



## Clinical trial results:

### **Efficacy and safety of semaglutide 1.0 mg once-weekly versus liraglutide 1.2 mg once-daily as add-on to 1–3 oral anti-diabetic drugs (OADs) in subjects with type 2 diabetes**

#### **Summary**

|                          |                                  |
|--------------------------|----------------------------------|
| EudraCT number           | 2016-004965-22                   |
| Trial protocol           | SI HU FR FI ES SE BG GB CZ PL IT |
| Global end of trial date | 13 August 2018                   |

#### **Results information**

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 22 August 2019 |
| First version publication date | 22 August 2019 |

#### **Trial information**

##### **Trial identification**

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | NN9535-4339 |
|-----------------------|-------------|

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

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | NCT03191396     |
| WHO universal trial number (UTN)   | U1111-1190-5868 |

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                       | 27 May 2019    |
| Is this the analysis of the primary completion data? | Yes            |
| Primary completion date                              | 09 July 2018   |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 13 August 2018 |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

To compare the effect of semaglutide s.c. 1.0 mg once-weekly versus liraglutide s.c. 1.2 mg once-daily on glycaemic control after 30 weeks of treatment in subjects with type 2 diabetes.

Protection of trial subjects:

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

Background therapy:

After screening, subjects were required to continue their oral anti-diabetic drug (OAD) pre-trial background medication (i.e. metformin, Sodium-glucose co-transporter-2 (SGLT-2) inhibitors, sulphonyl ureas, or combinations of these) throughout the entire trial.

Evidence for comparator:

Not applicable.

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 27 June 2017 |
| 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 | Bulgaria: 91        |
| Country: Number of subjects enrolled | Czech Republic: 29  |
| Country: Number of subjects enrolled | Spain: 45           |
| Country: Number of subjects enrolled | Finland: 54         |
| Country: Number of subjects enrolled | France: 31          |
| Country: Number of subjects enrolled | United Kingdom: 147 |
| Country: Number of subjects enrolled | Hungary: 48         |
| Country: Number of subjects enrolled | Italy: 35           |
| Country: Number of subjects enrolled | Poland: 30          |
| Country: Number of subjects enrolled | Slovenia: 30        |
| Country: Number of subjects enrolled | Sweden: 37          |
| Worldwide total number of subjects   | 577                 |
| EEA total number of subjects         | 577                 |

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)                      | 377 |
| From 65 to 84 years                       | 199 |
| 85 years and over                         | 1   |

## Subject disposition

### Recruitment

Recruitment details:

The trial was conducted at 77 sites in 11 countries as follows (number of sites that screened subjects/ number of sites that randomised subjects):

Bulgaria (9/ 9); Czech Republic (5/ 5); Finland (8/ 8); France (8/ 8); Hungary (8/ 8); Italy (4/ 4); Poland (3/ 3); Slovenia (4/ 4); Spain (5/ 5); Sweden (6/ 6); United Kingdom (17/ 17)

### Pre-assignment

Screening details:

After screening, subjects were required to continue their oral anti-diabetic drug (OAD) pre-trial background medication (i.e. metformin, Sodium-glucose co-transporter-2 (SGLT-2) inhibitors, sulphonyl ureas, or combinations of these) throughout the entire trial.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Not blinded                    |

### Arms

|                              |                    |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes                |
| <b>Arm title</b>             | Semaglutide 1.0 mg |

Arm description:

Subjects received 1.0 mg semaglutide once weekly for 30 weeks (including 8-week dose escalation period). Subjects also continued their OAD pre-trial background medication (i.e. metformin, SGLT-2 inhibitors, sulphonyl ureas, or combinations of these).

|                                        |                                 |
|----------------------------------------|---------------------------------|
| Arm type                               | Experimental                    |
| Investigational medicinal product name | Semaglutide B 1.34 mg/ml PDS290 |
| Investigational medicinal product code |                                 |
| Other name                             | Ozempic®                        |
| Pharmaceutical forms                   | Solution for injection          |
| Routes of administration               | Subcutaneous use                |

Dosage and administration details:

Subjects received 1.0 mg semaglutide once-weekly for 30 weeks (including 8-week dose escalation period). Semaglutide was administered subcutaneously by injections in the thigh, abdomen or upper arm once-weekly on the same weekday. Subjects started semaglutide at 0.25 mg and were dose escalated in 4-week increments until the final maintenance dose of 1.0 mg once-daily was reached (i.e. 0.25 mg from week 0 to week 4, 0.5 mg from week 4 to week 8 and 1.0 mg from week 8 to week 30).

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Liraglutide 1.2 mg |
|------------------|--------------------|

Arm description:

Subjects received 1.2 mg liraglutide once-daily for 30 weeks (including 1-week dose escalation period). Subjects also continued their OAD pre-trial background medication (i.e. metformin, SGLT-2 inhibitors, sulphonyl ureas, or combinations of these).

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

Dosage and administration details:

Subjects received 1.2 mg liraglutide once-daily for 30 weeks (including 1-week dose escalation period). Liraglutide was administered subcutaneously by injections in the thigh, abdomen or upper arm once daily and the time of injection recommended being consistent from one day to another. Subjects started liraglutide at 0.6 mg for 1

week and then were dose escalated to the maintenance dose of 1.2 mg once-daily.

| <b>Number of subjects in period 1</b> | Semaglutide 1.0 mg | Liraglutide 1.2 mg |
|---------------------------------------|--------------------|--------------------|
| Started                               | 290                | 287                |
| Completed                             | 287                | 282                |
| Not completed                         | 3                  | 5                  |
| Consent withdrawn by subject          | 3                  | 2                  |
| Lost to follow-up                     | -                  | 3                  |

## Baseline characteristics

### Reporting groups

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Semaglutide 1.0 mg |
|-----------------------|--------------------|

Reporting group description:

Subjects received 1.0 mg semaglutide once weekly for 30 weeks (including 8-week dose escalation period). Subjects also continued their OAD pre-trial background medication (i.e. metformin, SGLT-2 inhibitors, sulphonyl ureas, or combinations of these).

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Liraglutide 1.2 mg |
|-----------------------|--------------------|

Reporting group description:

Subjects received 1.2 mg liraglutide once-daily for 30 weeks (including 1-week dose escalation period). Subjects also continued their OAD pre-trial background medication (i.e. metformin, SGLT-2 inhibitors, sulphonyl ureas, or combinations of these).

| Reporting group values                    | Semaglutide 1.0 mg | Liraglutide 1.2 mg | Total |
|-------------------------------------------|--------------------|--------------------|-------|
| Number of subjects                        | 290                | 287                | 577   |
| Age categorical                           |                    |                    |       |
| Units: Subjects                           |                    |                    |       |
| Adults (18-64 years)                      | 178                | 199                | 377   |
| From 65-74 years                          | 96                 | 77                 | 173   |
| From 75-84 years                          | 15                 | 11                 | 26    |
| 85 years and over                         | 1                  | 0                  | 1     |
| Age Continuous                            |                    |                    |       |
| Units: Years                              |                    |                    |       |
| arithmetic mean                           | 60.1               | 58.9               |       |
| standard deviation                        | ± 10.5             | ± 10.0             | -     |
| Sex: Female, Male                         |                    |                    |       |
| Units: Subjects                           |                    |                    |       |
| Female                                    | 130                | 120                | 250   |
| Male                                      | 160                | 167                | 327   |
| Race (NIH/OMB)                            |                    |                    |       |
| Units: Subjects                           |                    |                    |       |
| American Indian or Alaska Native          | 0                  | 0                  | 0     |
| Asian                                     | 5                  | 3                  | 8     |
| Native Hawaiian or Other Pacific Islander | 0                  | 0                  | 0     |
| Black or African American                 | 2                  | 1                  | 3     |
| White                                     | 264                | 268                | 532   |
| Other                                     | 3                  | 0                  | 3     |
| Unknown or Not Reported                   | 16                 | 15                 | 31    |
| Ethnicity (NIH/OMB)                       |                    |                    |       |
| Units: Subjects                           |                    |                    |       |
| Hispanic or Latino                        | 6                  | 3                  | 9     |
| Not Hispanic or Latino                    | 268                | 269                | 537   |
| Unknown or Not Reported                   | 16                 | 15                 | 31    |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                            |                    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| Reporting group title                                                                                                                                                                                                                                                                      | Semaglutide 1.0 mg |
| Reporting group description:<br>Subjects received 1.0 mg semaglutide once weekly for 30 weeks (including 8-week dose escalation period). Subjects also continued their OAD pre-trial background medication (i.e. metformin, SGLT-2 inhibitors, sulphonyl ureas, or combinations of these). |                    |
| Reporting group title                                                                                                                                                                                                                                                                      | Liraglutide 1.2 mg |
| Reporting group description:<br>Subjects received 1.2 mg liraglutide once-daily for 30 weeks (including 1-week dose escalation period). Subjects also continued their OAD pre-trial background medication (i.e. metformin, SGLT-2 inhibitors, sulphonyl ureas, or combinations of these).  |                    |

### Primary: Change in HbA1c

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                 |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Change in HbA1c |
| End point description:<br>Mean change from baseline (week 0) to week 30 in glycosylated haemoglobin (HbA1c) %. The endpoint was evaluated based on the 'on-treatment without rescue medication period' where subjects were considered treated with trial product, but had not yet initiated rescue medication. Missing data were imputed using observed data from subjects within the same group defined by randomised treatment, using a regression model including stratification factor as categorical effect and data from baseline and all previous visits as covariates. |                 |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Primary         |
| End point timeframe:<br>From baseline to week 30                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                 |

| End point values                              | Semaglutide 1.0 mg | Liraglutide 1.2 mg |  |  |
|-----------------------------------------------|--------------------|--------------------|--|--|
| Subject group type                            | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed                   | 290                | 287                |  |  |
| Units: Percentage of glycosylated haemoglobin |                    |                    |  |  |
| arithmetic mean (standard deviation)          | -1.7 (± 0.9)       | -1.1 (± 1.0)       |  |  |

### Statistical analyses

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                         |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|
| Statistical analysis title                                                                                                                                                                                                                                                                                                                                                                                                                                           | Analysis 1                              |
| Statistical analysis description:<br>The responses are analysed using an ANCOVA with treatment and stratification factor as fixed factors and baseline value as covariate. Before analysis, missing data were multiple imputed using observed data from subjects within the same group defined by randomised treatment, using a regression model including stratification factor as categorical effect and data from baseline and all previous visits as covariates. |                                         |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Liraglutide 1.2 mg v Semaglutide 1.0 mg |

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 577                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority <sup>[1]</sup> |
| P-value                                 | < 0.0001 <sup>[2]</sup>        |
| Method                                  | ANCOVA                         |
| Parameter estimate                      | Treatment difference           |
| Point estimate                          | -0.69                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.82                          |
| upper limit                             | -0.56                          |

Notes:

[1] - HbA1c non-inferiority was tested using a non-inferiority margin of 0.3.

[2] - The non-inferiority p-value is calculated as two times the one-sided p-value from a t-distributed test statistic comparing the treatment contrast with 0.3.

|                                         |                                         |
|-----------------------------------------|-----------------------------------------|
| <b>Statistical analysis title</b>       | Analysis 2                              |
| Comparison groups                       | Semaglutide 1.0 mg v Liraglutide 1.2 mg |
| Number of subjects included in analysis | 577                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | < 0.0001                                |
| Method                                  | ANCOVA                                  |
| Parameter estimate                      | Treatment difference                    |
| Point estimate                          | -0.69                                   |
| Confidence interval                     |                                         |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | -0.82                                   |
| upper limit                             | -0.56                                   |

## Secondary: Change in body weight (kg)

|                 |                            |
|-----------------|----------------------------|
| End point title | Change in body weight (kg) |
|-----------------|----------------------------|

End point description:

Mean change from baseline (week 0) to week 30 in body weight measured in kilograms. Results are based on the 'on-treatment without rescue medication' observation period where subjects were considered treated with trial product, but had not yet initiated rescue medication. Missing data were imputed using observed data from subjects within the same group defined by randomised treatment, using a regression model including stratification factor as categorical effect and data from baseline and all previous visits as covariates.

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

End point timeframe:

From baseline to week 30

| End point values                     | Semaglutide 1.0 mg | Liraglutide 1.2 mg |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 290                | 287                |  |  |
| Units: kg                            |                    |                    |  |  |
| arithmetic mean (standard deviation) | -5.8 (± 4.7)       | -2.0 (± 4.1)       |  |  |

## Statistical analyses

| Statistical analysis title              | Analysis 1                              |
|-----------------------------------------|-----------------------------------------|
| Comparison groups                       | Semaglutide 1.0 mg v Liraglutide 1.2 mg |
| Number of subjects included in analysis | 577                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | < 0.0001                                |
| Method                                  | ANCOVA                                  |
| Parameter estimate                      | Treatment difference                    |
| Point estimate                          | -3.83                                   |
| Confidence interval                     |                                         |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | -4.57                                   |
| upper limit                             | -3.09                                   |

## Secondary: Change in fasting plasma glucose (FPG)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Change in fasting plasma glucose (FPG) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                        |
| Mean change from baseline in fasting plasma glucose measured in mmol/L. Results are based on the 'on-treatment without rescue medication' observation period where subjects were considered treated with trial product, but had not yet initiated rescue medication. Missing data were imputed using observed data from subjects within the same group defined by randomised treatment, using a regression model including stratification factor as categorical effect and data from baseline and all previous visits as covariates. |                                        |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Secondary                              |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                        |
| From baseline to week 30                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                        |

| End point values                     | Semaglutide 1.0 mg | Liraglutide 1.2 mg |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 286                | 285                |  |  |
| Units: mmol/L                        |                    |                    |  |  |
| arithmetic mean (standard deviation) | -2.65 (± 2.19)     | -1.46 (± 2.42)     |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in systolic blood pressure

|                 |                                   |
|-----------------|-----------------------------------|
| End point title | Change in systolic blood pressure |
|-----------------|-----------------------------------|

End point description:

Change in systolic blood pressure from baseline (week 0) to week 30 . Results are based on the 'on-treatment without rescue medication' period where subjects were considered treated with trial product, but had not yet initiated rescue medication. Missing data were imputed using observed data from subjects within the same group defined by randomised treatment, using a regression model including stratification factor as categorical effect and data from baseline and all previous visits as covariates.

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

End point timeframe:

From baseline to week 30

| End point values                     | Semaglutide 1.0 mg | Liraglutide 1.2 mg |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 290                | 287                |  |  |
| Units: mmHg                          |                    |                    |  |  |
| arithmetic mean (standard deviation) | -4.3 (± 13.4)      | -3.7 (± 13.8)      |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in diastolic blood pressure

|                 |                                    |
|-----------------|------------------------------------|
| End point title | Change in diastolic blood pressure |
|-----------------|------------------------------------|

End point description:

Change in diastolic blood pressure from baseline (week 0) to week 30 . Results are based on the 'on-treatment without rescue medication' period where subjects were considered treated with trial product, but had not yet initiated rescue medication. Missing data were imputed using observed data from subjects within the same group defined by randomised treatment, using a regression model including stratification factor as categorical effect and data from baseline and all previous visits as covariates.

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

End point timeframe:

From baseline to week 30

|                                      |                       |                       |  |  |
|--------------------------------------|-----------------------|-----------------------|--|--|
| <b>End point values</b>              | Semaglutide<br>1.0 mg | Liraglutide 1.2<br>mg |  |  |
| Subject group type                   | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed          | 290                   | 287                   |  |  |
| Units: mmHg                          |                       |                       |  |  |
| arithmetic mean (standard deviation) | -1.5 (± 8.6)          | -1.3 (± 8.4)          |  |  |

### Statistical analyses

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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 30) + post treatment follow-up of 42 days.

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 | 21     |

### Reporting groups

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Semaglutide 1.0 mg |
|-----------------------|--------------------|

Reporting group description:

Subjects received 1.0 mg semaglutide once weekly for 30 weeks (including 8-week dose escalation period). Subjects also continued their OAD pre-trial background medication (i.e. metformin, SGLT-2 inhibitors, sulphonyl ureas, or combinations of these).

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Liraglutide 1.2 mg |
|-----------------------|--------------------|

Reporting group description:

Subjects received 1.2 mg liraglutide once-daily for 30 weeks (including 1-week dose escalation period). Subjects also continued their OAD pre-trial background medication (i.e. metformin, SGLT-2 inhibitors, sulphonyl ureas, or combinations of these).

| Serious adverse events                                              | Semaglutide 1.0 mg | Liraglutide 1.2 mg |  |
|---------------------------------------------------------------------|--------------------|--------------------|--|
| Total subjects affected by serious adverse events                   |                    |                    |  |
| subjects affected / exposed                                         | 17 / 289 (5.88%)   | 22 / 287 (7.67%)   |  |
| number of deaths (all causes)                                       | 0                  | 0                  |  |
| number of deaths resulting from adverse events                      | 0                  | 0                  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                    |  |
| Benign neoplasm of bladder                                          |                    |                    |  |
| subjects affected / exposed                                         | 1 / 289 (0.35%)    | 0 / 287 (0.00%)    |  |
| occurrences causally related to treatment / all                     | 0 / 1              | 0 / 0              |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0              |  |
| Leiomyoma                                                           |                    |                    |  |
| subjects affected / exposed                                         | 1 / 289 (0.35%)    | 0 / 287 (0.00%)    |  |
| occurrences causally related to treatment / all                     | 0 / 1              | 0 / 0              |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0              |  |
| Medullary thyroid cancer                                            |                    |                    |  |

|                                                      |                 |                 |  |
|------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 289 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Prostatic adenoma                                    |                 |                 |  |
| subjects affected / exposed                          | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Rectal neoplasm                                      |                 |                 |  |
| subjects affected / exposed                          | 1 / 289 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Facial pain                                          |                 |                 |  |
| subjects affected / exposed                          | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Reproductive system and breast disorders             |                 |                 |  |
| Menopausal symptoms                                  |                 |                 |  |
| subjects affected / exposed                          | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Prostatitis                                          |                 |                 |  |
| subjects affected / exposed                          | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                                |                 |                 |  |
| Confusional state                                    |                 |                 |  |
| subjects affected / exposed                          | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Depression                                           |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Cardiovascular examination                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 289 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Bradycardia                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure congestive                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 289 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery disease                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Cognitive disorder                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 289 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lethargy                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye disorders                                   |                 |                 |  |
| Retinal vein occlusion                          |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 289 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Abdominal pain upper                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 289 (0.35%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colitis                                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal ulcer haemorrhage                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 289 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Inguinal hernia                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 289 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nausea                                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 289 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis acute                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Umbilical hernia                                |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 289 (0.35%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Cholecystitis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis acute                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholelithiasis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic steatosis                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Skin ulcer                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Calculus urinary                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematuria                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 289 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nephrolithiasis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 289 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Intervertebral disc disorder                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intervertebral disc protrusion                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteoarthritis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 289 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Periarthritis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Device related infection                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Localised infection                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyelonephritis                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 289 (0.69%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rectal abscess                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 289 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis                                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 289 (0.35%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 289 (0.00%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 289 (0.35%) | 1 / 287 (0.35%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetes mellitus inadequate control            |                 |                 |  |
| subjects affected / exposed                     | 1 / 289 (0.35%) | 0 / 287 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Semaglutide 1.0 mg | Liraglutide 1.2 mg |  |
|-------------------------------------------------------|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                    |                    |  |
| subjects affected / exposed                           | 139 / 289 (48.10%) | 113 / 287 (39.37%) |  |
| Nervous system disorders                              |                    |                    |  |
| Headache                                              |                    |                    |  |
| subjects affected / exposed                           | 27 / 289 (9.34%)   | 19 / 287 (6.62%)   |  |
| occurrences (all)                                     | 37                 | 32                 |  |
| Gastrointestinal disorders                            |                    |                    |  |
| Abdominal pain                                        |                    |                    |  |
| subjects affected / exposed                           | 15 / 289 (5.19%)   | 6 / 287 (2.09%)    |  |
| occurrences (all)                                     | 18                 | 6                  |  |
| Constipation                                          |                    |                    |  |
| subjects affected / exposed                           | 17 / 289 (5.88%)   | 10 / 287 (3.48%)   |  |
| occurrences (all)                                     | 17                 | 13                 |  |
| Diarrhoea                                             |                    |                    |  |
| subjects affected / exposed                           | 45 / 289 (15.57%)  | 35 / 287 (12.20%)  |  |
| occurrences (all)                                     | 56                 | 43                 |  |
| Nausea                                                |                    |                    |  |
| subjects affected / exposed                           | 62 / 289 (21.45%)  | 45 / 287 (15.68%)  |  |
| occurrences (all)                                     | 88                 | 54                 |  |
| Vomiting                                              |                    |                    |  |
| subjects affected / exposed                           | 29 / 289 (10.03%)  | 23 / 287 (8.01%)   |  |
| occurrences (all)                                     | 43                 | 32                 |  |
| Infections and infestations                           |                    |                    |  |
| Influenza                                             |                    |                    |  |
| subjects affected / exposed                           | 9 / 289 (3.11%)    | 15 / 287 (5.23%)   |  |
| occurrences (all)                                     | 12                 | 16                 |  |
| Nasopharyngitis                                       |                    |                    |  |
| subjects affected / exposed                           | 27 / 289 (9.34%)   | 30 / 287 (10.45%)  |  |
| occurrences (all)                                     | 30                 | 32                 |  |
| Metabolism and nutrition disorders                    |                    |                    |  |
| Decreased appetite                                    |                    |                    |  |
| subjects affected / exposed                           | 30 / 289 (10.38%)  | 17 / 287 (5.92%)   |  |
| occurrences (all)                                     | 31                 | 18                 |  |



## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported