Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial
## Supplementary information

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## Supplementary tables

**Supplementary Table 1 | Co-primary, confirmatory secondary, and selected supportive secondary and exploratory trial endpoints (trial product estimand).**

|                                | Semaglutide (n=152) | Placebo (n=152) | Treatment comparison (95% CI)† |
|--------------------------------|---------------------|----------------|-------------------------------|
| **Co-primary endpoints**       |                     |                |                               |
| Body weight change from baseline to week 104, % | -16.7% (0.9)  | -0.6% (0.9)   | ETD -16.0 (-18.6 to -13.5) |
| ≥5% weight loss at week 104    | 110/132 (83.3%)    | 38/109 (34.9%)| OR 18.1 (10.0 to 32.5)       |
| **Confirmatory secondary endpoints**|                     |                |                               |
| ≥10% weight loss at week 104   | 89/132 (67.4%)     | 14/109 (12.8%)| OR 17.6 (9.4 to 32.9)        |
| ≥15% weight loss at week 104   | 75/132 (56.8%)     | 7/109 (6.4%)  | OR 23.6 (10.4 to 53.8)       |
| Waist circumference – change from baseline to week 104, cm | -15.8 (0.9) | -3.7 (1.0)    | ETD -12.1 (-14.7 to -9.4)  |
| Systolic blood pressure – change from baseline to week 104, mm Hg | -6.1 (1.2) | -0.1 (1.2)    | ETD -6.1 (-9.4 to -2.7)     |
| **Supportive secondary endpoints**|                     |                |                               |
| ≥20% weight loss at week 104   | 52/132 (39.4%)     | 3/109 (2.8%)  | OR 26.7 (8.1 to 87.7)        |
| Body weight                    |                     |                |                               |
| Change from baseline to week 104, kg | -17.6 (1.0) | -0.8 (1.0)    | ETD -16.8 (-19.7 to -13.9)  |
| Change from baseline to week 52, % | -16.6% (0.7) | -2.3% (0.7)  | ETD -14.3% (-16.1% to -12.4%) |
| Body-mass index – change from baseline to week 104, kg/m² | -6.5 (0.4) | -0.3 (0.4)    | ETD -6.2 (-7.3 to -5.1)     |
| HbA1c – change from baseline to week 104, % | -0.5 (0.02) | -0.1 (0.02)  | ETD -0.4 (-0.5 to -0.3)      |
| Measure                                      | Baseline to Week 104, mmol/L | Change from Baseline to Week 104, %† | Estimated relative percentage difference |
|----------------------------------------------|------------------------------|-------------------------------------|------------------------------------------|
| Fasting plasma glucose                       | –0.5 (0.04)                  | 0.1 (0.05)                          | ETD –0.6 (–0.7 to –0.5)                  |
| Diastolic blood pressure                     | –4.4 (0.8)                   | –0.7 (0.8)                          | ETD –3.7 (–5.8 to –1.5)                  |
| Fasting serum insulin                        |                              |                                    | Estimated relative percentage difference |
|                                              |                              |                                    | –30.0% (–39.5% to –18.9%)               |
| Lipids – change from baseline to week 104, %‡ |                              |                                    | Estimated relative percentage difference |
| Total cholesterol                            | –4.6%                        | 2.4%                                | –6.8% (–9.9% to –3.5%)                  |
| HDL cholesterol                              | 10.3%                        | 7.4%                                | Estimated relative percentage difference |
|                                              |                              |                                    | 2.7% (–1.8% to 7.3%)                    |
| LDL cholesterol                              | –8.0%                        | 0.5%                                | Estimated relative percentage difference |
|                                              |                              |                                    | –8.4% (–13.1% to –3.4%)                 |
| VLDL cholesterol                             | –22.4%                       | 1.0%                                | Estimated relative percentage difference |
|                                              |                              |                                    | –23.2% (–29.7% to –16.2%)              |
| Free fatty acids                             | –4.2%                        | 6.0%                                | Estimated relative percentage difference |
|                                              |                              |                                    | –9.6% (–21.2% to 3.7%)                 |
| Triglycerides                                | –22.6%                       | 2.0%                                | Estimated relative percentage difference |
|                                              |                              |                                    | –24.1% (–30.6% to –16.9%)              |
| C-reactive protein – change from baseline     | –59.5%                       | –8.0%                               | Estimated relative percentage difference |
| to week 104, %‡                               |                              |                                    | –56.0% (–66.0% to –43.1%)              |

Data are mean (standard error) or observed n/N (%) unless stated otherwise. Participants in the full analysis set are included in the treatment comparisons. *The trial product estimand assesses treatment effect if trial product was taken as intended (i.e., if all participants adhered to treatment and did not receive rescue intervention); see Table 2 for corresponding data for the treatment policy estimand. Continuous endpoint analyses were conducted using a mixed model for repeated measures (MMRM) with randomized treatment as a factor and baseline endpoint value as a covariate. Analyses of categorical endpoints were conducted with the use of logistic regression, with categorization for missing data based on values predicted from the MMRM. Analyses of endpoints for the trial product estimand were not adjusted for multiplicity. †The difference is the estimated treatment difference between the groups except in the case of fasting serum insulin, lipid, and C-reactive protein levels, for which the comparison is the estimated relative percentage difference between groups. ‡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 percentage change and estimated relative percentage difference between groups, respectively, and were calculated with the following formula: (estimated ratio – 1) × 100. CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SEM, standard error of the mean; VLDL, very-low-density lipoprotein.
**Supplementary Table 2 | Malignant neoplasms by system organ class and preferred term (in-trial).**

| Neoplasms benign, malignant, and unspecified (including cysts and polyps) | Semaglutide (n=152) | Placebo (n=152) |
|---|---|---|
| Participants | Events | Events per 100 patient-years | Participants | Events | Events per 100 patient-years |
| Neoplasms benign, malignant, and unspecified (including cysts and polyps) | | | | | |
| 2 (1.3%) | 2 | 0.6 | 4 (2.6%) | 4 | 1.3 |
| Basal cell carcinoma | 1 (0.7%) | 1 | 0.3 | 0 (0.0%) | 0 |
| Bowen's disease | 1 (0.7%) | 1 | 0.3 | 0 (0.0%) | 0 |
| Invasive ductal breast carcinoma | 0 (0.0%) | 2 (1.3%) | 2 | 0.7 |
| Lung adenocarcinoma | 0 (0.0%) | 1 (0.7%) | 1 | 0.3 |
| Small cell lung cancer metastatic | 0 (0.0%) | 1 (0.7%) | 1 | 0.3 |

*Events observed during the in-trial period (the time from random assignment to last contact with a trial site, regardless of treatment discontinuation or rescue intervention).
Supplementary Table 3 | Supportive secondary safety endpoints (on-treatment).*

|                          | Semaglutide 2.4 mg | Placebo |
|--------------------------|-------------------|---------|
|                          | N     | Mean   | N     | Mean   |
| **Pulse – bpm**          |       |        |       |        |
| Baseline                 | 152   | 73±11  | 152   | 72±9   |
| Week 104                 | 130   | 76±9   | 106   | 71±10  |
| Change from baseline to week 104† | 111   | 3.3    | 96    | –0.8   |
| Estimated treatment difference (semaglutide vs placebo) [95% CI]† |       | 4.1 (2.0 to 6.2) |
| **Amylase – U/L**        |       |        |       |        |
| Baseline                 | 152   | 50 (39.7) | 152   | 52 (33.9) |
| Week 104                 | 130   | 57 (42.0) | 106   | 52 (33.3) |
| Ratio to baseline at week 104 | 130   | 1.13 (20.7) | 106   | 1.02 (15.1) |
| **Lipase – U/L**         |       |        |       |        |
| Baseline                 | 152   | 22 (54.4) | 152   | 23 (51.3) |
| Week 104                 | 130   | 33 (64.6) | 106   | 23 (52.0) |
| Ratio to baseline at week 104 | 130   | 1.47 (52.3) | 106   | 1.00 (34.4) |
| **Calcitonin – ng/L**    |       |        |       |        |
| Baseline                 | 152   | 1.3 (75.8) | 152   | 1.3 (82.1) |
| Week 104                 | 124   | 1.3 (69.6) | 102   | 1.4 (83.1) |
| Ratio to baseline at week 104 | 124   | 0.99 (21.5) | 102   | 0.97 (41.0) |

Data are descriptive statistics presented as arithmetic mean ± standard deviation or geometric mean (coefficient of variation), unless indicated otherwise. *During treatment with trial product (any dose of trial medication administered within the previous 2 weeks (i.e., any period of temporary treatment interruption with trial product was excluded)). †Trial product estimand data (assesses treatment effect if trial product was taken as intended (i.e., if all participants adhered to treatment and did not receive rescue intervention)) analyzed using a mixed model for repeated measurements. CI, confidence interval.
### Supplementary Table 4  | Statistical analysis methodology: 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.

| Objective | Endpoint | Test order | Endpoint type | Estimand | Analysis set | Statistical model | Imputation approach | Sensitivity analyses |
|-----------|----------|------------|---------------|----------|--------------|-------------------|---------------------|---------------------|
| **Primary endpoints** | | | | | | | | |
| Primary | % weight change | 1 | Continuous | Treatment policy* | FAS | ANCOVA | RD-MI | J2R-MI |
| | | | | | | | | S1-SI |
| | | | | | | | | S2-SI |
| | | | | | | | | TP-MI |
| | | | | | | | | MMRM |
| Primary | 5% responders | 2 | Binary | Treatment policy* | FAS | LR | RD-MI | J2R-MI |
| | | | | | | | | S1-SI |
| | | | | | | | | S2-SI |
| | | | | | | | | TP-MI |
| | | | | | | | | MMRM |
| | | | | | | | | Non-responder |
| **Confirmatory secondary endpoints** | | | | | | | | |
| Primary | 10% responders | 3 | Binary | Treatment policy* | FAS | LR | RD-MI | Non-responder |
| | | | | | | | | Non-responder |
| Primary | 15% responders | 4 | Binary | Treatment policy* | FAS | LR | RD-MI | Non-responder |
|                  |                   |              | Trial product† | FAS | LR     | MMRM |
|------------------|-------------------|--------------|---------------|-----|--------|------|
| **Primary**      | Waist circumference change (cm) | 5            | Continuous    | Treatment policy* | FAS | ANCOVA | RD-MI | J2R-MI |
|                  |                   |              | Trial product† | FAS | MMRM   |
| **Secondary**    | Systolic blood pressure change (mm Hg) | 6            | Continuous    | Treatment policy* | FAS | ANCOVA | RD-MI | J2R-MI |
|                  |                   |              | Trial product† | FAS | MMRM   |

*Designated as the primary estimand. †Designated as the secondary estimand. Test order refers to the order of the endpoint in the statistical test hierarchy. All analyses were performed using the full analysis set. All statistical tests were two-sided. ANCOVA, analysis of covariance; FAS, full analysis set; J2R-MI, jump to reference multiple imputation; LR, logistic regression; MMRM, mixed model for repeated measurements; RD-MI, multiple imputation using retrieved subjects; S1-SI and S2-SI, single imputation as done by Sacks; TP-MI, tipping point multiple imputation.