Supplemental Material

Long-term efficacy and safety of oral semaglutide, and the effect of switching from sitagliptin to oral semaglutide in patients with type 2 diabetes: a 52-week, randomized, open-label extension of the PIONEER 7 trial

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**Estimands**

According to International Council for Harmonisation (ICH) E9 (R1)*, an estimand description consists of the treatment condition of interest (e.g. the intervention of interest) plus four other components: 1) population, 2) endpoint, 3) intercurrent events and how they are accounted for, and 4) population level summary. In the table below, the attributes are described for the two estimands in the PIONEER program. Two intercurrent events were considered: trial product discontinuation and initiation of rescue medication.

### The attributes of the two estimands according to ICH E9 (R1)*

| Estimand         | Population                  | Strategy for accounting for intercurrent events                                                                 | Endpoints – switch part                                                                 | Population level summary – switch part                                                                 |
|------------------|-----------------------------|----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Treatment policy | All randomized patients     | Treatment policy strategy for both intercurrent events:                                                     | Change from weeks 52 to 104 in:                                                         | Mean difference between treatments in change from weeks 52 to 104                                   |
|                  |                             | • Trial product discontinuation                                                                               | • HbA\(_1c\)†                                                                        |                                                                                                    |
|                  |                             | • Initiation of rescue medication                                                                            | • Body weight (kg)†                                                                     |                                                                                                    |
|                  |                             |                                                                                                               | • Fasting plasma glucose                                                               |                                                                                                    |
|                  |                             |                                                                                                               | • Body weight (%)                                                                      |                                                                                                    |
|                  |                             |                                                                                                               | • Body mass index                                                                     |                                                                                                    |
|                  |                             |                                                                                                               | • Waist circumference                                                                  |                                                                                                    |
|                  |                             |                                                                                                               | • Amylase                                                                             |                                                                                                    |
|                  |                             |                                                                                                               | • Lipase                                                                               |                                                                                                    |
|                  |                             |                                                                                                               | • Pulse rate                                                                          |                                                                                                    |
|                  |                             |                                                                                                               | • Systolic blood pressure                                                             |                                                                                                    |
|                  |                             |                                                                                                               | • Diastolic blood pressure                                                            |                                                                                                    |
|                  |                             |                                                                                                               | • Patient-reported outcomes (Diabetes Treatment Satisfaction Questionnaire, Short Form-36 version 2 (acute version)) |                                                                                                    |
|                  |                             |                                                                                                               |                                                                                       |                                                                                                    |
|                  |                             |                                                                                                               | If a patient at week 104 achieves:                                                    | The odds ratio between treatments in reaching target                                               |
|                  |                             |                                                                                                               | • HbA\(_1c\)<7.0%                                                                     |                                                                                                    |
|                  |                             |                                                                                                               | • HbA\(_1c\)≤6.5%                                                                     |                                                                                                    |
|                  |                             |                                                                                                               | • Weight loss ≥5% compared to week 52                                                  |                                                                                                    |
|                  |                             |                                                                                                               | • Composite endpoint: HbA\(_1c\)<7.0% without severe or blood glucose-confirmed symptomatic hypoglycemia and no weight gain |                                                                                                    |
|                  |                             |                                                                                                               |                                                                                       |                                                                                                    |
|                  |                             |                                                                                                               | Time to additional glucose-lowering medication after week 52                          | The hazard ratio between treatments                                                               |
|                  |                             |                                                                                                               |                                                                                       |                                                                                                    |
|                  |                             |                                                                                                               |                                                                                       |                                                                                                    |
| Trial product    | All randomized patients     | Hypothetical strategy for both intercurrent events:                                                         | Change from baseline to week 104 in:                                                    | Mean difference between treatments in change from weeks 52 to 104                                   |
|                  |                             | • Trial product discontinuation                                                                               | • HbA\(_1c\)                                                                          |                                                                                                    |
|                  |                             | • Initiation of rescue medication                                                                            | • Body weight (kg)                                                                     |                                                                                                    |
|                  |                             |                                                                                                               | • Fasting plasma glucose                                                               |                                                                                                    |
|                  |                             |                                                                                                               | • Body weight (%)                                                                      |                                                                                                    |
|                  |                             |                                                                                                               | • Body mass index                                                                      |                                                                                                    |

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| Estimand | Population | Strategy for accounting for intercurrent events | Endpoints – switch part | Population level summary – switch part |
|----------|------------|-----------------------------------------------|------------------------|----------------------------------------|
|          |            |                                               | • Waist circumference  | Understand the impact of intercurrent events on outcomes. |
|          |            |                                               | • Amylase               |                                        |
|          |            |                                               | • Lipase                |                                        |
|          |            |                                               | • Pulse rate            |                                        |
|          |            |                                               | • Systolic blood pressure |                                       |
|          |            |                                               | • Diastolic blood pressure |                                       |
|          |            |                                               | • Patient-reported outcomes (Diabetes Treatment Satisfaction Questionnaire, Short Form-36 version 2 (acute version)) |                                        |

If a patient at week 104 achieves:
- HbA1c <7.0%
- HbA1c ≤6.5%
- Weight loss ≥5% compared to week 52
- Composite endpoint: HbA1c <7.0% without severe or blood glucose-confirmed symptomatic hypoglycemia and no weight gain

The odds ratio between treatments in reaching target

Time to rescue medication

The hazard ratio between treatments

*International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials E9 (R1). Final version, adopted on November 20, 2019. Available at: https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf. (Accessed Jan 17, 2020).

†Confirmatory secondary endpoint at week 104.

HbA1c, glycated hemoglobin.
**Statistical considerations**

A hierarchical closed-testing strategy was used to preserve the overall type-1 error rate in the strong sense at a nominal two-sided 5% significance level for the treatment policy estimand only. The statistical testing strategy was based on the principle that glycemic effect was to be established in terms of HbA\(_1c\) superiority before testing for added benefits in terms of body weight superiority.

The first hypothesis to be tested was superiority on glycated hemoglobin (HbA\(_1c\)) of oral semaglutide versus sitagliptin in the main phase. The hypothesis was tested at the overall significance level (5%), while allocating a 0% local significance level to the remaining hypotheses. If the hypothesis was confirmed, the significance level was reallocated as indicated by the arrows in the figure below. Each hypothesis was tested at its updated local significance level (\(\alpha\)-local) until all hypotheses had been confirmed or until no hypothesis could be confirmed.

As the two confirmatory hypotheses pertaining to the main phase of the trial were confirmed, the local significance level (\(\alpha\)-local) was reallocated to the two confirmatory hypotheses in the switch part as specified in the figure below.

![Diagram showing statistical testing strategy](image)

For the treatment policy estimand used in the switch part, the primary statistical analysis was based on a pattern mixture model using multiple imputation to impute missing data for week 104. It was assumed that the missing data mechanism was missing-at-random within the groups used for imputation. Missing data for week 104 were imputed within four groups of patients, depending on the treatment arm and treatment status. For this imputation approach, it was assumed that the distribution of missing data for patients in a specific treatment arm resembled the distribution of available data for other patients in the same treatment group and with the same treatment status at week 104.

**Missing values for each group were imputed as follows:**

- An analysis of covariance (ANCOVA) with region and stratification factors as categorical fixed effects and week 52 measurements as a covariate was fitted to observed values of the change from week 52 in HbA\(_1c\), or body weight at week 104.
- The estimated parameters for location and dispersion were used to impute 1000 values for each subject with missing week 104 data based on region and stratification factors as categorical fixed effects and week 52 measurements as a covariate. Thus, 1000 complete datasets were generated including observed and imputed values.
Subsequently, the analysis was done as follows:

- An ANCOVA model with treatment, region, and stratification factors as fixed effects and week 52 measurements as a covariate was fitted for each of the imputed datasets.
- The resulting 1000 estimates and variances were combined using Rubin’s rule, and the estimated treatment difference between oral semaglutide and sitagliptin together with two-sided 95% confidence interval and two-sided p value for testing no difference are presented.

For the trial product estimand used in the switch part for the confirmatory secondary endpoints, the primary analysis was based on a mixed model for repeated measurements (MMRM) that accounts for the uncertainty pertaining to missing data. The MMRM approach assumes that data are missing-at-random. As dependent variables, the MMRM model includes all post-week 52 values collected at scheduled visits up to and including week 104. The independent effects were treatment, region, and stratification factors as categorical fixed effects and the week 52 measurements as covariate, all nested within visit. An unstructured covariance matrix was employed for measurements within the same subject, assuming that measurements from different patients were independent. A restricted maximum likelihood approach was used.

For the switch part, the supportive continuous secondary efficacy endpoints were analyzed using similar statistical model approaches as for the confirmatory secondary endpoints, with the associated week 52 response as a covariate.

For the switch part, supportive binary secondary efficacy endpoints were analyzed using a logistic regression model with treatment, region, and stratification factors as fixed effects and the associated week 52 measurements as a covariate. To account for missing data, multiple imputation was used. As an exception, the binary endpoint ‘HbA\textsubscript{1c} <7.0% (53 mmol/mol) and no need for rescue medication after week 52’ was only summarized descriptively.

For the switch part, the time to additional anti-diabetic medication/rescue medication endpoints were evaluated as specified below:

- Time to additional anti-diabetic medication (treatment policy estimand): time from rerandomization to initiation and/or intensification by a dose increase >20% of an additional anti-diabetic medication. Patients who had not initiated additional anti-diabetic medication were censored the day before the end-of-treatment visit (visit 19). The follow-up period was excluded, because some patients discontinued study drug at the end-of-treatment visit and might have needed additional glucose-lowering medication during the follow-up period. Patients who withdrew from the trial or were lost to follow-up were considered as having initiated an additional anti-diabetic medication.
- Time to rescue medication (trial product estimand): time from rerandomization to initiation and/or intensification of rescue medication. Patients who had not initiated rescue medication during the on-treatment period were censored one day before the last date on study drug.

The time-to-event endpoints were analyzed using a Cox proportional hazards model with treatment, region, and stratification factors as fixed effects and the week 52 HbA\textsubscript{1c} measurements as a covariate.

The safety evaluation was primarily based on the on-treatment observation period, except for deaths and adverse event types with potentially long latency between onset and diagnosis, for which the in-trial observation period was used.

In-trial observation period:

- Durability part: starts at the date of randomization (visit 2) in the main phase; switch part: starts at the date of rerandomization (visit 10) in the extension phase.
- Includes the period after initiation of rescue medication and/or premature study drug discontinuation, if any.
On-treatment observation period:

- Durability: starts at the date of first dose of study drug in the main phase; switch: starts at the date of first dose of rerandomized study drug in the extension phase.
- Includes the period after initiation of rescue medication, if any.
- Excludes the period after premature study drug discontinuation, if any.

On-treatment without rescue medication observation period:

- Durability: starts at the date of first dose of study drug in the main phase; switch: starts at the date of first dose of rerandomized study drug in the extension phase.
- Excludes the period after initiation of rescue medication and/or premature study drug discontinuation, if any.

The trial sample size was calculated to ensure at least 90% power to confirm superiority of oral semaglutide versus sitagliptin for the primary endpoint (treatment policy estimand) of the main phase of the trial, with planned enrolment of 500 patients and random assignment to treatment to ensure this power was achieved. It was assumed that there would be an absolute difference in proportions of 15% and that the proportion of sitagliptin responders was distributed around 20–50%. Assumptions used in the sample size and power calculation for the main phase and extension phase (switch) are shown in the table below.

| Endpoint                  | Assumptions | Power calculation |
|---------------------------|-------------|-------------------|
|                           | Treatment effect | Standard deviation | Number of subjects | Marginal power | Conditional power |
| **Main phase**            |             |                   |                   |                |                  |
| HbA1c <7.0% (yes/no)      | 15%-point difference |                   | 500               | 90%            | 90%              |
| Change in body weight (kg)| 2.5         | 4.0               | 500               | >99%           | 90%              |
| **Extension phase (switch)** |             |                   |                   |                |                  |
| Change in HbA1c (%-point) | 0.4         | 1.1               | 190               | 49%            | 44%              |
| Change in body weight (kg)| 2.5         | 4.0               | 190               | 91%            | 40%              |

1. Little RJA, Rubin DB. Statistical analysis with missing data. New York, NY: John Wiley & Sons 1987.
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|                    | Durability* (weeks 0 to 104) | Switch† (weeks 52 to 104) |        |        |        |        |
|--------------------|-----------------------------|---------------------------|--------|--------|--------|--------|
|                    | Oral semaglutide (n=253)    | Oral semaglutide (n=100)  | Sitagliptin (n=98) |        |        |        |
|                    | Additional glucose-lowering medication‡ n (%) | Rescue medication‡ n (%) | Additional glucose-lowering medication‡ n (%) | Rescue medication‡ n (%) | Additional glucose-lowering medication‡ n (%) | Rescue medication‡ n (%) |
| Any                | 46 (18.2)                  | 25 (9.9)                  | 15 (15.0)      | 9 (9.0) | 26 (26.5) | 23 (23.5) |
| Sulfonylureas      | 15 (5.9)                   | 10 (4.0)                  | 7 (7.0)        | 5 (5.0) | 10 (10.2) | 10 (10.2) |
| SGLT-2 inhibitors  | 12 (4.7)                   | 8 (3.2)                   | 3 (3.0)        | 2 (2.0) | 10 (10.2) | 10 (10.2) |
| DPP-4 inhibitors   | 10 (4.0)                   | 0                         | 4 (4.0)        | 0       | 0        | 0       |
| Insulins           | 8 (3.2)                    | 3 (1.2)                   | 4 (4.0)        | 2 (2.0) | 4 (4.1)  | 4 (4.1)  |
| GLP-1 analogs     | 2 (0.8)                    | 0                         | 0              | 0       | 2 (2.0)  | 0       |
| Other              | 2 (0.8)                    | 2 (0.8)                   | 0              | 0       | 0        | 0       |
| Metformin          | 1 (0.4)                    | 1 (0.4)                   | 0              | 0       | 1 (1.0)  | 0       |
| Alpha glucosidase inhibitors | 1 (0.4) | 1 (0.4)                  | 0              | 0       | 0        | 0       |
| Thiazolidinediones | 1 (0.4)                    | 1 (0.4)                   | 1 (1.0)        | 0       | 7 (7.1)  | 7 (7.1)  |

*Includes all patients randomized to oral semaglutide at baseline (week 0).
†Includes all patients previously randomized to sitagliptin at baseline (week 0) and rerandomized to either oral semaglutide or sitagliptin at the start of the extension phase (week 52).
‡Additional glucose-lowering medication: defined as glucose-lowering medication (or a dose increase >20% of concomitant glucose-lowering medication) given to the subject after randomization (week 0) for the durability part or after rerandomization (week 52) for the switch part, and before the planned end-of-treatment visit. Rescue medication: a subset of additional glucose-lowering medication and defined as glucose-lowering medication given as add-on to study drug (i.e. before the last day on study drug).

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose co-transporter 2.
Online Supplemental Table 2  Supportive secondary endpoints not reported in the main text for the durability part (weeks 0 to 104)

|                          | Oral semaglutide (n=253) |                          |
|--------------------------|--------------------------|--------------------------|
|                          | In-trial observation     | On-treatment without      |
|                          | period                   | rescue observation        |
| Fasting plasma glucose, mmol/L |                          |                          |
| **Week 52***             |                          |                          |
| n                        | 182                      | 175                      |
| Observed mean change from baseline (SD) | −2.59 (2.15) | −2.51 (2.12) |
| **Week 104**             |                          |                          |
| n                        | 178                      | 148                      |
| Observed mean change from baseline (SD) | −2.19 (2.84) | −2.12 (2.32) |
| Body weight, %           |                          |                          |
| **Week 52***             |                          |                          |
| n                        | 185                      | 178                      |
| Observed mean change from baseline (SD) | −3.06 (4.26) | −3.11 (4.29) |
| **Week 104**             |                          |                          |
| n                        | 180                      | 154                      |
| Observed mean change from baseline (SD) | −4.03 (5.75) | −4.36 (5.98) |
| BMI, kg/m²                |                          |                          |
| **Week 52***             |                          |                          |
| n                        | 185                      | 178                      |
| Observed mean change from baseline (SD) | −1.0 (1.4)  | −1.0 (1.4)    |
| **Week 104**             |                          |                          |
| n                        | 180                      | 154                      |
| Observed mean change from baseline (SD) | −1.3 (1.9)  | −1.4 (2.0)    |
| Waist circumference, cm  |                          |                          |
| **Week 52***             |                          |                          |
| n                        | 183                      | 176                      |
| Observed mean change from baseline (SD) | −2.5 (5.3)  | −2.4 (5.4)    |
| **Week 104**             |                          |                          |
| n                        | 178                      | 152                      |
| Observed mean change from baseline (SD) | −2.5 (6.3)  | −3.0 (6.3)    |
| HbA₁c <7.0% (<53 mmol/mol) |                          |                          |
| **Week 52***             |                          |                          |
| Outcome                                                                 | Oral semaglutide (n=253) | In-trial observation period | On-treatment without rescue observation period |
|------------------------------------------------------------------------|---------------------------|-----------------------------|-----------------------------------------------|
| n                                                                      | 183                       | 177                         |
| Observed proportion achieving outcome, n (%)                           | 115 (62.8)                | 114 (64.4)                  |
| **Week 104**                                                           |                           |                             |
| n                                                                      | 180                       | 150                         |
| Observed proportion achieving outcome, n (%)                           | 101 (56.1)                | 91 (60.7)                   |
| **HbA\(_1c\) ≤6.5% (<48 mmol/mol)**                                     |                           |                             |
| **Week 52**                                                            |                           |                             |
| n                                                                      | 183                       | 177                         |
| Observed proportion achieving outcome, n (%)                           | 65 (35.5)                 | 64 (36.2)                   |
| **Week 104**                                                           |                           |                             |
| n                                                                      | 180                       | 150                         |
| Observed proportion achieving outcome, n (%)                           | 63 (35.0)                 | 59 (39.3)                   |
| **Body weight loss ≥5%**                                                |                           |                             |
| **Week 52**                                                            |                           |                             |
| n                                                                      | 185                       | 178                         |
| Observed proportion achieving outcome, n (%)                           | 49 (26.5)                 | 48 (27.0)                   |
| **Week 104**                                                           |                           |                             |
| n                                                                      | 180                       | 154                         |
| Observed proportion achieving outcome, n (%)                           | 64 (33.9)                 | 58 (37.7)                   |
| **HbA\(_1c\) <7.0% (<53 mmol/mol) without severe or BG-confirmed symptomatic hypoglycemic episodes† and without body weight gain** |                           |                             |
| **Week 52**                                                            |                           |                             |
| n                                                                      | 183                       | 177                         |
| Observed proportion achieving outcome, n (%)                           | 90 (49.2)                 | 89 (50.3)                   |
| **Week 104**                                                           |                           |                             |
| n                                                                      | 180                       | 150                         |
| Observed proportion achieving outcome, n (%)                           | 73 (40.6)                 | 67 (44.7)                   |
| **HbA\(_1c\) <7.0% (<53 mmol/mol) or HbA\(_1c\) reduction ≥1% point (<10.9 mmol/mol)** |                           |                             |
| **Week 52**                                                            |                           |                             |
| n                                                                      | 183                       | 177                         |
| Observed proportion achieving outcome, n (%)                           | 155 (84.7)                | 154 (87.0)                  |
|                      | Oral semaglutide (n=253) |
|----------------------|--------------------------|
|                      | In-trial observation     | On-treatment without rescue |
|                      | period                   | observation period          |
| **Week 104**         |                          |                            |
| n                    | 180                      | 150                        |
| Observed proportion  | 126 (70.0)               | 113 (75.3)                 |
| achieving outcome, n |                          |                            |
| (%)                  |                          |                            |

*Among patients continuing from the main phase into the extension phase.

†An episode that is severe according to the American Diabetes Association classification or BG-confirmed by a plasma glucose value <3.1 mmol/L (<56 mg/dL) with symptoms consistent with hypoglycemia.

BG, blood glucose; BMI, body mass index; HbA₁c, glycated hemoglobin; n, number of patients with non-missing information; SD, standard deviation.
**Online Supplemental Table 3** On-treatment adverse events by system organ class*

| Patients with events, n (%) | Durability† (weeks 0 to 104) | Switch‡ (weeks 52 to 104) |
|-----------------------------|-------------------------------|--------------------------|
|                             | Oral semaglutide (n=253)      | Oral semaglutide (n=100)  | Sitagliptin (n=97)§ |
| Any event                   | 215 (85.0)                    | 75 (75.0)                | 67 (69.1)         |
| Gastrointestinal disorders  | 126 (49.8)                    | 41 (41.0)                | 14 (14.4)         |
| Infections and infestations | 99 (39.1)                     | 27 (27.0)                | 26 (26.8)         |
| Musculoskeletal and connective tissue | 61 (24.1) | 14 (14.0) | 19 (19.6) |
| Nervous system disorders    | 57 (22.5)                     | 14 (14.0)                | 13 (13.4)         |
| Metabolism and nutrition disorders | 50 (19.8) | 10 (10.0) | 8 (8.2) |
| Investigations              | 38 (15.0)                     | 7 (7.0)                  | 8 (8.2)           |
| General disorders and administration | 35 (13.8) | 6 (6.0) | 4 (4.1) |
| Eye disorders               | 28 (11.1)                     | 13 (13.0)                | 12 (12.4)         |
| Injury, poisoning, and procedural complications | 26 (10.3) | 6 (6.0) | 7 (7.2) |
| Skin and subcutaneous tissue disorders | 23 (9.1) | 7 (7.0) | 10 (10.3) |
| Renal and urinary disorders | 22 (8.7)                      | 2 (2.0)                  | 2 (2.1)           |
| Cardiac disorders           | 17 (6.7)                      | 4 (4.0)                  | 6 (6.2)           |
| Respiratory, thoracic, and mediastinal disorders | 17 (6.7) | 5 (5.0) | 13 (13.4) |
| Vascular disorders          | 17 (6.7)                      | 5 (5.0)                  | 6 (6.2)           |
| Neoplasms benign, malignant, and unspecified (incl. cysts and polyps) | 15 (5.9) | 2 (2.0) | 2 (2.1) |
| Reproductive system and breast disorders | 12 (4.7) | 2 (2.0) | 1 (1.0) |
| Psychiatric disorders       | 10 (4.0)                      | 2 (2.0)                  | 2 (2.1)           |
| Hepatobiliary disorders     | 8 (3.2)                       | 2 (2.0)                  | 2 (2.1)           |
| Ear and labyrinth disorders | 7 (2.8)                       | 3 (3.0)                  | 1 (1.0)           |
| Blood and lymphatic system disorders | 6 (2.4) | 2 (2.0) | 4 (4.1) |
| Endocrine disorders         | 6 (2.4)                       | 3 (3.0)                  | 2 (2.1)           |
| Immune system disorders     | 4 (1.6)                       | 0                        | 1 (1.0)           |
| Surgical and medical procedures | 4 (1.6) | 1 (1.0) | 2 (2.1) |
| Congenital, familial, and genetic disorders | 3 (1.2) | 0 | 0 |
Social circumstances

|          | 1 (0.4) | 0 | 1 (1.0) |
|----------|---------|---|---------|

*MedDRA version 20.1.

†Patients randomized to oral semaglutide at baseline (week 0).

‡Patients previously randomized to sitagliptin at baseline (week 0) and rerandomized to either oral semaglutide or sitagliptin at the start of the extension phase (week 52).

§One patient was rerandomized to sitagliptin, but was not exposed to the study drug and was therefore included in the full analysis set for the sitagliptin group (n=98) and excluded from the safety analysis set (n=97).

MedDRA, Medical Dictionary for Regulatory Activities.
### Online Supplemental Table 4 On-treatment adverse events leading to premature trial product discontinuation

|                              | Durability* (weeks 0 to 104) | Switch† (weeks 52 to 104) |
|------------------------------|-----------------------------|--------------------------|
|                              | Oral semaglutide (n=253)    | Oral semaglutide (n=100)  | Sitagliptin (n=97)‡  |
|                              | Patients with at least one event n (%) | Episodes, n | Patients with at least one event n (%) | Episodes, n | Patients with at least one event n (%) | Episodes, n |
| Gastrointestinal disorders   | 15 (5.9)                    | 20                        | 4 (4)                      | 7             | 0             | 0             |
| Nausea                       | 7 (2.8)                     | 7                         | 2 (2)                      | 2             | 0             | 0             |
| Diarrhea                     | 3 (1.2)                     | 3                         | 1 (1)                      | 1             | 0             | 0             |
| Abdominal pain               | 2 (0.8)                     | 2                         | 0                          | 0             | 0             | 0             |
| Abdominal pain upper         | 2 (0.8)                     | 2                         | 2 (2)                      | 2             | 0             | 0             |
| Dyspepsia                    | 2 (0.8)                     | 2                         | 0                          | 0             | 0             | 0             |
| Vomiting                     | 2 (0.8)                     | 2                         | 1 (1)                      | 1             | 0             | 0             |
| Abdominal discomfort         | 1 (0.4)                     | 1                         | 0                          | 0             | 0             | 0             |
| Crohn's disease              | 1 (0.4)                     | 1                         | 0                          | 0             | 0             | 0             |
| Constipation                 | 0                          | 0                         | 1 (1)                      | 1             | 0             | 0             |
| Neoplasms benign, malignant and unspecified | 5 (2.0) | 5 | 0 | 0 | 0 | 0 |
| Adenocarcinoma of colon      | 2 (0.8)                     | 2                         | 0                          | 0             | 0             | 0             |
| Choroid melanoma             | 1 (0.4)                     | 1                         | 0                          | 0             | 0             | 0             |
| Hepatocellular carcinoma     | 1 (0.4)                     | 1                         | 0                          | 0             | 0             | 0             |
| Prostate cancer              | 1 (0.4)                     | 1                         | 0                          | 0             | 0             | 0             |
| Lung cancer metastatic       | 0                          | 0                         | 1 (1)                      | 1             | 0             | 0             |
| Other system organ class          | 10 (4.0) | 11 | 2 (2) | 2 | 0 | 0 |
|----------------------------------|----------|----|-------|---|---|---|
| Pancreatic enzymes increased     | 1 (0.4)  | 1  | 0     | 0 | 0 | 0 |
| Weight decreased                 | 1 (0.4)  | 1  | 0     | 0 | 0 | 0 |
| Decreased appetite               | 2 (0.8)  | 2  | 0     | 0 | 0 | 0 |
| Dysgeusia                        | 2 (0.8)  | 2  | 0     | 0 | 0 | 0 |
| Dizziness                        | 1 (0.4)  | 1  | 0     | 0 | 0 | 0 |
| Tachycardia                      | 1 (0.4)  | 1  | 0     | 0 | 0 | 0 |
| Fatigue                          | 1 (0.4)  | 2  | 0     | 0 | 0 | 0 |
| Pruritus                         | 1 (0.4)  | 1  | 0     | 0 | 0 | 0 |
| Eyelid edema                     | 0        | 0  | 1 (1) | 1 | 0 | 0 |
| Urticaria                        | 0        | 0  | 1 (1) | 1 | 0 | 0 |

*Includes all patients randomized to oral semaglutide at baseline (week 0).
†Includes all patients previously randomized to sitagliptin at baseline (week 0) and rerandomized to either oral semaglutide or sitagliptin at the start of the extension phase (week 52).
‡One patient was rerandomized to sitagliptin, but was not exposed to the study drug and was therefore included in the full analysis set for the sitagliptin group (n=98) and excluded from the safety analysis set (n=97).
# Online Supplemental Table 5 On-treatment hypoglycemic episodes

|                                      | Durability* (weeks 0 to 104) | Switch† (weeks 52 to 104) |
|--------------------------------------|-----------------------------|--------------------------|
|                                      | Oral semaglutide (n=253)    | Oral semaglutide (n=100) | Sitagliptin (n=97)‡ |
| **Patients with at least one event** | Patients with at least one event n (%) | Episodes, n | Patients with at least one event n (%) | Episodes, n | Patients with at least one event n (%) | Episodes, n |
| Severe hypoglycemic episodes§        | 0                          | 0                        | 0                          | 0                        | 0                          | 0                        |
| Severe or BG-confirmed symptomatic hypoglycemic episodes¶ | 18 (7.1)                   | 45                       | 2 (2.0)                    | 2                        | 4 (4.1)                    | 12                       |
| Nocturnal                            | 4 (1.6)                    | 8                        | 0                          | 0                        | 0                          | 0                        |
| Episodes in patients on SU           | 17 (13.7)**                 | 44                       | 1 (2.0)**                  | 1                        | 2 (4.3)**                  | 10                       |
|                                      | (n=124)                     |                           | (n=51)                     |                           | (n=47)                     |                           |
| Episodes in patients not on SU       | 1 (0.8)**                  | 1                        | 1 (2.0)**                  | 1                        | 2 (4.0)**                  | 2                        |
|                                      | (n=129)                     |                           | (n=49)                     |                           | (n=50)                     |                           |
| Hypoglycemic episodes by ADA classification†† | 58 (22.9)                  | 328                      | 9 (9.0)                    | 43                       | 13 (13.4)                  | 52                       |
| Episodes in patients on SU           | 46 (37.1)**                 | 311                      | 6 (11.8)**                 | 39                       | 7 (14.9)**                 | 43                       |
|                                      | (n=124)                     |                           | (n=51)                     |                           | (n=47)                     |                           |
| Episodes in patients not on SU       | 12 (9.3)**                 | 17                       | 3 (6.1)**                  | 4                        | 6 (12.0)**                 | 9                        |
|                                      | (n=129)                     |                           | (n=49)                     |                           | (n=50)                     |

*Includes all patients randomized to oral semaglutide at baseline (week 0).
†Includes all patients previously randomized to sitagliptin at baseline (week 0) and rerandomized to either oral semaglutide or sitagliptin at the start of the extension phase (week 52).
‡One patient was rerandomized to sitagliptin, but was not exposed to the study drug and was therefore included in the full analysis set for the sitagliptin group (n=98) and excluded from the safety analysis set (n=97).
§An episode that is severe according to ADA classification (requiring assistance from another person to actively administer carbohydrates, glucagon, or take other corrective actions).¹

¶An episode that is severe according to ADA classification§ or BG-confirmed by a plasma glucose value <3.1 mmol/L (<56 mg/dL) with symptoms consistent with hypoglycemia.

**Percentages relative to the total number of patients (n) within the relevant SU treatment status group.

††An episode of hypoglycemia that meets ADA classification for hypoglycemia, including episodes classified as severe hypoglycemia, documented symptomatic hypoglycemia, asymptomatic hypoglycemia, probable symptomatic hypoglycemia, pseudo-hypoglycemia, and unclassifiable (n=1, four episodes)

ADA, American Diabetes Association; BG, blood glucose; SU, sulfonylurea.

1. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care 2013;36(5):1384–95.
### Online Supplemental Table 6 EAC-confirmed events, excluding malignant neoplasms

| Event Type                  | Durability* (weeks 0 to 104) | Switch† (weeks 52 to 104) |
|----------------------------|------------------------------|---------------------------|
|                            | Oral semaglutide (n=253)     | Oral semaglutide (n=100)  | Sitagliptin (n=97)‡ |
|                            | Patients with at least one event n (%) | Events, n | Patients with at least one event n (%) | Events, n | Patients with at least one event n (%) | Events, n |
| Deaths                     |                              |                           |                      |
| In-trial                   | 0                            | 0                         | 0                    |
| Acute kidney injury        |                              |                           |                      |
| On-treatment               | 2 (0.8)                      | 2                         | 0                    |
| Acute pancreatitis         |                              |                           |                      |
| On-treatment               | 0                            | 0                         | 0                    |
| Cardiovascular events      |                              |                           |                      |
| In-trial                   | 1 (0.4)                      | 1                         | 0                    |
| Acute coronary syndrome    | 1 (0.4)                      | 1                         | 0                    |
| Acute myocardial infarction| 1 (0.4)                      | 1                         | 0                    |
| Cerebrovascular events     | 0                            | 0                         | 0                    |
| Heart failure requiring hospitalization | 0 | 0 | 0 | 1 (1.0) | 1 |
| Lactic acidosis            |                              |                           |                      |
| On-treatment               | 0                            | 0                         | 0                    |
| Thyroid-related events | Durability* (weeks 0 to 104) | Switch† (weeks 52 to 104) |
|------------------------|-------------------------------|----------------------------|
|                        | Oral semaglutide (n=253)     | Oral semaglutide (n=100)   | Sitagliptin (n=97)‡ |
| Patients with at least one event n (%) | Events, n | Patients with at least one event n (%) | Events, n | Patients with at least one event n (%) | Events, n |
| In-trial               | 0                          | 0                          | 0                          | 0                          | 0                          |

*Patients randomized to oral semaglutide at baseline (week 0).
†Patients previously randomized to sitagliptin at baseline (week 0) and rerandomized to either oral semaglutide or sitagliptin at the start of the extension phase (week 52).
‡One patient was rerandomized to sitagliptin but was not exposed to the study drug, and was therefore included in the full analysis set for the sitagliptin group (n=98) and excluded from the safety analysis set (n=97).

EAC, event adjudication committee.
### Online Supplemental Table 7 EAC-confirmed malignant neoplasms

| Malignant neoplasm | Durability* (weeks 0 to 104) | Switch† (weeks 52 to 104) | Sitagliptin (n=97)‡ |
|--------------------|-----------------------------|---------------------------|-------------------|
|                    | Oral semaglutide (n=253)    | Oral semaglutide (n=100)  |                    |
|                    | Patients with at least one event n (%) | Events, n | Events per 100 PY | Time of onset (day)§ | Patients with at least one event n (%) | Events, n | Events per 100 PY | Time of onset (day)§ | Patients with at least one event n (%) | Events, n | Events per 100 PY | Time of onset (day)§ |
| In-trial           | 11 (4.3)                    | 12                        | 2.6               | 2 (2.0)             | 2                         | 1.8               | 0                        | 0                        | 0                        | -                        |
| Breast cancer      | 2 (0.8)                     | 2                         | 0.4               | 315                  | 367                       | 0                        | 0                        | 0                        | 0                        | 0                        | -                        |
| Colorectal cancer  | 2 (0.8)                     | 2                         | 0.4               | 297                  | 221                       | 0                        | 0                        | 0                        | 0                        | 0                        | -                        |
| Gastrointestinal cancer | 2 (0.8)                | 2                         | 0.4               | 0                    | 0                         | 0                        | 0                        | 0                        | 0                        | 0                        | -                        |
| Liver              | 1 (0.4)                     | 1                         | 0.2               | 249                  |                            | 0                        | 0                        | 0                        | 0                        | 0                        | -                        |
| Stomach            | 1 (0.4)                     | 1                         | 0.2               | 330                  |                            | 0                        | 0                        | 0                        | 0                        | 0                        | -                        |
| Genitourinary cancer | 0                         | 0                         | 0                  | 1 (1.0)             |                            | 0                        | 0                        | 0                        | 0                        | 0                        | -                        |
| Kidney             | 0                           | 0                         | 0                  | -                    | 1 (1.0)                   | 1                        | 0.9                      | 132                     | 0                        | 0                        | -                        |
| Gynecologic cancer | 1 (0.4)                     | 2                         | 0.4               | 0                    | 0                         | 0                        | 0                        | 0                        | 0                        | 0                        | -                        |
| Ovary              | 1 (0.4)                     | 1                         | 0.2               | 697                  |                            | 0                        | 0                        | 0                        | 0                        | 0                        | -                        |
| Uterus             | 1 (0.4)                     | 1                         | 0.2               | 697                  |                            | 0                        | 0                        | 0                        | 0                        | 0                        | -                        |
|                                   | Durability* (weeks 0 to 104) |                   |                   | Switch† (weeks 52 to 104) |                   |                   |
|-----------------------------------|-----------------------------|-------------------|-------------------|---------------------------|-------------------|-------------------|
|                                   | Oral semaglutide (n=253)    | Oral semaglutide (n=100) | Sitagliptin (n=97)‡ |                          |                   |                   |
| Patients with at least one event n (%) | Events, n | Events per 100 PY | Time of onset (day)§ | Patients with at least one event n (%) | Events, n | Events per 100 PY | Time of onset (day)§ | Patients with at least one event n (%) | Events, n | Events per 100 PY | Time of onset (day)§ |
| Lung and pleura cancer            | 0 | 0 | 0 | 1 (1.0) | 1 | 0.9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lung cancer                       | 0 | 0 | 0 | - | 1 (1.0) | 1 | 0.9 | 258 | 0 | 0 | 0 | 0 | - |
| Skin cancer                       | 2 (0.8) | 2 | 0.4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Malignant melanoma                | 1 (0.4) | 1 | 0.2 | 594 | 0 | 0 | 0 | - | 0 | 0 | 0 | 0 | - |
| Skin cancer other than melanoma   | 1 (0.4) | 1 | 0.2 | 254 | 0 | 0 | 0 | - | 0 | 0 | 0 | 0 | - |
| Other primary site                | 1 (0.4) | 1 | 0.2 | 11 | 0 | 0 | 0 | - | 0 | 0 | 0 | 0 | - |
| Prostate cancer                   | 1 (0.4) | 1 | 0.2 | 315 | 0 | 0 | 0 | - | 0 | 0 | 0 | 0 | - |

*Patients randomized to oral semaglutide at baseline (week 0).
†Patients previously randomized to sitagliptin at baseline (week 0) and rerandomized to either oral semaglutide or sitagliptin at the start of the extension phase (week 52).
‡One patient was rerandomized to sitagliptin, but was not exposed to the study drug and was therefore included in the full analysis set for the sitagliptin group (n=98) and excluded from the safety analysis set (n=97).
§Time of onset: for the durability part, trial day of onset of event according to EAC. For switch part, trial day relative to rerandomization (week 52) of onset of event according to EAC.
¶One event of malignant anorectal neoplasm in the durability part was reported after database lock; this event had onset during the trial, but was not sent for adjudication due to being reported after database lock.

EAC, event adjudication committee; PY, patient years.
Online Supplemental Table 8  In-trial diabetic retinopathy and related complications

|                  | Durability* (weeks 0 to 104) | Switch† (weeks 52 to 104) |
|------------------|------------------------------|----------------------------|
|                  | Oral semaglutide (n=253)     | Oral semaglutide (n=100)   | Sitagliptin (n=97)‡ |
| Patients with at least one event n (%) | Events, n | Patients with at least one event n (%) | Events, n | Patients with at least one event n (%) | Events, n |
| Events           | 13 (5.1) | 16 | 4 (4.0) | 4 | 2 (2.1) | 2 |
| Preferred terms§ |
| Diabetic retinopathy | 10 (4.0) | 11 | 3 (3.0) | 3 | 1 (1.0) | 1 |
| Retinal hemorrhage | 2 (0.8) | 2 | 0 | 0 | 1 (1.0) | 1 |
| Macular edema     | 1 (0.4) | 1 | 0 | 0 | 0 | 0 |
| Retinopathy       | 1 (0.4) | 1 | 0 | 0 | 0 | 0 |
| Vitreous detachment | 1 (0.4) | 1 | 1 (1.0) | 1 | 0 | 0 |

*Patients randomized to oral semaglutide at baseline (week 0).
†Patients previously randomized to sitagliptin at baseline (week 0) and rerandomized to either oral semaglutide or sitagliptin at the start of the extension phase (week 52).
‡One patient was rerandomized to sitagliptin, but was not exposed to the study drug and was therefore included in the full analysis set for the sitagliptin group (n=98) and excluded from the safety analysis set (n=97).
§MedDRA version 20.1.
MedDRA, Medical Dictionary for Regulatory Activities.
### Online Supplemental Table 9 Other safety assessments in the durability part (weeks 0 to 104)

|                          | Oral semaglutide (n=253) |          |          |
|--------------------------|--------------------------|----------|----------|
|                          |                          | In-trial | On-treatment |
|                          |                          | observation period | observation period |
| **Systolic blood pressure, mm Hg** |                          |          |          |
| **Week 52**              |                          |          |          |
| n                        | 185                      | 185      |          |
| Observed mean (SD) change from baseline | –4 (14) | –4 (14) |          |
| **Week 104**             |                          |          |          |
| n                        | 180                      | 176      |          |
| Observed mean (SD) change from baseline | –3 (14) | –3 (14) |          |
| **Diastolic blood pressure, mm Hg** |                          |          |          |
| **Week 52**              |                          |          |          |
| n                        | 185                      | 185      |          |
| Observed mean (SD) change from baseline | –1 (9)    | –1 (9)   |          |
| **Week 104**             |                          |          |          |
| n                        | 180                      | 176      |          |
| Observed mean (SD) change from baseline | –1 (9)    | –1 (9)   |          |
| **Pulse rate, beats/min** |                          |          |          |
| **Week 52**              |                          |          |          |
| n                        | 185                      | 185      |          |
| Observed mean (SD) change from baseline | 2 (9)      | 2 (9)    |          |
| **Week 104**             |                          |          |          |
| n                        | 180                      | 176      |          |
| Observed mean (SD) change from baseline | 2 (9)      | 2 (9)    |          |
| **eGFR, mL/min/1.73 m²** |                          |          |          |
| **Week 52**              |                          |          |          |
| n                        | 184                      | 184      |          |
| Geometric mean (CV) ratio to baseline | 0.99 (7.8) | 0.99 (7.8) |          |
### Oral semaglutide (n=253)

|                              | In-trial observation period | On-treatment observation period |
|------------------------------|-----------------------------|---------------------------------|
| n                            | 179                         | 170                             |
| Geometric mean (CV) ratio to baseline | 0.96 (10.4)                | 0.97 (9.5)                      |

*Among patients continuing from the main phase into the extension phase.

CV, coefficient of variation; eGFR, estimated glomerular filtration rate; n, number of patients contributing to the summary statistics.
### Online Supplemental Table 10
Supportive endpoints at week 104 not reported in the main text for switch part

|                        | Treatment policy estimand | Trial product estimand |
|------------------------|---------------------------|------------------------|
|                        | Oral semaglutide (n=100)  | Sitagliptin (n=98)     |
|                        | Oral semaglutide (n=100)  | Sitagliptin (n=98)     |
| **Body weight, %**     |                           |                        |
| n                      | 100                       | 98                     |
| Estimated mean change from baseline | –2.9                | –0.7                   |
| ETD (95% CI)           | –2.1 (–3.5 to −0.7)       | −2.5 (–4.1 to −1.0)    |
| P value                | 0.0036                    | 0.0015                 |
| **BMI, kg/m²**         |                           |                        |
| n                      | 100                       | 98                     |
| Estimated mean change from baseline | –0.8                | –0.4                   |
| ETD (95% CI)           | –0.4 (–0.9 to 0.1)        | −0.6 (–1.1 to 0.0)     |
| P value                | 0.1032                    | 0.0543                 |
| **Waist circumference, cm** |                       |                        |
| n                      | 100                       | 98                     |
| Estimated mean change from baseline | –1.5                | –0.9                   |
| ETD (95% CI)           | –0.6 (–2.0 to 0.9)        | −1.3 (–3.0 to 0.3)     |
| P value                | 0.4386                    | 0.1042                 |

BMI, body mass index; ETD, estimated treatment difference; n, number of patients contributing to the analysis.
**Online Supplemental Table 11** Other safety assessments in the switch part (on-treatment)

|                              | Oral semaglutide (n=100) | Sitagliptin (n=97) |
|------------------------------|--------------------------|-------------------|
| **Systolic blood pressure, mm Hg** |                          |                   |
| n                            | 100                      | 97                |
| Estimated mean change from baseline at week 104 | −3                     | 2                 |
| ETD (95% CI)                 | −5 (−9 to −1)            |                   |
| P value                      |                          | 0.0204            |
| **Diastolic blood pressure, mm Hg** |                          |                   |
| n                            | 100                      | 97                |
| Estimated mean change from baseline at week 104 | −1                     | −0                |
| ETD (95% CI)                 | −1 (−4 to 2)             |                   |
| P value                      |                          | 0.4213            |
| **Pulse rate, beats/min**    |                          |                   |
| n                            | 100                      | 97                |
| Estimated mean change from baseline at week 104 | 1                      | −0                |
| ETD (95% CI)                 | 2 (−1 to 4)              |                   |
| P value                      |                          | 0.1787            |
| **eGFR, mL/min/1.73 m²**     |                          |                   |
| n                            | 84                       | 92                |
| Geometric mean (CV) ratio to baseline at week 104 | 0.97 (9.0)              | 0.97 (10.2)       |

CV, coefficient of variation; eGFR, estimated glomerular filtration rate; ETD, estimated treatment difference; n, number of patients contributing to the analysis.
Online Supplemental Figure 1 Trial design

*After 52 weeks, patients could either undergo a 5-week follow-up period and complete the trial or, after consenting, they could continue in the 52-week extension phase. The extension phase is marked in grey; the durability part (main + extension phase) and the switch part (extension phase only) are marked in red.
Online Supplemental Figure 2 Patient disposition

### Durability part
253 patients randomized to oral semaglutide flexible dose in main phase
253 received treatment

- 211 eligible for extension phase durability part
  - 26 not enrolled in extension
    - 12 due to no IEC/IRB approval*
    - 14 did not consent
  - 185 enrolled in extension phase durability part
    - 184 received treatment
    - 1 did not receive treatment

- 76 discontinued treatment
  - 23 due to adverse events
  - 5 due to violation of inclusion or exclusion criteria
  - 4 withdrew
  - 44 other reasons
- 71 withdrew from the trial
- 177 completed treatment
  - 150 completed without rescue medication
  - 182 completed trial
- 59 lost to follow-up
- 6 withdrew
- 56 other reasons

### Switch part
251 patients randomized to sitagliptin in main phase
250 received treatment
1 did not receive treatment

- 227 eligible for extension phase switch part
  - 29 not enrolled in extension
    - 18 due to no IEC/IRB approval*
    - 11 did not consent
  - 108 enrolled in switch part

- 100 randomly assigned to oral semaglutide with flexible dose
  - 100 received treatment
  - 12 discontinued treatment
    - 6 due to adverse events
    - 6 other reasons
    - 1 withdrew from the trial
    - 1 other reasons
- 88 completed treatment
  - 80 completed without rescue medication
  - 99 completed trial

- 98 randomly assigned to sitagliptin
  - 97 received treatment
  - 1 did not receive treatment
  - 3 discontinued treatment
    - 2 other reasons
    - 1 not exposed
- 95 completed treatment
  - 73 completed without rescue medication
  - 98 completed trial

*IEC/IRB approval was not secured in time for the start of the extension phase for the two study sites in Brazil.

IEC, Independent Ethics Committee; IRB, Institutional Review Board.
In the durability part, among the 184 patients continuing into the extension phase who were exposed to study drug at week 52, 16 were receiving oral semaglutide 3 mg, 51 were receiving oral semaglutide 7 mg, and 117 were receiving oral semaglutide 14 mg; among the 177 patients still receiving treatment at the week 100 time point, 10, 37, and 123 patients were receiving oral semaglutide 3, 7, and 14 mg, respectively.

In the switch part, of the 100 patients rerandomized to oral semaglutide at week 52, 88 patients remained on-treatment at week 100, with 13, 19, and 56 patients receiving oral semaglutide 3, 7, and 14 mg, respectively.
Online Supplemental Figure 4 Change from week 52 in Diabetes Treatment Satisfaction Questionnaire scores at week 104 in the switch part

| Item                          | ETD (95% CI)                      |
|-------------------------------|-----------------------------------|
| Item 1: Satisfaction with treatment | Favors sita 100 mg | Favors oral sema | 0.30 (0.02 to 0.63) |
| Item 2: Feeling of unacceptably high blood sugars | Favors oral sema | Favors sita 100 mg | 0.05 (-0.50 to 0.60) |
| Item 3: Feeling of unacceptably low blood sugars | Favors oral sema | Favors sita 100 mg | -0.21 (-0.68 to 0.26) |
| Item 4: Convenience of treatment | Favors sita 100 mg | Favors oral sema | -0.01 (-0.28 to 0.25) |
| Item 5: Flexibility of treatment | Favors sita 100 mg | Favors oral sema | -0.01 (-0.33 to 0.22) |
| Item 6: Satisfaction with understanding of diabetes | Favors sita 100 mg | Favors oral sema | -0.04 (-0.34 to 0.26) |
| Item 7: Recommending treatment to others | Favors sita 100 mg | Favors oral sema | 0.12 (-0.15 to 0.36) |
| Item 8: Satisfaction to continue with present treatment | Favors sita 100 mg | Favors oral sema | 0.07 (-0.24 to 0.38) |
| Total treatment satisfaction | Favors sita 100 mg | Favors oral semaglutide | 0.34 (-0.98 to 1.66) |

ETD, estimated treatment difference; flex, flexible dosing; sema, semaglutide; sita, sitagliptin.
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*Trial sites that were approved by independent ethics committee/institutional review board and participated in main phase but not extension phase of trial.
Independent ethics committees/institutional review boards

Argentina: Comité de Ética e Investigación, Fundación Sanatorio Güemes, F. Acuña de Figueroa 1240 20th floor – CABA; Comité de Bioética del Instituto de Investigaciones Clínicas Rosario Paraguay 160 – Rosario; Comité Provincial de Bioética Maipú 835 2nd floor – Rosario; Comité de Bioética en Investigación de Ciencias de la Salud Moreno 1240 – Corrientes.

Austria: Ethikkommission der Medizinischen Universität Graz Auenbruggerplatz 2, 8036 Graz; Ethikkommission der Stadt Wien TownTown, Thomas-Klestil-Platz 8, 1030 Wien; Ethikkommission des Landes Steiermark Abt. 8, FAGP-Sanitätsdirektion, Amt der Steiermärkischen Landesregierung, Friedrichgasse 9/E/28 8010, Graz.

Belgium: Commissie Medische Ethiek – Toetsingscommissie, UZ Leuven - Campus Gasthuisberg, Secretariaat EC, Herestraat 49, 3000 Leuven; Comité d’Éthique CHR Mons-Hainaut - Site Saint-Joseph, Avenue Baudouin de Constantinople 5, 7000 Mons; Comité d’Éthique Hospitalo-Facultaire Cliniques universitaires Saint-Luc, Avenue Hippocrate 55, 14 Tour Harvey, niveau 0, 1200 Brussels; Comité d’Ethique Hospitalo-Facultaire Universitaire de Liège, CHU de Liège - Sart Tilman, Domaine Universitaire du Sart Tilman, Bâtiment B35, Avenue de l’Hôpital 1, 4000 Liège; UZ Gent Commissie voor Medische Ethiek, De Pintepark II Ingang 75 – 2e verdieping, Corneel Heymanslaan 10, 9000 Gent; Ethisch Comité UZA, UZ Antwerpen, Secretariaat Ethisch Comité, Wilrijkstraat 10, 2650 Edegem; Commissie Medische Ethiek, AZ Imelda, Imeldalaan 9, 2820 Bonheiden.

Brazil: Central EC: Comissão Nacional de Ética em Pesquisa (CONEP), SEPN 510 Norte, Bloco A, 3 andar, Edificio Ex-INAN, Unidade II – Ministério da Saúde Asa Norte, Brasília/DF 70750-521*; Comitê de Ética em Pesquisa em Seres, Humanos da Iramandae da Santa Casa de Misericórdia de São Paulo, Rua Santa Isabel, 305, 4 andar Santa Cecília, São Paulo/SP 01277-900*; Comitê de Ética em Pesquisa do Hospital Moinhos de Vento, Rua Tiradentes, 198, Subsolo, Floresta, Porto Alegre/RS 90560-030*.

Egypt: Ethics Committee, Faculty of Medicine, Alexandria University; General Organization for Teaching Hospitals and Institutes (GOTHI) Research Ethics Committee; Cairo University, Faculty of Medicine Research Ethics Committee; Ain Shams University, Faculty of Medicine Research Ethics Committee (REC).

Norway: Regional komité for medisinsk og helsefaglig forskningsetikk, REK sør-øst B Gullhaugveien 1-3, NO-0484 Oslo.

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Turkey: MoH Istanbul Medeniyet University, Göztepe Training and Research Hospital, Clinical Research Ethics Committee; Marmara University Medical Faculty Clinical Research Ethics Committee.
USA: Sterling Institutional Review Board, 6300 Powers Ferry Road, Suite 600-351, Atlanta, GA 30339; University of North Carolina, UNC Diabetes Care Center, Office of Human Research Ethics, 720 Martin Luther King Jr. Blvd, Building #385, Second Floor, CB 7097, Chapel Hill, NC 27559-7097; Weill Cornell Medical College New York Presbyterian Institutional Review Board, 407 E. 61st Street, RR-110, New York, NY 10065.

*Approved sites for main phase but not extension phase of trial.