



## Clinical trial results:

### **Efficacy and Safety of Oral Semaglutide versus Liraglutide and versus Placebo in Subjects with Type 2 Diabetes Mellitus. A 52-week randomised, double-blind, active- and placebo-controlled trial.**

#### **Summary**

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2015-005210-30    |
| Trial protocol           | SK LV HU DE CZ HR |
| Global end of trial date | 30 March 2018     |

#### **Results information**

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 14 April 2019 |
| First version publication date | 14 April 2019 |

#### **Trial information**

##### **Trial identification**

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | NN9924-4224 |
|-----------------------|-------------|

##### **Additional study identifiers**

|                                    |  |
|------------------------------------|--|
| ISRCTN number                      | -  |
| ClinicalTrials.gov id (NCT number) | NCT02863419                                  |
| WHO universal trial number (UTN)   | U1111-1176-6029                              |
| Other trial identifiers            | Japanese trial registration: JapicCTI-163358 |

Notes:

##### **Sponsors**

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Novo Nordisk A/S  |
| Sponsor organisation address | Novo Allé, Bagsvaerd, Denmark, 2880   |
| Public contact               | Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com |
| Scientific contact           | Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com |

Notes:

##### **Paediatric regulatory details**

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 07 November 2018 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 19 August 2017   |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 30 March 2018    |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To compare the effect of once-daily dosing of 14 mg oral semaglutide versus 1.8 mg liraglutide subcutaneous and versus placebo, all in combination with metformin with or without a sodium-glucose co-transporter-2 (SGLT-2) inhibitor, on glycaemic control in subjects with type 2 diabetes mellitus (T2DM).

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2013), ICH Good Clinical Practice, including archiving of essential documents (1996), and 21 CFR 312.120.

Background therapy:

The subjects continued on their anti-diabetic background medication (metformin alone or in combination with a SGLT-2 inhibitor) throughout the entire trial.

Evidence for comparator:

Not applicable.

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 10 August 2016 |
| Long term follow-up planned                               | No             |
| Independent data monitoring committee (IDMC) involvement? | No             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                          |
|--------------------------------------|--------------------------|
| Country: Number of subjects enrolled | United Arab Emirates: 24 |
| Country: Number of subjects enrolled | Czech Republic: 30       |
| Country: Number of subjects enrolled | Germany: 59              |
| Country: Number of subjects enrolled | Croatia: 30              |
| Country: Number of subjects enrolled | Hungary: 80              |
| Country: Number of subjects enrolled | Japan: 75                |
| Country: Number of subjects enrolled | Latvia: 30               |
| Country: Number of subjects enrolled | Poland: 73               |
| Country: Number of subjects enrolled | Slovakia: 39             |
| Country: Number of subjects enrolled | Ukraine: 40              |
| Country: Number of subjects enrolled | United States: 179       |
| Country: Number of subjects enrolled | South Africa: 52         |
| Worldwide total number of subjects   | 711                      |
| EEA total number of subjects         | 341                      |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 561 |
| From 65 to 84 years                       | 150 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

The trial was conducted at 101 sites in 12 countries as follows: Croatia (5), Czech Republic (3), Germany (8), Hungary (9), Japan (9), Latvia (4), Poland (9), Slovakia (5), South Africa (5), Ukraine (3), United Arab Emirates (2), United States (39).

### Pre-assignment

Screening details:

Not applicable.

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Overall Study (overall period)                  |
| Is this the baseline period? | Yes   |
| Allocation method            | Randomised - controlled                         |
| Blinding used                | Double blind                                    |
| Roles blinded                | Subject, Investigator, Monitor, Carer, Assessor |

Blinding implementation details:

The trial was double-blinded and the clinical study group and the investigator remained blinded throughout the trial. For both oral semaglutide and liraglutide, the active and corresponding placebo products were visually identical. Furthermore, all semaglutide tablets were visually identical to each other, irrespective of the dose levels.

### Arms

|                              |                        |
|------------------------------|------------------------|
| Are arms mutually exclusive? | Yes                    |
| <b>Arm title</b>             | Oral semaglutide 14 mg |

Arm description:

Subjects were to receive once-daily oral semaglutide tablets for 52 weeks. Subjects started oral semaglutide at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52). The subjects also received liraglutide placebo once-daily as subcutaneous injection (under the skin) for 52 weeks where they initiated liraglutide placebo at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg.

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Oral semaglutide 3 mg |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Tablet                |
| Routes of administration               | Oral use              |

Dosage and administration details:

Oral semaglutide 3 mg was administered from week 0 to week 4, as part of dose escalation regimen. The tablet was taken once daily in the morning in a fasting state and at least 30 minutes before the first meal of the day. The trial product could be taken with up to a half a glass of water (approximately 120 mL/4 fluid oz) and was to be swallowed whole and not broken or chewed. Oral medication other than trial product could be taken 30 minutes after administration of trial product

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | Oral semaglutide 7 mg |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Tablet                |
| Routes of administration               | Oral use              |

Dosage and administration details:

Oral semaglutide 3 mg was administered from week 4 to week 8, as part of dose escalation regimen. The tablet was taken once daily in the morning in a fasting state and at least 30 minutes before the first meal of the day. The trial product could be taken with up to a half a glass of water (approximately 120 mL/4 fluid oz) and was to be swallowed whole and not broken or chewed. Oral medication other than

trial product could be taken 30 minutes after administration of trial product

|  |                        |
|--|------------------------|
| Investigational medicinal product name | Oral semaglutide 14 mg |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Tablet                 |
| Routes of administration               | Oral use               |

Dosage and administration details:

Oral semaglutide 14 mg was administered from week 8 to week 52, once daily in the morning in a fasting state and at least 30 minutes before the first meal of the day. The trial product could be taken with up to a half a glass of water (approximately 120 mL/4 fluid oz) and was to be swallowed whole and not broken or chewed. Oral medication other than trial product could be taken 30 minutes after administration of trial product

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Liraglutide 1.8 mg |
|------------------|--------------------|

Arm description:

Subjects were to receive liraglutide for 52 weeks. Liraglutide was administered once-daily as subcutaneous injection (under the skin) in the abdomen, thigh or upper arm and was taken with or without food, preferably at the same time each day. Subjects initiated liraglutide at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg. The subjects also received once daily oral semaglutide placebo 14 mg tablets for 52 weeks where they started oral semaglutide placebo at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52).

|  |                        |
|--|------------------------|
| Arm type                               | Active comparator      |
| Investigational medicinal product name | Liraglutide            |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

Liraglutide 1.8 mg was administered once-daily as sub-cutaneous injection (under the skin) in the abdomen, thigh or upper arm; it was to be taken with or without food, and preferably at the same time each day.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Subjects were to receive both semaglutide placebo and liraglutide placebo for 52 weeks. Subjects started semaglutide placebo tablets at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52). Liraglutide placebo was administered once-daily as subcutaneous injection (under the skin) in the abdomen, thigh or upper arm and was taken with or without food, preferably at the same time each day. Subjects initiated liraglutide placebo injection at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg.

|  |                          |
|--|--------------------------|
| Arm type                               | Placebo                  |
| Investigational medicinal product name | Oral semaglutide placebo |
| Investigational medicinal product code |                          |
| Other name                             |                          |
| Pharmaceutical forms                   | Tablet                   |
| Routes of administration               | Oral use                 |

Dosage and administration details:

Oral semaglutide placebo was administered once daily in the morning in a fasting state and at least 30 minutes before the first meal of the day. The trial product could be taken with up to a half a glass of water (approximately 120 mL/4 fluid oz) and was to be swallowed whole and not broken or chewed. Oral medication other than trial product could be taken 30 minutes after administration of trial product.

|  |                        |
|--|------------------------|
| Investigational medicinal product name | Liraglutide placebo    |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |

|                          |                  |
|--------------------------|------------------|
| Routes of administration | Subcutaneous use |
|--------------------------|------------------|

Dosage and administration details:

Liraglutide placebo was administered once-daily as sub-cutaneous injection (under the skin) in the abdomen, thigh or upper arm; it was to be taken with or without food, and preferably at the same time each day.

| <b>Number of subjects in period 1</b> | Oral semaglutide 14 mg | Liraglutide 1.8 mg | Placebo |
|---------------------------------------|------------------------|--------------------|---------|
| Started                               | 285                    | 284                | 142     |
| Completed                             | 277                    | 274                | 134     |
| Not completed                         | 8                      | 10                 | 8       |
| Consent withdrawn by subject          | 5                      | 5                  | 3       |
| Died                                  | 3                      | 4                  | 1       |
| Lost to follow-up                     | -                      | 1                  | 4       |

## Baseline characteristics

### Reporting groups

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | Oral semaglutide 14 mg |
|-----------------------|------------------------|

Reporting group description:

Subjects were to receive once-daily oral semaglutide tablets for 52 weeks. Subjects started oral semaglutide at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52). The subjects also received liraglutide placebo once-daily as subcutaneous injection (under the skin) for 52 weeks where they initiated liraglutide placebo at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Liraglutide 1.8 mg |
|-----------------------|--------------------|

Reporting group description:

Subjects were to receive liraglutide for 52 weeks. Liraglutide was administered once-daily as subcutaneous injection (under the skin) in the abdomen, thigh or upper arm and was taken with or without food, preferably at the same time each day. Subjects initiated liraglutide at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg. The subjects also received once daily oral semaglutide placebo 14 mg tablets for 52 weeks where they started oral semaglutide placebo at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52).

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects were to receive both semaglutide placebo and liraglutide placebo for 52 weeks. Subjects started semaglutide placebo tablets at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52). Liraglutide placebo was administered once-daily as subcutaneous injection (under the skin) in the abdomen, thigh or upper arm and was taken with or without food, preferably at the same time each day. Subjects initiated liraglutide placebo injection at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg.

| Reporting group values               | Oral semaglutide 14 mg | Liraglutide 1.8 mg | Placebo |
|--------------------------------------|------------------------|--------------------|---------|
| Number of subjects                   | 285                    | 284                | 142     |
| Age categorical<br>Units: Subjects   |                        |                    |         |
| Adults (18-64 years)                 | 232                    | 220                | 109     |
| From 65 to 74                        | 48                     | 56                 | 27      |
| From 75 to 84                        | 5                      | 8                  | 6       |
| 85 and above                         | 0                      | 0                  | 0       |
| Age Continuous<br>Units: Years       |                        |                    |         |
| arithmetic mean                      | 56                     | 56                 | 57      |
| standard deviation                   | ± 10                   | ± 10               | ± 10    |
| Sex: Female, Male<br>Units: Subjects |                        |                    |         |
| Female                               | 138                    | 135                | 68      |
| Male                                 | 147                    | 149                | 74      |
| Race (NIH/OMB)<br>Units: Subjects    |                        |                    |         |
| American Indian or Alaska Native     | 0                      | 1                  | 1       |
| Asian                                | 39                     | 36                 | 19      |

|   |        |        |        |
|---|--------|--------|--------|
| Native Hawaiian or Other Pacific Islander | 0      | 1      | 0      |
| Black or African American                 | 12     | 9      | 8      |
| White                                     | 208    | 212    | 99     |
| More than one race                        | 3      | 8      | 3      |
| Unknown or Not Reported                   | 23     | 17     | 12     |
| Ethnicity (NIH/OMB)                       |        |        |        |
| Units: Subjects                           |        |        |        |
| Hispanic or Latino                        | 17     | 18     | 5      |
| Not Hispanic or Latino                    | 268    | 266    | 137    |
| Unknown or Not Reported                   | 0      | 0      | 0      |
| HbA1c                                     |        |        |        |
| Glycosylate haemoglobin                   |        |        |        |
| Units: %-point                            |        |        |        |
| arithmetic mean                           | 8.0    | 8.0    | 7.9    |
| standard deviation                        | ± 0.7  | ± 0.7  | ± 0.7  |
| Body weight                               |        |        |        |
| Units: kg                                 |        |        |        |
| arithmetic mean                           | 92.9   | 95.5   | 93.2   |
| standard deviation                        | ± 20.6 | ± 21.9 | ± 20.0 |

|   |       |  |  |
|---|-------|--|--|
| <b>Reporting group values</b>             | Total |  |  |
| Number of subjects                        | 711   |  |  |
| Age categorical                           |       |  |  |
| Units: Subjects                           |       |  |  |
| Adults (18-64 years)                      | 561   |  |  |
| From 65 to 74                             | 131   |  |  |
| From 75 to 84                             | 19    |  |  |
| 85 and above                              | 0     |  |  |
| Age Continuous                            |       |  |  |
| Units: Years                              |       |  |  |
| arithmetic mean                           | -     |  |  |
| standard deviation                        | -     |  |  |
| Sex: Female, Male                         |       |  |  |
| Units: Subjects                           |       |  |  |
| Female                                    | 341   |  |  |
| Male                                      | 370   |  |  |
| Race (NIH/OMB)                            |       |  |  |
| Units: Subjects                           |       |  |  |
| American Indian or Alaska Native          | 2     |  |  |
| Asian                                     | 94    |  |  |
| Native Hawaiian or Other Pacific Islander | 1     |  |  |
| Black or African American                 | 29    |  |  |
| White                                     | 519   |  |  |
| More than one race                        | 14    |  |  |
| Unknown or Not Reported                   | 52    |  |  |
| Ethnicity (NIH/OMB)                       |       |  |  |
| Units: Subjects                           |       |  |  |
| Hispanic or Latino                        | 40    |  |  |
| Not Hispanic or Latino                    | 671   |  |  |
| Unknown or Not Reported                   | 0     |  |  |



|                         |   |  |  |
|-------------------------|---|--|--|
| HbA1c                   |   |  |  |
| Glycosylate haemoglobin |   |  |  |
| Units: %-point          |   |  |  |
| arithmetic mean         |   |  |  |
| standard deviation      | - |  |  |
| Body weight             |   |  |  |
| Units: kg               |   |  |  |
| arithmetic mean         |   |  |  |
| standard deviation      | - |  |  |

## End points

### End points reporting groups

|  |                        |
|--|------------------------|
| Reporting group title  | Oral semaglutide 14 mg |
| Reporting group description:<br>Subjects were to receive once-daily oral semaglutide tablets for 52 weeks. Subjects started oral semaglutide at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52). The subjects also received liraglutide placebo once-daily as subcutaneous injection (under the skin) for 52 weeks where they initiated liraglutide placebo at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg.   |                        |
| Reporting group title  | Liraglutide 1.8 mg     |
| Reporting group description:<br>Subjects were to receive liraglutide for 52 weeks. Liraglutide was administered once-daily as subcutaneous injection (under the skin) in the abdomen, thigh or upper arm and was taken with or without food, preferably at the same time each day. Subjects initiated liraglutide at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg. The subjects also received once daily oral semaglutide placebo 14 mg tablets for 52 weeks where they started oral semaglutide placebo at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52). |                        |
| Reporting group title  | Placebo                |
| Reporting group description:<br>Subjects were to receive both semaglutide placebo and liraglutide placebo for 52 weeks. Subjects started semaglutide placebo tablets at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52). Liraglutide placebo was administered once-daily as subcutaneous injection (under the skin) in the abdomen, thigh or upper arm and was taken with or without food, preferably at the same time each day. Subjects initiated liraglutide placebo injection at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg.                           |                        |

### Primary: Change in HbA1c (in-trial observation period) (week 26)

|   |   |
|---|---|
| End point title   | Change in HbA1c (in-trial observation period) (week 26) |
| End point description:<br>Observed mean change from baseline (week 0) to week 26 in glycosylated haemoglobin. The endpoint was evaluated based on data from the in-trial observation period. In-trial observation period: the time period from when a subject was randomised until the final scheduled visit, including any period after initiation of rescue medication or premature discontinuation of trial product. Full analysis set comprised of all randomised subjects. "Number analysed"=subjects with available data. |   |
| End point type  | Primary   |
| End point timeframe:<br>From baseline to week 26  |   |

| End point values                     | Oral semaglutide 14 mg | Liraglutide 1.8 mg | Placebo         |  |
|--------------------------------------|------------------------|--------------------|-----------------|--|
| Subject group type                   | Reporting group        | Reporting group    | Reporting group |  |
| Number of subjects analysed          | 278                    | 272                | 134             |  |
| Units: %-point                       |                        |                    |                 |  |
| arithmetic mean (standard deviation) | -1.2 (± 0.9)           | -1.1 (± 0.9)       | -0.1 (± 0.7)    |  |

## Statistical analyses

| Statistical analysis title   | Oral semaglutide versus Placebo  |
|--|----------------------------------|
| Statistical analysis description:  |                                  |
| The endpoint was analysed using an ANCOVA model with treatment, stratification factor and region as categorical fixed effects and baseline HbA1c as covariate. The null hypothesis (H0) and the alternate hypothesis (HA) were: H0: $\mu \geq 0.0\%$ -points against HA: $\mu < 0.0\%$ . ( $\mu$ denotes mean treatment difference). The analysis was based on a pattern mixture model that used multiple imputation to impute missing week-26 data, assuming that such data were missing at random. |                                  |
| Comparison groups  | Oral semaglutide 14 mg v Placebo |
| Number of subjects included in analysis  | 412                              |
| Analysis specification   | Pre-specified                    |
| Analysis type  | superiority <sup>[1]</sup>       |
| P-value  | < 0.0001 <sup>[2]</sup>          |
| Method   | ANCOVA                           |
| Parameter estimate   | Treatment difference             |
| Point estimate   | -1.1                             |
| Confidence interval  |                                  |
| level  | 95 %                             |
| sides  | 2-sided                          |
| lower limit  | -1.2                             |
| upper limit  | -0.9                             |

Notes:

[1] - The analysis was based on treatment policy estimand. This hypothesis was controlled for multiplicity. "Subjects in this analysis"=number of subjects with available data; all subjects in the FAS (N=427) with data contributed to the analysis.

[2] - Unadjusted two-sided p-value for test of no difference from 0.

| Statistical analysis title   | Oral semaglutide versus Liraglutide         |
|--|---|
| Statistical analysis description:  |   |
| Change from baseline was analysed using an ANCOVA model with treatment, strata, and region as categorical fixed effects and baseline value as covariate for each of the 1000 imputed complete datasets, and pooled by Rubin's rule to draw inference. The hypothesis tested was: H0: $\mu \geq 0.4\%$ -points against HA: $\mu < 0.4\%$ . A value of 0.4% (the non-inferiority margin) was added to imputed values at week 26 for the oral semaglutide treatment arm only. |   |
| Comparison groups  | Oral semaglutide 14 mg v Liraglutide 1.8 mg |
| Number of subjects included in analysis  | 550   |
| Analysis specification   | Pre-specified                               |
| Analysis type  | non-inferiority <sup>[3]</sup>              |
| P-value  | < 0.0001 <sup>[4]</sup>                     |
| Method   | ANCOVA                                      |
| Parameter estimate   | Treatment difference                        |
| Point estimate   | -0.1  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided                                     |
| lower limit  | -0.3  |
| upper limit  | 0   |

Notes:

[3] - The analysis was based on treatment policy estimand. This hypothesis was controlled for multiplicity. HbA1c non-inferiority was tested using a non-inferiority margin of 0.4%-points. "Subjects in this analysis"=number of subjects with available data; all subjects in the FAS (N=569) contributed with data to the analysis.

[4] - Unadjusted two-sided p-value for test of no difference from the non-inferiority margin.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Oral semaglutide versus Liraglutide         |
| Statistical analysis description:   |   |
| Change from baseline was analysed using an ANCOVA model with treatment, strata, and region as categorical fixed effects and baseline value as covariate for each of the 1000 imputed complete datasets, and pooled by Rubin's rule to draw inference. The null hypothesis (H0) and the alternate hypothesis (HA) were: H0: $\mu \geq 0.0\%$ -points against HA: $\mu < 0.0\%$ . ( $\mu$ denotes mean treatment difference). |   |
| Comparison groups   | Oral semaglutide 14 mg v Liraglutide 1.8 mg |
| Number of subjects included in analysis   | 550   |
| Analysis specification  | Pre-specified                               |
| Analysis type   | superiority <sup>[5]</sup>                  |
| P-value   | = 0.0645 <sup>[6]</sup>                     |
| Method  | ANCOVA                                      |
| Parameter estimate  | Treatment difference                        |
| Point estimate  | -0.1  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided                                     |
| lower limit   | -0.3  |
| upper limit   | 0   |

Notes:

[5] - The analysis was based on treatment policy estimand. This hypothesis was controlled for multiplicity. "Subjects in this analysis"=number of subjects with available data; all subjects in the FAS (N=569) contributed with data to the analysis.

[6] - Unadjusted two-sided p-value for test of no difference from 0.

### **Primary: Change in HbA1c (on-treatment without rescue medication observation period) (week 26)**

|  |   |
|--|---|
| End point title  | Change in HbA1c (on-treatment without rescue medication observation period) (week 26) |
| End point description:   |   |
| Observed mean change from baseline (week 0) to week 26 in glycosylated haemoglobin. The primary endpoint was analysed based on data from the on-treatment without rescue medication observation period. On-treatment without rescue medication observation period: the time period when a subject was on treatment with trial product, excluding any period after initiation of rescue medication. Full analysis set comprised of all randomised subjects. "Number analysed"=subjects with available data. |   |
| End point type   | Primary   |
| End point timeframe:   |   |
| From baseline to week 26   |   |

| End point values                     | Oral semaglutide 14 mg | Liraglutide 1.8 mg | Placebo         |  |
|--------------------------------------|------------------------|--------------------|-----------------|--|
| Subject group type                   | Reporting group        | Reporting group    | Reporting group |  |
| Number of subjects analysed          | 238                    | 245                | 112             |  |
| Units: %-points                      |                        |                    |                 |  |
| arithmetic mean (standard deviation) | -1.4 (± 0.9)           | -1.2 (± 0.9)       | -0.1 (± 0.7)    |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Oral semaglutide 14 mg vs. Liraglutide      |
| Statistical analysis description:   |   |
| Changes from baseline were analysed using a mixed model for repeated measurements model with treatment, strata, and region as categorical fixed effects and baseline value as covariate, all nested within visit, and an unstructured residual covariance matrix. The hypothesis tested was: H0: $\mu \geq 0.4\%$ -points against HA: $\mu < 0.4\%$ . ( $\mu$ denotes mean treatment difference). |   |
| Comparison groups   | Oral semaglutide 14 mg v Liraglutide 1.8 mg |
| Number of subjects included in analysis   | 483   |
| Analysis specification  | Pre-specified                               |
| Analysis type   | non-inferiority <sup>[7]</sup>              |
| P-value   | < 0.0001 <sup>[8]</sup>                     |
| Method  | Mixed model for repeated measurements       |
| Parameter estimate  | Treatment difference                        |
| Point estimate  | -0.2  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided                                     |
| lower limit   | -0.3  |
| upper limit   | -0.1  |

Notes:

[7] - The analysis was based on hypothetical estimand. This hypothesis was not controlled for multiplicity. HbA1c non-inferiority was tested using a non-inferiority margin of 0.4%-points. "Subjects in this analysis"=number of subjects with available data; all subjects in the FAS (N=569) with data contributed to the analysis.

[8] - Unadjusted two-sided p-value for test of no difference from the non-inferiority margin.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Oral semaglutide 14 mg vs. Liraglutide 1.8 mg |
| Statistical analysis description:   |   |
| Changes from baseline were analysed using a mixed model for repeated measurements model with treatment, strata, and region as categorical fixed effects and baseline value as covariate, all nested within visit, and an unstructured residual covariance matrix. The null hypothesis (H0) and the alternate hypothesis (HA) were: H0: $\mu \geq 0.0\%$ -points against HA: $\mu < 0.0\%$ . ( $\mu$ denotes mean treatment difference). |   |
| Comparison groups   | Oral semaglutide 14 mg v Liraglutide 1.8 mg   |
| Number of subjects included in analysis   | 483   |
| Analysis specification  | Pre-specified                                 |
| Analysis type   | superiority <sup>[9]</sup>                    |
| P-value   | = 0.0056 <sup>[10]</sup>                      |
| Method  | Mixed model for repeated measurements         |
| Parameter estimate  | Treatment difference                          |
| Point estimate  | -0.2  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided                                       |
| lower limit   | -0.3  |
| upper limit   | -0.1  |

Notes:

[9] - Analysis was based on hypothetical estimand. This hypothesis was not controlled for multiplicity. "Subjects in this analysis"=number of subjects with available data; all subjects in the FAS (N=569) with data contributed to the analysis.

[10] - Unadjusted two-sided p-value for test of no difference from 0.

|                                   |                                    |
|-----------------------------------|------------------------------------|
| <b>Statistical analysis title</b> | Oral semaglutide 14 mg vs. Placebo |
|-----------------------------------|------------------------------------|

Statistical analysis description:

Changes from baseline were analysed using a mixed model for repeated measurements model with treatment, strata, and region as categorical fixed effects and baseline value as covariate, all nested within visit, and an unstructured residual covariance matrix. The null hypothesis (H0) and the alternate hypothesis (HA) were: H0:  $\mu \geq 0.0\%$ -points against HA:  $\mu < 0.0\%$ . ( $\mu$  denotes mean treatment difference).

|   |  |
|---|--|
| Comparison groups                       | Oral semaglutide 14 mg v Placebo       |
| Number of subjects included in analysis | 350                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority <sup>[11]</sup>            |
| P-value                                 | < 0.0001 <sup>[12]</sup>               |
| Method                                  | Mixed model for repeated measurements. |
| Parameter estimate                      | Treatment difference                   |
| Point estimate                          | -1.2                                   |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -1.4                                   |
| upper limit                             | -1                                     |

Notes:

[11] - The analysis was based on hypothetical estimand. This hypothesis was not controlled for multiplicity. "Subjects in this analysis"=number of subjects with available data; all subjects in the FAS (N=427) with data contributed to the analysis.

[12] - Unadjusted two-sided p-value for test of no difference from 0.

## Secondary: Change in body weight (in-trial observation period) (week 26)

|                 |   |
|-----------------|---|
| End point title | Change in body weight (in-trial observation period) (week 26) |
|-----------------|---|

End point description:

Change from baseline (week 0) in body weight to week 26. The endpoint was evaluated based on data from the in-trial observation period. Results are based on full analysis set comprised of all randomised subjects. "Number of subjects analysed"=subjects with available data.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline to week 26

| End point values                     | Oral semaglutide 14 mg | Liraglutide 1.8 mg | Placebo         |  |
|--------------------------------------|------------------------|--------------------|-----------------|--|
| Subject group type                   | Reporting group        | Reporting group    | Reporting group |  |
| Number of subjects analysed          | 278                    | 271                | 134             |  |
| Units: kg                            |                        |                    |                 |  |
| arithmetic mean (standard deviation) | -4.4 (± 4.4)           | -3.2 (± 3.7)       | -0.6 (± 3.1)    |  |

## Statistical analyses

| Statistical analysis title   | Oral semaglutide versus Placebo  |
|--|----------------------------------|
| Statistical analysis description:  |                                  |
| The endpoint was analysed using an ANCOVA model with treatment, stratification factor and region as categorical fixed effects and the baseline body weight value as the covariate. The null hypothesis (H0) and the alternate hypothesis (HA) were: H0: $\mu \geq 0.0$ kg against HA: $\mu < 0.0$ kg ( $\mu$ denotes mean treatment difference). The analysis was based on a pattern mixture model that used multiple imputation to impute missing week-26 data, assuming that such data were missing at random. |                                  |
| Comparison groups  | Oral semaglutide 14 mg v Placebo |
| Number of subjects included in analysis  | 412                              |
| Analysis specification   | Pre-specified                    |
| Analysis type  | superiority <sup>[13]</sup>      |
| P-value  | < 0.0001 <sup>[14]</sup>         |
| Method   | ANCOVA                           |
| Parameter estimate   | Treatment difference             |
| Point estimate   | -3.8                             |
| Confidence interval  |                                  |
| level  | 95 %                             |
| sides  | 2-sided                          |
| lower limit  | -4.7                             |
| upper limit  | -3                               |

Notes:

[13] - The analysis was for the treatment policy estimand. This hypothesis was controlled for multiplicity. Subjects in this analysis=number of subjects with available data; all subjects in the FAS (N=427) contributed with data to the analysis.

[14] - Unadjusted two-sided p-value for test of no difference from 0.

| Statistical analysis title  | Oral semaglutide versus Liraglutide         |
|---|---|
| Statistical analysis description:   |   |
| The endpoint was analysed using an ANCOVA model with treatment, stratification factor and region as categorical fixed effects and the baseline body weight value as the covariate. The null hypothesis (H0) and the alternate hypothesis (HA) were: H0: $\mu \geq 0.0$ kg against HA: $\mu < 0.0$ kg ( $\mu$ denotes mean treatment difference). The analysis was based on a pattern mixture model that used multiple imputation to impute missing week-26 data, assuming that such data were missing at random |   |
| Comparison groups   | Oral semaglutide 14 mg v Liraglutide 1.8 mg |
| Number of subjects included in analysis   | 549   |
| Analysis specification  | Pre-specified                               |
| Analysis type   | superiority <sup>[15]</sup>                 |
| P-value   | = 0.0003 <sup>[16]</sup>                    |
| Method  | ANCOVA                                      |
| Parameter estimate  | Treatment difference                        |
| Point estimate  | -1.2  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided                                     |
| lower limit   | -1.9  |
| upper limit   | -0.6  |

Notes:

[15] - The analysis was for the treatment policy estimand. This hypothesis was controlled for multiplicity. Subjects in this analysis=number of subjects with available data; all subjects in the FAS (N=569) contributed with data to the analysis

[16] - Unadjusted two-sided p-value for test of no difference from 0.

## Secondary: Change in body weight (on-treatment without rescue medication observation period) (week 26)

|   |   |
|---|---|
| End point title   | Change in body weight (on-treatment without rescue medication observation period) (week 26) |
| End point description:<br>Observed mean change from baseline (week 0) to week 26 in body weight. The endpoint was evaluated based on data from the on-treatment without rescue medication observation period. Full analysis set comprised of all randomised subjects. "Number analysed"=subjects with available data. |   |
| End point type  | Secondary   |
| End point timeframe:<br>From baseline to week 26  |   |

| End point values                     | Oral semaglutide 14 mg | Liraglutide 1.8 mg | Placebo         |  |
|--------------------------------------|------------------------|--------------------|-----------------|--|
| Subject group type                   | Reporting group        | Reporting group    | Reporting group |  |
| Number of subjects analysed          | 223                    | 230                | 83              |  |
| Units: kg                            |                        |                    |                 |  |
| arithmetic mean (standard deviation) | -5.0 (± 5.2)           | -3.3 (± 4.3)       | -1.5 (± 3.3)    |  |

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Oral semaglutide 14 mg vs. Liraglutide 1.8 mg |
| Statistical analysis description:<br>Changes from baseline were analysed using a mixed model for repeated measurements model with treatment, strata, and region as categorical fixed effects and baseline value as covariate, all nested within visit, and an unstructured residual covariance matrix. |   |
| Comparison groups  | Oral semaglutide 14 mg v Liraglutide 1.8 mg   |
| Number of subjects included in analysis  | 453   |
| Analysis specification   | Pre-specified                                 |
| Analysis type  | superiority <sup>[17]</sup>                   |
| P-value  | < 0.0001 <sup>[18]</sup>                      |
| Method   | Mixed model for repeated measurements         |
| Parameter estimate   | Treatment difference                          |
| Point estimate   | -1.5  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided                                       |
| lower limit  | -2.2  |
| upper limit  | -0.9  |

Notes:

[17] - The analysis was for hypothetical estimand. This hypothesis was not controlled for multiplicity. "Subjects in this analysis"=number of subjects with available data at week 26; all subjects in the FAS (N=569) contributed to the analysis.

[18] - Unadjusted two sided p-value for test of no difference from 0.

|  |                                    |
|--|------------------------------------|
| <b>Statistical analysis title</b>  | Oral semaglutide 14 mg vs. Placebo |
| Statistical analysis description:<br>Changes from baseline were analysed using a mixed model for repeated measurements model with treatment, strata, and region as categorical fixed effects and baseline value as covariate, all nested within visit, and an unstructured residual covariance matrix. |                                    |
| Comparison groups  | Oral semaglutide 14 mg v Placebo   |



|   |                                       |
|---|---------------------------------------|
| Number of subjects included in analysis | 306                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority <sup>[19]</sup>           |
| P-value                                 | < 0.0001                              |
| Method                                  | Mixed model for repeated measurements |
| Parameter estimate                      | Treatment difference                  |
| Point estimate                          | -4                                    |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -4.8                                  |
| upper limit                             | -3.2                                  |

Notes:

[19] - Analysis was for the hypothetical estimand. This hypothesis was not controlled for multiplicity. Subjects in this analysis"=number of subjects with available data at week 26; all subjects in the FAS (N=427) contributed to the analysis.

### Secondary: Change in HbA1c (week 52)

|  |                           |
|--|---------------------------|
| End point title  | Change in HbA1c (week 52) |
| End point description:   |                           |
| Change from baseline (week 0) in HbA1c to week 52. The endpoint was evaluated based on data from the in-trial observation period. Results are based on full analysis set comprised of all randomised subjects. "Number of subjects analysed"=subjects with available data. |                           |
| End point type   | Secondary                 |
| End point timeframe:   |                           |
| From baseline to week 52   |                           |

| End point values                     | Oral semaglutide 14 mg | Liraglutide 1.8 mg | Placebo         |  |
|--------------------------------------|------------------------|--------------------|-----------------|--|
| Subject group type                   | Reporting group        | Reporting group    | Reporting group |  |
| Number of subjects analysed          | 275                    | 269                | 133             |  |
| Units: %-point                       |                        |                    |                 |  |
| arithmetic mean (standard deviation) | -1.2 (± 1.0)           | -0.9 (± 1.0)       | -0.1 (± 0.9)    |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in body weight (kg) (week 52)

|  |                                      |
|--|--------------------------------------|
| End point title  | Change in body weight (kg) (week 52) |
| End point description:   |                                      |
| Change from baseline (week 0) in body weight to week 52. The endpoint was evaluated based on data from the in-trial observation period. Results are based on full analysis set comprised of all randomised subjects. "Number of subjects analysed"=subjects with available data. |                                      |
| End point type   | Secondary                            |
| End point timeframe:   |                                      |
| From baseline to week 52   |                                      |

| End point values                     | Oral semaglutide 14 mg | Liraglutide 1.8 mg | Placebo         |  |
|--------------------------------------|------------------------|--------------------|-----------------|--|
| Subject group type                   | Reporting group        | Reporting group    | Reporting group |  |
| Number of subjects analysed          | 275                    | 269                | 133             |  |
| Units: kg                            |                        |                    |                 |  |
| arithmetic mean (standard deviation) | -4.94 (± 6.37)         | -3.25 (± 4.33)     | -0.99 (± 4.12)  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in fasting plasma glucose (week 26)

|   |  |
|---|--|
| End point title   | Change in fasting plasma glucose (week 26) |
| End point description:<br>Change from baseline (week 0) in fasting plasma glucose to week 26. The endpoint was evaluated based on data from the in-trial observation period. Results are based on full analysis set comprised of all randomised subjects. "Number of subjects analysed"=subjects with available data. |  |
| End point type  | Secondary                                  |
| End point timeframe:<br>From baseline to week 26  |  |

| End point values                     | Oral semaglutide 14 mg | Liraglutide 1.8 mg | Placebo         |  |
|--------------------------------------|------------------------|--------------------|-----------------|--|
| Subject group type                   | Reporting group        | Reporting group    | Reporting group |  |
| Number of subjects analysed          | 276                    | 269                | 133             |  |
| Units: mmol/L                        |                        |                    |                 |  |
| arithmetic mean (standard deviation) | -2.04 (± 2.28)         | -1.91 (± 2.05)     | -0.33 (± 2.03)  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in fasting plasma glucose (week 52)

|   |  |
|---|--|
| End point title   | Change in fasting plasma glucose (week 52) |
| End point description:<br>Change from baseline (week 0) in fasting plasma glucose to week 52. The endpoint was evaluated based on data from the in-trial observation period. Results are based on full analysis set comprised of all randomised subjects. "Number of subjects analysed"=subjects with available data. |  |
| End point type  | Secondary                                  |

End point timeframe:  
From baseline to week 52

| End point values                     | Oral<br>semaglutide 14<br>mg | Liraglutide 1.8<br>mg | Placebo         |  |
|--------------------------------------|------------------------------|-----------------------|-----------------|--|
| Subject group type                   | Reporting group              | Reporting group       | Reporting group |  |
| Number of subjects analysed          | 273                          | 269                   | 132             |  |
| Units: mmol/L                        |                              |                       |                 |  |
| arithmetic mean (standard deviation) | -1.91 (± 2.41)               | -1.54 (± 2.41)        | -0.66 (± 1.99)  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Achieved HbA1c < 7.0 % (53 mmol/mol) American Diabetes Association target (yes/no) (week 26)

|                 |  |
|-----------------|--|
| End point title | Achieved HbA1c < 7.0 % (53 mmol/mol) American Diabetes Association target (yes/no) (week 26) |
|-----------------|--|

End point description:

Number of subjects achieving HbA1c < 7.0 % (53 mmol/mol) according to American Diabetes Association (ADA) target, at week 26. The endpoint was evaluated based on data from the in-trial observation period. Results are based on full analysis set comprised of all randomised subjects. "Number of subjects analysed"=subjects with available data.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At week 26

| End point values            | Oral<br>semaglutide 14<br>mg | Liraglutide 1.8<br>mg | Placebo         |  |
|-----------------------------|------------------------------|-----------------------|-----------------|--|
| Subject group type          | Reporting group              | Reporting group       | Reporting group |  |
| Number of subjects analysed | 278                          | 272                   | 134             |  |
| Units: percentage           |                              |                       |                 |  |
| number (not applicable)     |                              |                       |                 |  |
| Yes                         | 67.6                         | 61.8                  | 14.2            |  |
| No                          | 32.4                         | 38.2                  | 85.8            |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Achieved HbA1c < 7.0 % (53 mmol/mol) American Diabetes Association target (yes/no) (week 52)

|   |  |
|---|--|
| End point title   | Achieved HbA1c < 7.0 % (53 mmol/mol) American Diabetes Association target (yes/no) (week 52) |
| End point description:<br>Number of subjects achieving HbA1c < 7.0 % (53 mmol/mol) according to American Diabetes Association (ADA) target, at week 52. The endpoint was evaluated based on data from the in-trial observation period. Results are based on full analysis set comprised of all randomised subjects. "Number of subjects analysed"=subjects with available data. |  |
| End point type  | Secondary  |
| End point timeframe:<br>At week 52  |  |

| End point values            | Oral semaglutide 14 mg | Liraglutide 1.8 mg | Placebo         |  |
|-----------------------------|------------------------|--------------------|-----------------|--|
| Subject group type          | Reporting group        | Reporting group    | Reporting group |  |
| Number of subjects analysed | 275                    | 269                | 133             |  |
| Units: percentage           |                        |                    |                 |  |
| number (not applicable)     |                        |                    |                 |  |
| Yes                         | 60.7                   | 55.0               | 15.0            |  |
| No                          | 39.3                   | 45.0               | 85.0            |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of treatment-emergent adverse events

|  |   |
|--|---|
| End point title  | Number of treatment-emergent adverse events |
| End point description:<br>A treatment-emergent adverse event (TEAE) is defined as an adverse event with onset in the on-treatment observation period (the time period where subjects are considered treated with trial product). The safety analysis set (SAS) included all randomised subjects who received at least one dose of trial product. "Number of subjects analysed"=subjects with available data. |   |
| End point type   | Secondary                                   |
| End point timeframe:<br>During exposure to trial product, assessed up to approximately 57 weeks  |   |

| End point values            | Oral semaglutide 14 mg | Liraglutide 1.8 mg | Placebo         |  |
|-----------------------------|------------------------|--------------------|-----------------|--|
| Subject group type          | Reporting group        | Reporting group    | Reporting group |  |
| Number of subjects analysed | 285                    | 284                | 142             |  |
| Units: Events               | 973                    | 927                | 300             |  |

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes**

---

|                 |   |
|-----------------|---|
| End point title | Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes |
|-----------------|---|

End point description:

Hypoglycaemic episodes defined as treatment-emergent if the onset of the episode occurs within the on-treatment observation period. Severe or BG-confirmed symptomatic hypoglycaemia is an episode that is severe according to the American Diabetes Association classification or blood glucose-confirmed by a plasma glucose value <3.1 mmol/L (56mg/dL) with symptoms consistent with hypoglycaemia. The safety analysis set (SAS) included all randomised subjects who received at least one dose of trial product. "Number of subjects analysed"=subjects with available data.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During exposure to trial product, assessed up to approximately 57 weeks

---

| End point values            | Oral semaglutide 14 mg | Liraglutide 1.8 mg | Placebo         |  |
|-----------------------------|------------------------|--------------------|-----------------|--|
| Subject group type          | Reporting group        | Reporting group    | Reporting group |  |
| Number of subjects analysed | 285                    | 284                | 142             |  |
| Units: Episodes             | 2                      | 9                  | 3               |  |

---

**Statistical analyses**

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the date of first dose of trial product (week 0) to end of treatment (week 52) + 5 weeks of follow-up (until week 57).

Adverse event reporting additional description:

Evaluation of safety was based on safety analysis set (SAS) which comprised of all randomised subjects who received at least one dose of trial product.

AEs with onset during the on-treatment observation period (the period when subjects were exposed to trial product) were considered treatment-emergent.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |    |
|--------------------|----|
| Dictionary version | 20 |
|--------------------|----|

### Reporting groups

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | Oral Semaglutide 14 mg |
|-----------------------|------------------------|

Reporting group description:

Subjects were to receive once-daily oral semaglutide tablets for 52 weeks. Subjects started oral semaglutide at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52). The subjects also received liraglutide placebo once-daily as subcutaneous injection (under the skin) for 52 weeks where they initiated liraglutide placebo at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Liraglutide 1.8 mg |
|-----------------------|--------------------|

Reporting group description:

Subjects were to receive liraglutide for 52 weeks. Liraglutide was administered once-daily as subcutaneous injection (under the skin) in the abdomen, thigh or upper arm and was taken with or without food, preferably at the same time each day. Subjects initiated liraglutide at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg. The subjects also received once daily oral semaglutide placebo 14 mg tablets for 52 weeks where they started oral semaglutide placebo at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52).

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects were to receive both semaglutide placebo and liraglutide placebo for 52 weeks. Subjects started semaglutide placebo tablets at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52). Liraglutide placebo was administered once-daily as subcutaneous injection (under the skin) in the abdomen, thigh or upper arm and was taken with or without food, preferably at the same time each day. Subjects initiated liraglutide placebo injection at 0.6 mg once-daily, and were dose escalated after 1 week to 1.2 mg, and then dose escalated after 1 week to the recommended maximum dose of 1.8 mg.

| Serious adverse events                            | Oral Semaglutide 14 mg | Liraglutide 1.8 mg | Placebo           |
|---|------------------------|--------------------|-------------------|
| Total subjects affected by serious adverse events |                        |                    |                   |
| subjects affected / exposed                       | 31 / 285 (10.88%)      | 22 / 284 (7.75%)   | 15 / 142 (10.56%) |
| number of deaths (all causes)                     | 3                      | 4                  | 1                 |
| number of deaths resulting from adverse events    | 0                      | 0                  | 0                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                 |                 |
| Benign neoplasm of thyroid gland                                    |                 |                 |                 |
| subjects affected / exposed   | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| Colon adenoma   |                 |                 |                 |
| subjects affected / exposed   | 0 / 285 (0.00%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| Invasive ductal breast carcinoma                                    |                 |                 |                 |
| subjects affected / exposed   | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung adenocarcinoma   |                 |                 |                 |
| subjects affected / exposed   | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 1           | 0 / 0           | 0 / 0           |
| Oral fibroma  |                 |                 |                 |
| subjects affected / exposed   | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |
| Ovarian cancer metastatic   |                 |                 |                 |
| subjects affected / exposed   | 0 / 285 (0.00%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 1           | 0 / 0           |
| Pancreatic carcinoma  |                 |                 |                 |
| subjects affected / exposed   | 0 / 285 (0.00%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 1           | 0 / 0           |
| Papillary thyroid cancer  |                 |                 |                 |
| subjects affected / exposed   | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Parathyroid tumour benign<br>subjects affected / exposed  | 0 / 285 (0.00%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to<br>treatment / all        | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| Thyroid cancer metastatic<br>subjects affected / exposed  | 0 / 285 (0.00%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to<br>treatment / all        | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders  |                 |                 |                 |
| Diabetic vascular disorder<br>subjects affected / exposed | 0 / 285 (0.00%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to<br>treatment / all        | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertension<br>subjects affected / exposed               | 0 / 285 (0.00%) | 0 / 284 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to<br>treatment / all        | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| Orthostatic hypotension<br>subjects affected / exposed    | 0 / 285 (0.00%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to<br>treatment / all        | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| Varicose vein<br>subjects affected / exposed              | 0 / 285 (0.00%) | 0 / 284 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to<br>treatment / all        | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| Surgical and medical procedures                           |                 |                 |                 |
| Hospitalisation<br>subjects affected / exposed            | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to<br>treatment / all        | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| Thyroidectomy<br>subjects affected / exposed              | 0 / 285 (0.00%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to<br>treatment / all        | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |



|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| General disorders and administration site conditions |                 |                 |                 |
| Death  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 285 (0.00%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 1           | 0 / 0           |
| Non-cardiac chest pain                               |                 |                 |                 |
| subjects affected / exposed                          | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Reproductive system and breast disorders             |                 |                 |                 |
| Menometrorrhagia                                     |                 |                 |                 |
| subjects affected / exposed                          | 0 / 285 (0.00%) | 0 / 284 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders      |                 |                 |                 |
| Epistaxis  |                 |                 |                 |
| subjects affected / exposed                          | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Investigations                                       |                 |                 |                 |
| Hepatic enzyme increased                             |                 |                 |                 |
| subjects affected / exposed                          | 0 / 285 (0.00%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Investigation  |                 |                 |                 |
| subjects affected / exposed                          | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Lipase increased                                     |                 |                 |                 |
| subjects affected / exposed                          | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Weight decreased                                     |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Accidental overdose                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 0 / 284 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Ankle fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Meniscus injury                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Muscle rupture                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Spinal compression fracture                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subdural haematoma                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Tibia fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Congenital, familial and genetic disorders      |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Respiratory tract malformation<br>subjects affected / exposed       | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to<br>treatment / all                  | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                       | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders   |                 |                 |                 |
| Acute myocardial infarction<br>subjects affected / exposed          | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to<br>treatment / all                  | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                       | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial fibrillation<br>subjects affected / exposed                  | 1 / 285 (0.35%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to<br>treatment / all                  | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all                       | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial flutter<br>subjects affected / exposed                       | 0 / 285 (0.00%) | 0 / 284 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to<br>treatment / all                  | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                       | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrioventricular block second degree<br>subjects affected / exposed | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to<br>treatment / all                  | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                       | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure chronic<br>subjects affected / exposed              | 0 / 285 (0.00%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to<br>treatment / all                  | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all                       | 0 / 0           | 0 / 0           | 0 / 0           |
| Coronary artery disease<br>subjects affected / exposed              | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to<br>treatment / all                  | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                       | 0 / 0           | 0 / 0           | 0 / 0           |
| Coronary artery occlusion<br>subjects affected / exposed            | 0 / 285 (0.00%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to<br>treatment / all                  | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all                       | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial infarction   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 285 (0.70%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Ventricular extrasystoles                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Aphasia   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 0 / 284 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Carpal tunnel syndrome                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebellar syndrome                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 0 / 284 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebral infarction                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebrovascular disorder                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 0 / 284 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diabetic neuropathy                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dizziness                                       |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Facial paresis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 0 / 284 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Headache  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 0 / 284 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hemiparesis                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 0 / 284 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ischaemic stroke                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 0 / 284 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sciatica  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 0 / 284 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Syncope   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Trigeminal neuralgia                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ear and labyrinth disorders                     |                 |                 |                 |
| Vertigo positional                              |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 285 (0.00%) | 0 / 284 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye disorders                                   |                 |                 |                 |
| Ophthalmic vein thrombosis                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Duodenal ulcer                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 0 / 284 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastritis                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastroesophageal reflux disease                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 0 / 284 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hiatus hernia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Large intestine polyp                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nausea  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vomiting  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Hepatobiliary disorders</b>                  |                 |                 |                 |
| Cholecystitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cholelithiasis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Drug-induced liver injury                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatic haematoma                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Renal and urinary disorders</b>              |                 |                 |                 |
| Nephrolithiasis                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal failure                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ureterolithiasis                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Endocrine disorders</b>                      |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Thyroid mass                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Arthralgia                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 0 / 284 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Back pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 1 / 284 (0.35%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bursitis  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intervertebral disc protrusion                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ligamentitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 2 / 284 (0.70%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Spinal osteoarthritis                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Tendon disorder                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                 |                 |                 |
| Cellulitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic sinusitis                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 285 (0.00%) | 0 / 284 (0.00%) | 1 / 142 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Erysipelas                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Herpes zoster                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Otitis media                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Postoperative wound infection                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Sepsis  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary tract infection                         |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Cachexia  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 285 (0.35%) | 0 / 284 (0.00%) | 0 / 142 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

Frequency threshold for reporting non-serious adverse events: 5 %

| <b>Non-serious adverse events</b>                     | Oral Semaglutide 14 mg | Liraglutide 1.8 mg | Placebo           |
|---|------------------------|--------------------|-------------------|
| Total subjects affected by non-serious adverse events |                        |                    |                   |
| subjects affected / exposed                           | 148 / 285 (51.93%)     | 120 / 284 (42.25%) | 47 / 142 (33.10%) |
| Investigations  |                        |                    |                   |
| Blood glucose increased                               |                        |                    |                   |
| subjects affected / exposed                           | 0 / 285 (0.00%)        | 2 / 284 (0.70%)    | 9 / 142 (6.34%)   |
| occurrences (all)                                     | 0                      | 2                  | 10                |
| Nervous system disorders                              |                        |                    |                   |
| Headache  |                        |                    |                   |
| subjects affected / exposed                           | 27 / 285 (9.47%)       | 17 / 284 (5.99%)   | 8 / 142 (5.63%)   |
| occurrences (all)                                     | 33                     | 24                 | 12                |
| Gastrointestinal disorders                            |                        |                    |                   |
| Abdominal pain  |                        |                    |                   |
| subjects affected / exposed                           | 16 / 285 (5.61%)       | 6 / 284 (2.11%)    | 3 / 142 (2.11%)   |
| occurrences (all)                                     | 16                     | 6                  | 3                 |
| Constipation  |                        |                    |                   |
| subjects affected / exposed                           | 22 / 285 (7.72%)       | 11 / 284 (3.87%)   | 4 / 142 (2.82%)   |
| occurrences (all)                                     | 23                     | 12                 | 4                 |
| Diarrhoea   |                        |                    |                   |
| subjects affected / exposed                           | 43 / 285 (15.09%)      | 31 / 284 (10.92%)  | 11 / 142 (7.75%)  |
| occurrences (all)                                     | 59                     | 42                 | 11                |
| Dyspepsia   |                        |                    |                   |
| subjects affected / exposed                           | 16 / 285 (5.61%)       | 12 / 284 (4.23%)   | 0 / 142 (0.00%)   |
| occurrences (all)                                     | 26                     | 13                 | 0                 |
| Nausea  |                        |                    |                   |

|  |                         |                         |                         |
|--|-------------------------|-------------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)   | 55 / 285 (19.30%)<br>69 | 51 / 284 (17.96%)<br>67 | 5 / 142 (3.52%)<br>5    |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 24 / 285 (8.42%)<br>28  | 13 / 284 (4.58%)<br>24  | 3 / 142 (2.11%)<br>3    |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 11 / 285 (3.86%)<br>13  | 17 / 284 (5.99%)<br>19  | 5 / 142 (3.52%)<br>6    |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)               | 41 / 285 (14.39%)<br>60 | 37 / 284 (13.03%)<br>59 | 15 / 142 (10.56%)<br>18 |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all)     | 16 / 285 (5.61%)<br>17  | 20 / 284 (7.04%)<br>23  | 0 / 142 (0.00%)<br>0    |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 15 December 2016 | Key changes:<br>1. Introduction of additional eye examinations and additional data collection on diabetic retinopathy<br>2. Added bicarbonate as a part of the biochemistry laboratory assessment<br>3. Added text to highlight investigator's responsibility in ensuring evaluation and management of certain risk factors and complications<br>4. Clarification of the criteria for completion, withdrawal and lost to follow-up<br>5. Other minor corrections and clarifications |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported