |
| Week 68 geometric mean (CV) | 1·3 (22·9) | 1·2 (23·5) | 1·2 (23·1) | Semaglutide 2·4 mg / placebo; ETR: 1·05 (1·03 to 1·07) |
| Ratio to baseline† | 1·09 | 1·06 | 1·04 | Semaglutide 2·4 mg / semaglutide 1·0 mg; ETR: 1·03 (1·01 to 1·05) |
| LDL cholesterol — mmol/L |  |  |  |  |
| n | 350 | 350 | 338 |  |
| Week 68 geometric mean (CV) | 2·3 (40·0) | 2·3 (41·1) | 2·4 (38·8) | Semaglutide 2·4 mg / placebo; ETR: 0·98 (0·94 to 1·03) |
| Ratio to baseline† | 1·00 | 0·99 | 1·01 | Semaglutide 2·4 mg / semaglutide 1·0 mg; ETR: 1·01 (0·97 to 1·06) |
| VLDL cholesterol — mmol/L |  |  |  |  |
| n | 350 | 350 | 338 |  |
| Week 68 geometric mean (CV) | 0·6 (49·6) | 0·7 (54·5) | 0·7 (53·2) | Semaglutide 2·4 mg / placebo; ETR: 0·83 (0·79 to 0·88) |
| Ratio to baseline† | 0·77 | 0·81 | 0·92 | Semaglutide 2·4 mg / semaglutide 1·0 mg; ETR: 0·95 (0·89 to 1·00) |
| Free fatty acids — mmol/L |  |  |  |  |
| n | 342 | 339 | 327 |  |
| Week 68 geometric mean (CV) | 0·5 (61·8) | 0·5 (55·5) | 0·6 (55·9) | Semaglutide 2·4 mg / placebo; ETR: 0·82 (0·75 to 0·88) |
| Ratio to baseline† | 0·81 | 0·83 | 0·99 | Semaglutide 2·4 mg / semaglutide 1·0 mg; ETR: 0·94 (0·89 to 1·00) |
| Triglycerides — mmol/L |  |  |  |  |
| n | 350 | 350 | 338 |  |
| Week 68 geometric mean (CV) | 1·3 (50·3) | 1·5 (56·6) | 1·7 (58·2) | Semaglutide 2·4 mg / placebo; ETR: 0·82 (0·77 to 0·87) |
| Ratio to baseline† | 0·75 | 0·80 | 0·92 | Semaglutide 2·4 mg / semaglutide 1·0 mg; ETR: 0·94 (0·89 to 1·00) |
| C-reactive protein change — mg/dL |  |  |  |  |
| n | 350 | 350 | 338 |  |
| Week 68 geometric mean (CV) | 1·58 (220·0) | 1·89 (194·5) | 2·64 (178·5) | Semaglutide 2·4 mg / placebo; ETR: 0·57 (0·49 to 0·65) |
| Ratio to baseline† | 0·46 | 0·55 | 0·81 | Semaglutide 2·4 mg / semaglutide 1·0 mg; ETR: 0·83 (0·72 to 0·95) |

\*The trial product estimand assesses treatment effect if all patients adhered to treatment and did not start any rescue intervention. All patients in the full analysis set are included in the treatment comparisons

†Data presented as ratio from baseline to week 68 (ratio to baseline and corresponding baseline were log-transformed prior to analysis).

Continuous endpoints were analysed using a mixed model for repeated measurements. Binary endpoints were analysed using logistic regression with the same model as for continuous endpoints. Analyses of endpoint for the trial product estimand were not adjusted for multiplicity.

BMI=body mass index. CI=confidence interval. CV=coefficient of variation in percent. ETD=estimated treatment difference. ETR=estimated treatment ratio. HbA1c=glycated haemoglobin. HDL=high-density lipoprotein. LDL=low-density lipoprotein. OR=odds ratio. SD=standard deviation. SE=standard error. VLDL=very low-density lipoprotein.

## Table S3: Exploratory secondary safety endpoints (on-treatment)\*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Semaglutide 2·4 mg** | | **Semaglutide 1·0 mg** | | **Placebo** | |
|  | **N** | **Mean** | **N** | **Mean** | **N** | **Mean** |
| Pulse rate — bpm |  |  |  |  |  |  |
| Baseline | 403 | 75 ± 11 | 402 | 76 ± 11 | 402 | 76 ± 11 |
| Week 68 | 351 | 78 ± 10 | 353 | 77 ± 10 | 340 | 75 ± 11 |
| Change from baseline to week 68 (SE)† | 320 | 2·5 (0·5) | 326 | 1·8 (0·5) | 313 | –0·2 (0·5) |
| Estimated treatment difference (95% CI)† | Semaglutide 2·4 mg *vs* placebo | | | Semaglutide 2·4 mg *vs* 1·0 mg | | |
|  | 2·71 (1·43 to 3·99) | | | 0·71 (–0·56 to 1·99) | | |
| Amylase — U/L |  |  |  |  |  |  |
| Baseline | 403 | 50 (44·3) | 402 | 50 (45·0) | 402 | 50 (47·3) |
| Week 68 | 350 | 62 (45·6) | 350 | 59 (47·4) | 338 | 53 (45·3) |
| Ratio to baseline at week 68 | 350 | 1·24 (28·3) | 350 | 1·19 (32·8) | 338 | 1·06 (25·0) |
| Lipase — U/L |  |  |  |  |  |  |
| Baseline | 403 | 33 (64·3) | 402 | 34 (63·4) | 402 | 34 (73·9) |
| Week 68 | 350 | 46 (71·8) | 350 | 43 (69·2) | 338 | 34 (71·3) |
| Ratio to baseline at week 68 | 350 | 1·41 (57·2) | 350 | 1.31 (57·2) | 338 | 0.99 (51·8) |
| Alanine aminotransferase — U/L |  |  |  |  |  |  |
| Baseline | 401 | 27 (60·3) | 401 | 29 (65·9) | 402 | 28 (62·9) |
| Week 68 | 347 | 20 (56·1) | 350 | 21 (65·9) | 334 | 24 (61·3) |
| Ratio to baseline at week 68 | 347 | 0·74 (66·1) | 349 | 0·76 (57·1) | 334 | 0·85 (44·4) |
| Aspartate aminotransferase — U/L |  |  |  |  |  |  |
| Baseline | 402 | 22 (52·0) | 398 | 22 (47·6) | 402 | 22 (49·9) |
| Week 68 | 348 | 19 (37·7) | 347 | 20 (37·9) | 335 | 20 (45·6) |
| Ratio to baseline at week 68 | 347 | 0·88 (55·5) | 344 | 0·89 (41·8) | 335 | 0·93 (35·8) |
| Gamma-glutamyl transferase — U/L |  |  |  |  |  |  |
| Baseline | 403 | 33 (65·9) | 402 | 35 (63·3) | 402 | 34 (69·7) |
| Week 68 | 350 | 24 (66·5) | 350 | 27 (62·7) | 338 | 29 (67·4) |
| Ratio to baseline at week 68 | 350 | 0·71 (48·7) | 350 | 0·75 (41·0) | 338 | 0·86 (36·3) |
| Calcitonin — ng/L |  |  |  |  |  |  |
| Baseline | 403 | 1·7 (111·9) | 401 | 1·8 (112·6) | 402 | 1·7 (108·1) |
| Week 68 | 348 | 1·6 (107·5) | 350 | 1·6 (105·9) | 339 | 1·6 (94·2) |
| Ratio to baseline at week 68 | 348 | 0·94 (60·3) | 349 | 0·95 (50·9) | 339 | 0·96 (38·6) |
| Urine albumin-to-creatinine ratio |  |  |  |  |  |  |
| Baseline | 266 | 2·3 (225·7) | 293 | 2·2 (211·9) | 281 | 2·3 (190·9) |
| Week 68 | 254 | 1·6 (148·4) | 253 | 1·8 (192·3) | 260 | 2·7 (196·4) |
| Ratio to baseline at week 68 | 186 | 0·76 (116·5) | 209 | 0·87 (128·1) | 207 | 1·17 (118·1) |

Data are descriptive statistics presented as arithmetic mean ± standard deviation or geometric mean (coefficient of variation in percent), unless indicated otherwise. All patients in the safety analysis set are included in the treatment comparison of change in pulse from baseline to week 68.

\*Excluding number of treatment-emergent adverse events and serious adverse events from baseline to week 75, which are reported in the main publication.

†Trial product estimand data (assesses treatment effect if all participants adhered to treatment and did not start any rescue intervention) analysed using an MMRM; for missing data, categorisation was based on values predicted from an MMRM.

CI=confidence interval. MMRM=mixed model for repeated measurements. SE=standard error.

## Figure S1: STEP 2 study design



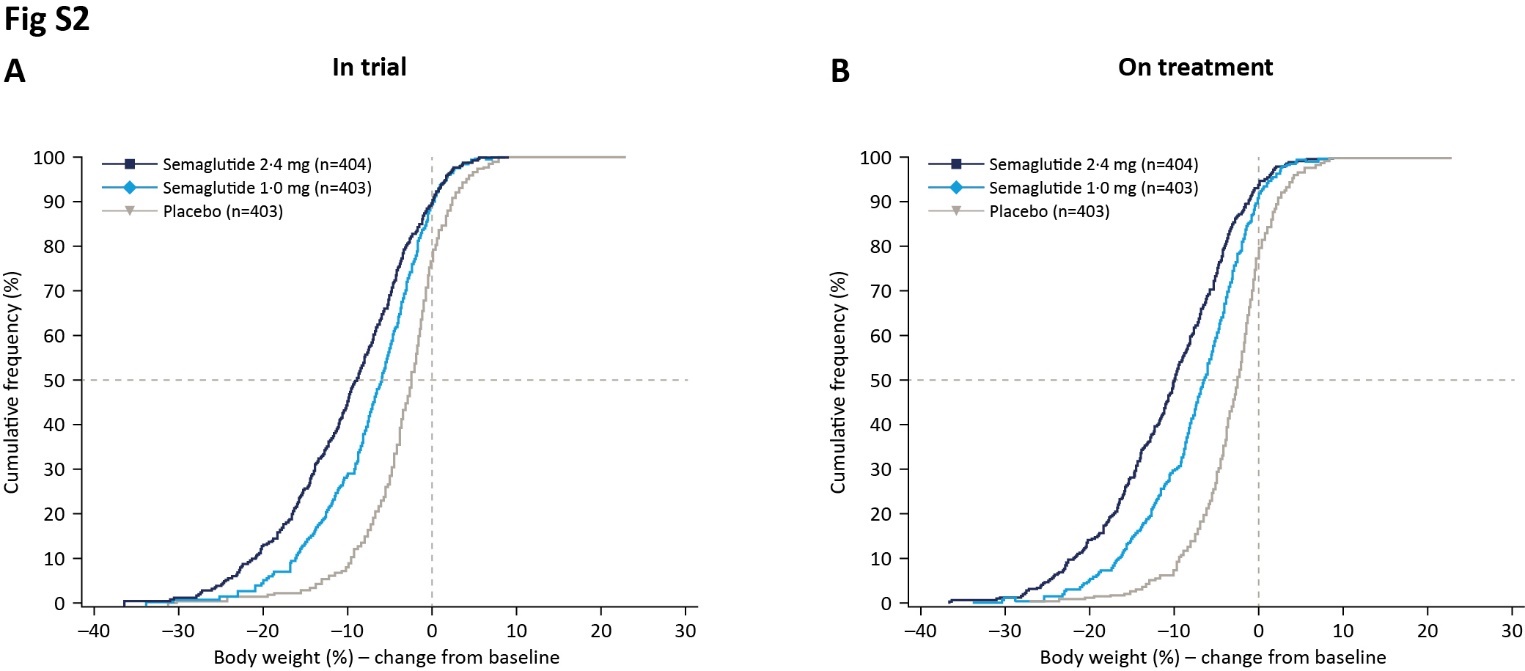
All treatment groups were as an adjunct to lifestyle intervention (–500 kcal/day diet plus 150 min/week physical activity). The end of treatment was followed by a 7-week off-drug follow-up period.

Randomisation of patients was stratified according to diabetes treatment (diet and physical activity alone or monotherapy with metformin or sodium–glucose co-transporter-2 inhibitors, and monotherapy with sulfonylureas or glitazone, or combination treatment with up to three antihyperglycemic agents), and glycated haemoglobin (<8·5% or ≥8·5%).

Patients unable to tolerate the target dose of semaglutide due to side effects were permitted to stay at the lower dose level, at the investigator’s discretion, but investigators were encouraged to attempt dose reescalation once symptoms were resolved or diminished.

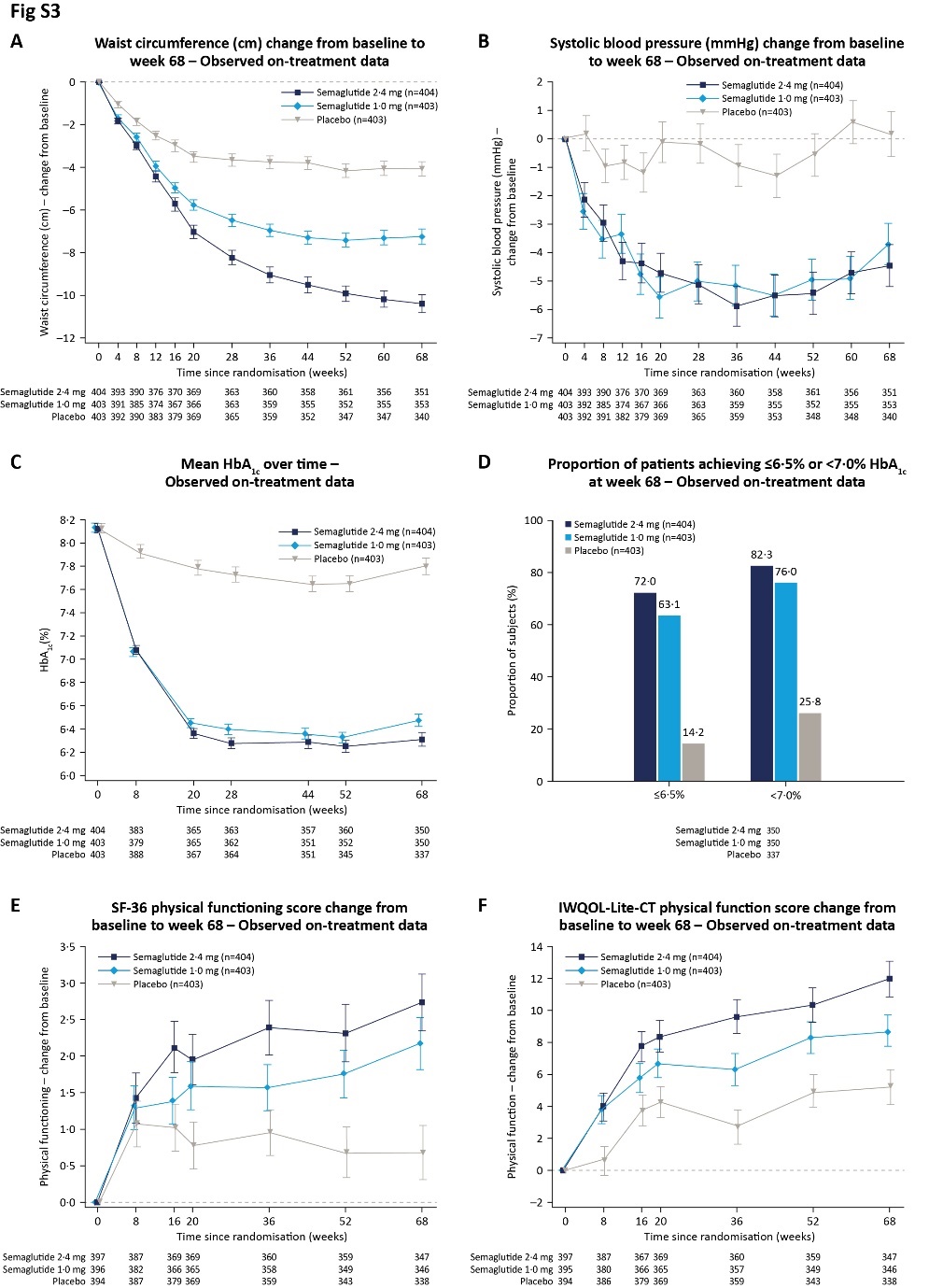
OW=once weekly. s.c.=subcutaneous.

## Figure S2: Cumulative distribution plots of percentage change in body weight from baseline to week 68 for the in-trial (A) and on-treatment (B) observation periods



Cumulative distribution plot of observed percentage change from baseline to week 68 in body weight for patients in the full analysis set during the in-trial and on-treatment observation periods. A time point was considered as on-treatment if any dose of trial product had been administered within the prior 14 days.

## Figure S3: Change in selected confirmatory and exploratory secondary endpoints (baseline to week 68)



Line graphs show the observed mean change from baseline over time in waist circumference (A), systolic blood pressure (B), HbA1c (C), SF-36 physical functioning score (E), and IWQOL-Lite-CT physical function score (F) for participants in the full analysis set during the on-treatment observation period.

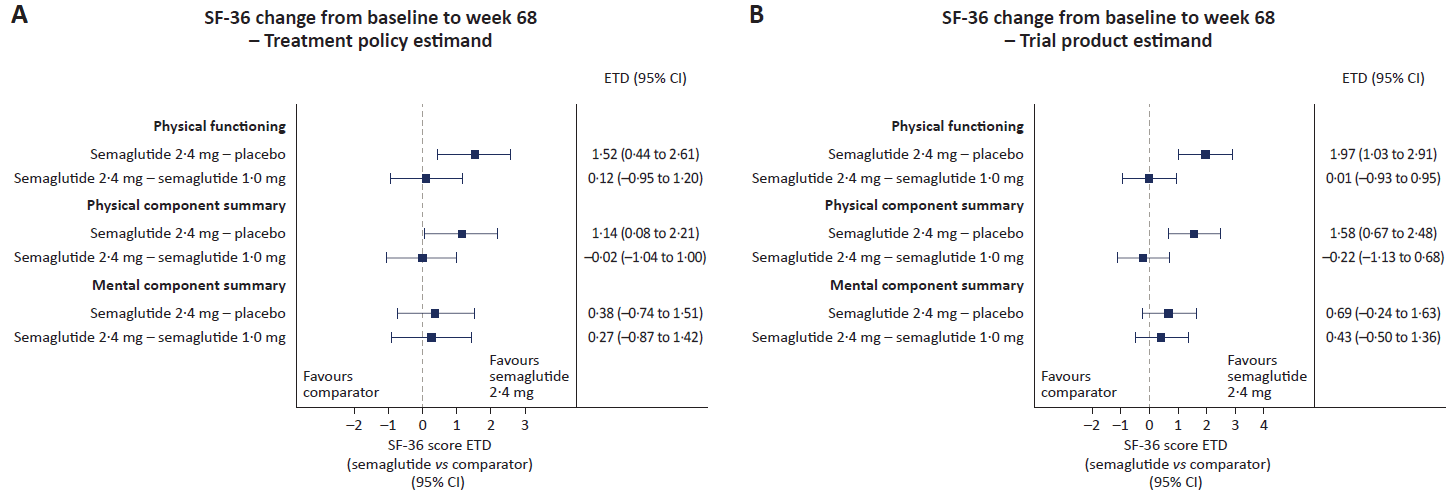
Error bars are ± standard error of the mean. Numbers shown in the lower panel are patients contributing to the mean.

Panel D shows proportion of patients achieving HbA1c targets of ≤6·5% or <7·0% at week 68 for the in-trial period.

Data are for the full analysis set.

CI=confidence interval. HbA1c=glycated haemoglobin.

## Figure S4: Patient-reported outcomes (SF-36 and IWQOL-Lite-CT)





Data presented as estimated treatment differences for semaglutide versus placebo (boxes) and associated 95% confidence intervals (whiskers) for patients in the full analysis set based on the treatment policy (assesses treatment effect regardless of treatment discontinuation or rescue intervention) and trial product (assesses treatment effect if all participants adhered to treatment and did not start any rescue intervention) estimands. Endpoints were analysed using analysis of covariance, with randomised treatment as a factor and baseline endpoint value as a covariate, and a multiple imputation approach for missing data.3 SF-36 scores are normative-based scores (NBS), i.e. scores transformed to a scale where the 2009 US general population has a mean of 50 and a standard deviation of 10.

CI=confidence interval. ETD=estimated treatment difference. IWQOL-Lite-CT=Impact of Weight on Quality of Life-Lite Clinical Trials Version. NBS=norm-based scores. SF-36=Short Form36v2® Health Survey, Acute Version.

## Figure S5: Prevalence and duration of gastrointestinal events by severity

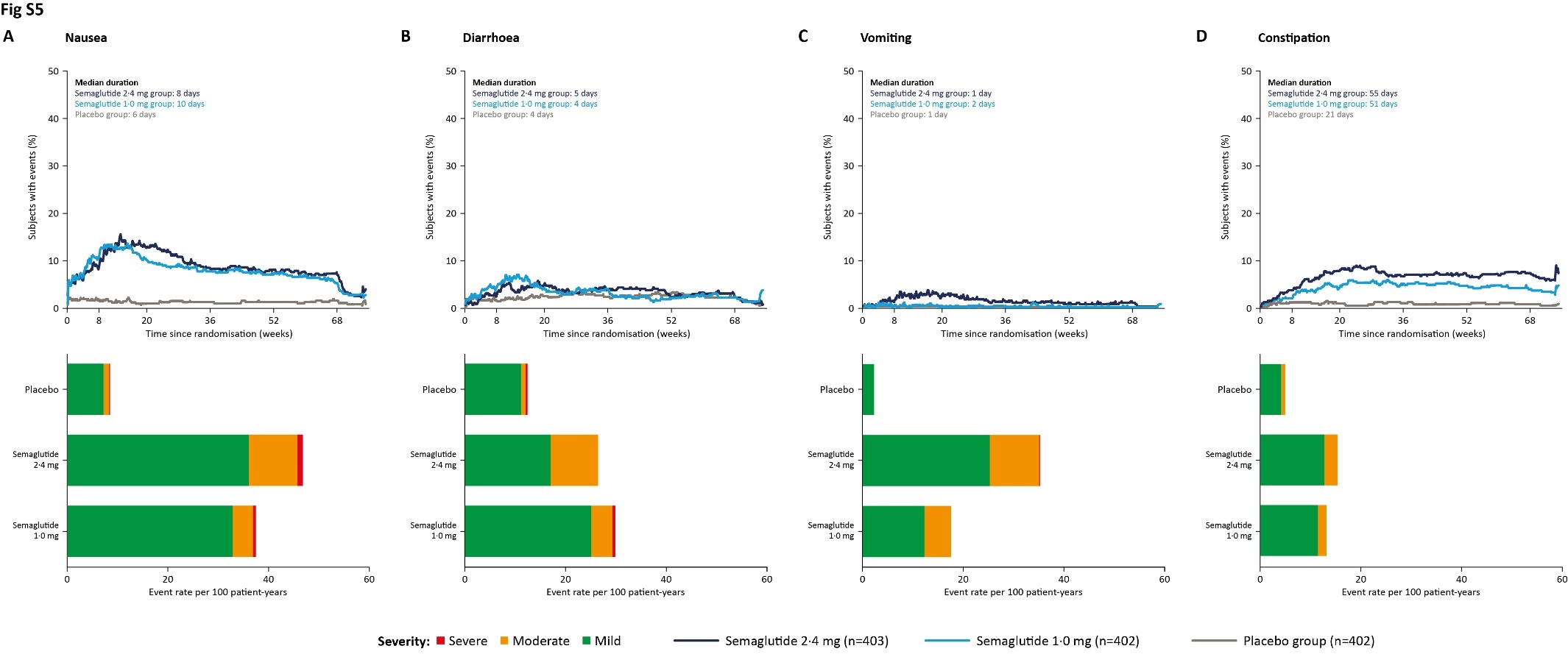
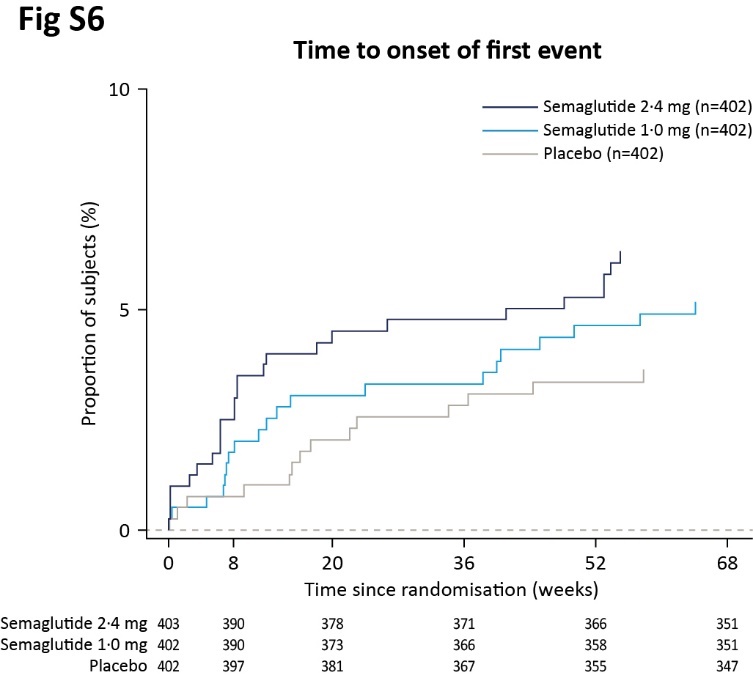


Figure presents the proportion of patients receiving semaglutide or placebo who reported nausea (A), diarrhoea (B), vomiting (C), or constipation (D) events classified as mild, moderate, or severe, over the course of the treatment period. Data are on-treatment observation period data (during treatment with trial product [any dose of trial medication administered within the previous 49 days (i.e. any period of temporary treatment interruption with trial product was excluded)]).

## Figure S6: Time to onset of first adverse events leading to permanent trial product discontinuation



Data are on-treatment observation period data (during treatment with trial product [any dose of trial medication administered within the previous 49 days (i.e. any period of temporary treatment interruption with trial product was excluded)]).

# References

1. Ware JE Jr, Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. *J Clin Epidemiol* 1998; **51:** 903–12.

2. Kolotkin RL, Williams VSL, Ervin CM, et al. Validation of a new measure of quality of life in obesity trials: Impact of Weight on Quality of Life-Lite Clinical Trials version. *Clin Obes* 2019; **9:** e12310.

3. Kushner RF, Calanna S, Davies M, et al. Semaglutide 2.4 mg for the treatment of obesity: key elements of the STEP trials 1 to 5. *Obesity (Silver Spring)* 2020; **28:** 1050–61.

# Redacted protocol