



## Clinical trial results:

**A 52 week study comparing the efficacy and safety of once weekly IcoSema and once weekly semaglutide, both treatment arms with or without oral anti diabetic drugs, in participants with type 2 diabetes inadequately controlled with a GLP 1 receptor agonist. COMBINE 2 Summary**

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2020-005308-21  |
| Trial protocol           | SK GR SE HU     |
| Global end of trial date | 16 January 2024 |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 01 February 2025 |
| First version publication date | 01 February 2025 |

### Trial information

#### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | NN1535-4592 |
|-----------------------|-------------|

#### Additional study identifiers

|                                    |                                                                                            |
|------------------------------------|--------------------------------------------------------------------------------------------|
| ISRCTN number                      | -                                                                                          |
| ClinicalTrials.gov id (NCT number) | NCT05259033                                                                                |
| WHO universal trial number (UTN)   | U1111-1260-8268                                                                            |
| Other trial identifiers            | jRCT2051220044: Japanese trial registration number, CTR20220767: China Drug Trials (China) |

Notes:

### Sponsors

|                              |                                                                                    |
|------------------------------|------------------------------------------------------------------------------------|
| Sponsor organisation name    | Novo Nordisk A/S                                                                   |
| Sponsor organisation address | Novo Allé, Bagsvaerd, Denmark, 2880                                                |
| Public contact               | Clinical Reporting Office (2834), Novo Nordisk A/S, clinicaltrials@novonordisk.com |
| Scientific contact           | Clinical Reporting Office (2834), 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                       | 01 March 2024   |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 16 January 2024 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To confirm superiority of once weekly IcoSema compared with once weekly semaglutide, both treatment arms with or without OADs, in terms of glycaemic control measured by change in HbA1c from baseline after 52 weeks in participants with T2D inadequately controlled with a GLP 1 receptor agonist.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki (64th World Medical Association [WMA] General Assembly, Fortaleza, Brazil. Oct 2013) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice, including archiving of essential documents.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 11 April 2022 |
| 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 | Brazil: 63         |
| Country: Number of subjects enrolled | Canada: 35         |
| Country: Number of subjects enrolled | Switzerland: 13    |
| Country: Number of subjects enrolled | China: 50          |
| Country: Number of subjects enrolled | France: 35         |
| Country: Number of subjects enrolled | Greece: 72         |
| Country: Number of subjects enrolled | Hungary: 34        |
| Country: Number of subjects enrolled | Israel: 35         |
| Country: Number of subjects enrolled | Japan: 100         |
| Country: Number of subjects enrolled | Slovakia: 46       |
| Country: Number of subjects enrolled | Sweden: 9          |
| Country: Number of subjects enrolled | Taiwan: 20         |
| Country: Number of subjects enrolled | United States: 171 |
| Worldwide total number of subjects   | 683                |
| EEA total number of subjects         | 196                |

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)                      | 455 |
| From 65 to 84 years                       | 228 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Trial was conducted at 124 sites in 13 countries as follows (number of sites that screened subjects/number of sites that randomised subjects): Brazil (6/6); Canada (10/9); China Mainland (11/11); France (5/5); Greece (8/8); Hungary (4/4); Israel (6/6); Japan (9/9); Slovakia (6/6); Sweden (3/3); Switzerland (3/3); Taiwan (5/5); United States (48/46).

### Pre-assignment

Screening details:

Subjects were randomised in 1:1 ratio to receive subcutaneous (s.c.) injection of either IcoSema or semaglutide once weekly. The trial had a 52-week treatment period followed by a 5-week follow-up period.

### 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>             | IcoSema |

Arm description:

Subjects received once weekly 700 units per millilitre (U/mL) of insulin icodec and 2 milligram per millilitre (mg/mL) of semaglutide subcutaneously for 52 weeks. Participants were to perform once daily pre-breakfast self-monitoring plasma glucose (SMPG). The dose was adjusted based on 3 pre-breakfast SMPG values measured on the 2 previous days and the day of the contact. If at least one pre-breakfast SMPG value was: < 4.4 mmol/L: dose re-duced by 10 U; 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: dose increased by 10 U. Dose titration of IcoSema was based on the respective premeal(s) and bedtime self-measured plasma glucose (SMPG) measured weekly.

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

Dosage and administration details:

Subjects received icodec once weekly subcutaneously.

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

Arm description:

Subjects received once weekly semaglutide subcutaneously in a dose escalation manner, with dose increases every 4 weeks for up to week 8 (0.25 milligrams [mg], 0.5 mg) followed by 1.0 mg once weekly up to the end of treatment period.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | Semaglutide            |
| Investigational medicinal product code |                        |
| Other name                             | Ozempic                |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

Subjects received semaglutide once weekly subcutaneously.

| <b>Number of subjects in period 1</b> | IcoSema | Semaglutide |
|---------------------------------------|---------|-------------|
| Started                               | 342     | 341         |
| Full analysis set (FAS)               | 342     | 341         |
| Safety analysis set (SAS)             | 341     | 340         |
| Exposed                               | 341     | 340         |
| Completed                             | 329     | 336         |
| Not completed                         | 13      | 5           |
| Consent withdrawn by subject          | 10      | 5           |
| Death                                 | 2       | -           |
| Lost to follow-up                     | 1       | -           |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |             |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | IcoSema     |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |             |
| Subjects received once weekly 700 units per millilitre (U/mL) of insulin icodec and 2 milligram per millilitre (mg/mL) of semaglutide subcutaneously for 52 weeks. Participants were to perform once daily pre-breakfast self-monitoring plasma glucose (SMPG). The dose was adjusted based on 3 pre-breakfast SMPG values measured on the 2 previous days and the day of the contact. If at least one pre-breakfast SMPG value was: < 4.4 mmol/L: dose re-duced by 10 U; 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: dose increased by 10 U. Dose titration of IcoSema was based on the respective premeal(s) and bedtime self-measured plasma glucose (SMPG) measured weekly. |             |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Semaglutide |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |             |
| Subjects received once weekly semaglutide subcutaneously in a dose escalation manner, with dose increases every 4 weeks for up to week 8 (0.25 milligrams [mg], 0.5 mg) followed by 1.0 mg once weekly up to the end of treatment period.                                                                                                                                                                                                                                                                                                                                                                                                                                        |             |

| Reporting group values                             | IcoSema | Semaglutide | Total |
|----------------------------------------------------|---------|-------------|-------|
| Number of subjects                                 | 342     | 341         | 683   |
| Age categorical                                    |         |             |       |
| Units: Subjects                                    |         |             |       |
| In utero                                           | 0       | 0           | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0       | 0           | 0     |
| Newborns (0-27 days)                               | 0       | 0           | 0     |
| Infants and toddlers (28 days-23 months)           | 0       | 0           | 0     |
| Children (2-11 years)                              | 0       | 0           | 0     |
| Adolescents (12-17 years)                          | 0       | 0           | 0     |
| Adults (18-64 years)                               | 213     | 242         | 455   |
| From 65-84 years                                   | 129     | 99          | 228   |
| 85 years and over                                  | 0       | 0           | 0     |
| Age Continuous                                     |         |             |       |
| Units: Years                                       |         |             |       |
| arithmetic mean                                    | 59.9    | 58.3        |       |
| standard deviation                                 | ± 10.5  | ± 9.8       | -     |
| Sex: Female, Male                                  |         |             |       |
| Units: Participants                                |         |             |       |
| Female                                             | 141     | 145         | 286   |
| Male                                               | 201     | 196         | 397   |

## End points

### End points reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | IcoSema |
|-----------------------|---------|

Reporting group description:

Subjects received once weekly 700 units per millilitre (U/mL) of insulin icodec and 2 milligram per millilitre (mg/mL) of semaglutide subcutaneously for 52 weeks. Participants were to perform once daily pre-breakfast self-monitoring plasma glucose (SMPG). The dose was adjusted based on 3 pre-breakfast SMPG values measured on the 2 previous days and the day of the contact. If at least one pre-breakfast SMPG value was: < 4.4 mmol/L: dose reduced by 10 U; 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: dose increased by 10 U. Dose titration of IcoSema was based on the respective premeal(s) and bedtime self-measured plasma glucose (SMPG) measured weekly.

|                       |             |
|-----------------------|-------------|
| Reporting group title | Semaglutide |
|-----------------------|-------------|

Reporting group description:

Subjects received once weekly semaglutide subcutaneously in a dose escalation manner, with dose increases every 4 weeks for up to week 8 (0.25 milligrams [mg], 0.5 mg) followed by 1.0 mg once weekly up to the end of treatment period.

### Primary: Change in glycosylated haemoglobin (HbA1c)

|                 |                                            |
|-----------------|--------------------------------------------|
| End point title | Change in glycosylated haemoglobin (HbA1c) |
|-----------------|--------------------------------------------|

End point description:

Change from baseline (week 0) to week 52 in HbA1c is presented. The outcome measure was evaluated based on the data from in study period, where all data from randomisation until last date of any of the following: 1) last direct subjects-site contact; 2) subjects who withdrew their informed consent; 3) last subjects-investigator contact as defined by the investigator for subjects who lost to follow-up (i.e. possibly an unscheduled phone visit); 4) death of subjects who died before any of the above. Full Analysis Set (FAS) which comprised all randomised subjects. Number of subjects analyzed = subjects with available data for this outcome measure.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From baseline week 0 (V2) to week 52 (V54)

| End point values                     | IcoSema         | Semaglutide     |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 325             | 335             |  |  |
| Units: Percentage point of HbA1c     |                 |                 |  |  |
| arithmetic mean (standard deviation) | -1.40 (± 0.91)  | -0.86 (± 0.96)  |  |  |

### Statistical analyses

|                            |                       |
|----------------------------|-----------------------|
| Statistical analysis title | IcoSema - Semaglutide |
|----------------------------|-----------------------|

Statistical analysis description:

Hypothetical estimand

|                   |                       |
|-------------------|-----------------------|
| Comparison groups | IcoSema v Semaglutide |
|-------------------|-----------------------|

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 660                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           |                                |
| P-value                                 | < 0.0001                       |
| Method                                  | ANCOVA                         |
| Parameter estimate                      | Estimated treatment difference |
| Point estimate                          | -0.44                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.56                          |
| upper limit                             | -0.33                          |

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

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Change in fasting plasma glucose (FPG) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                        |
| Change from baseline (week 0) to week 52 in FPG is presented. The outcome measure was evaluated based on the data from in study period, where all data from randomisation until last date of any of the following: 1) last direct subjects-site contact; 2) subjects who withdrew their informed consent; 3) last subjects-investigator contact as defined by the investigator for subjects who lost to follow-up (i.e. possibly an unscheduled phone visit); 4) death of subjects who died before any of the above. FAS which comprised all randomised subjects. Number of subjects analyzed = subjects with available data for this outcome measure. |                                        |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Secondary                              |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                        |
| From baseline week 0 (V2) to week 52 (V54)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                        |

| End point values                     | IcoSema         | Semaglutide     |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 313             | 317             |  |  |
| Units: Millimoles per litre (mmol/L) |                 |                 |  |  |
| arithmetic mean (standard deviation) | -2.74 (± 2.85)  | -1.41 (± 2.89)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of severe hypoglycaemic episodes (level 3)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                   |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Number of severe hypoglycaemic episodes (level 3) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                   |
| Hypoglycaemic episodes were classified according to the American Diabetes Association/ International Hypoglycaemia Study Group, where glycemic criteria for level 3 had no specific glucose threshold. The outcome measure was evaluated based on data from on treatment period, where all data from date of first dose of randomised treatment as recorded on the electronic case report form (eCRF) until the first date of any of the following: 1) last follow-up visit (V56); 2) last date on randomised treatment +6 weeks (corresponding to 5 weeks after the end of the dosing interval for both treatment arms); 3) end-date for the in-study data points sets. SAS included all subjects exposed to randomised treatment. |                                                   |

|                                            |           |
|--------------------------------------------|-----------|
| End point type                             | Secondary |
| End point timeframe:                       |           |
| From baseline week 0 (V2) to week 57 (V56) |           |

| End point values            | IcoSema         | Semaglutide     |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 341             | 340             |  |  |
| Units: Episodes             |                 |                 |  |  |
| number (not applicable)     | 0               | 0               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in body weight

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                       |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Change in body weight |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                       |
| Change from baseline (week 0) to week 52 in body weight is presented. The outcome measure was evaluated based on the data from in study period, where all data from randomisation until last date of any of the following: 1) last direct subjects-site contact; 2) subjects who withdrew their informed consent; 3) last subjects-investigator contact as defined by the investigator for subjects who lost to follow-up (i.e. possibly an unscheduled phone visit); 4) death of subjects who died before any of the above. FAS which comprised all randomised subjects. Number of subjects analyzed = subjects with available data for this outcome measure. |                       |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Secondary             |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                       |
| From baseline week 0 (V2) to week 52 (V54)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                       |

| End point values                     | IcoSema         | Semaglutide     |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 325             | 336             |  |  |
| Units: Kilogram (kg)                 |                 |                 |  |  |
| arithmetic mean (standard deviation) | 0.89 (± 4.36)   | -3.77 (± 4.60)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L [54 mg/dL], confirmed by blood glucose [BG] meter) or severe hypoglycaemic episodes (level 3)

|                 |                                                                                                                            |
|-----------------|----------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L [54 mg/dL], confirmed by blood glucose [BG] |
|-----------------|----------------------------------------------------------------------------------------------------------------------------|

meter) or severe hypoglycaemic episodes (level 3)

End point description:

Hypoglycaemic episodes were classified according to the American Diabetes Association/ International Hypoglycaemia Study Group, where glycemic criteria for level 2 was less than (<) 3.0 mmol/L (54 milligram per decilitre [mg/dL]) and level 3 had no specific glucose threshold. The outcome measure was evaluated based on data from on treatment period, where all data from date of first dose of randomised treatment as recorded on the electronic case report form (eCRF) until the first date of any of the following: 1)last follow-up visit (V56); 2) last date on randomised treatment +6 weeks (corresponding to 5 weeks after the end of the dosing interval for both treatment arms); 3) end-date for the in-study data points sets. Safety Analysis Set (SAS) included all subjects exposed to randomised treatment.

End point type Secondary

End point timeframe:

From baseline week 0 (V2) to week 57 (V56)

| End point values            | IcoSema         | Semaglutide     |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 341             | 340             |  |  |
| Units: Episodes             |                 |                 |  |  |
| number (not applicable)     | 15              | 13              |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter)

End point title Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter)

End point description:

Hypoglycaemic episodes were classified according to the American Diabetes Association/ International Hypoglycaemia Study Group, where glycemic criteria for level 2 was < 3.0 mmol/L (54 mg/dL). The outcome measure was evaluated based on data from on treatment period, where all data from date of first dose of randomised treatment as recorded on the electronic case report form (eCRF) until the first date of any of the following: 1)last follow-up visit (V56); 2) last date on randomised treatment +6 weeks (corresponding to 5 weeks after the end of the dosing interval for both treatment arms); 3) end-date for the in-study data points sets. SAS included all subjects exposed to randomised treatment.

End point type Secondary

End point timeframe:

From baseline week 0 (V2) to week 57 (V56)

| End point values            | IcoSema         | Semaglutide     |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 341             | 340             |  |  |
| Units: Episodes             |                 |                 |  |  |
| number (not applicable)     | 15              | 13              |  |  |

## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Week 0 to week 57.

Adverse event reporting additional description:

Presented AEs are TEAEs, defined as event with onset during on treatment period. Results are based on SAS including all subjects exposed to randomised treatment.

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 22 |
|--------------------|----|

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Semaglutide |
|-----------------------|-------------|

Reporting group description:

Subjects received once weekly semaglutide subcutaneously in a dose escalation manner, with dose increases every 4 weeks for up to week 8 (0.25 milligrams [mg], 0.5 mg) followed by 1.0 mg once weekly up to the end of treatment period.

|                       |         |
|-----------------------|---------|
| Reporting group title | IcoSema |
|-----------------------|---------|

Reporting group description:

Subjects received once weekly 700 units per millilitre (U/mL) of insulin icodec and 2 milligram per millilitre (mg/mL) of semaglutide subcutaneously for 52 weeks. Participants were to perform once daily pre-breakfast self-monitoring plasma glucose (SMPG). The dose was adjusted based on 3 pre-breakfast SMPG values measured on the 2 previous days and the day of the contact. If at least one pre-breakfast SMPG value was: < 4.4 mmol/L: dose re-duced by 10 U; 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: dose increased by 10 U. Dose titration of IcoSema was based on the respective premeal(s) and bedtime self-measured plasma glucose (SMPG) measured weekly.

| Serious adverse events                                              | Semaglutide      | IcoSema           |  |
|---------------------------------------------------------------------|------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                  |                   |  |
| subjects affected / exposed                                         | 21 / 340 (6.18%) | 38 / 341 (11.14%) |  |
| number of deaths (all causes)                                       | 0                | 2                 |  |
| number of deaths resulting from adverse events                      | 0                | 0                 |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                   |  |
| Acoustic neuroma                                                    |                  |                   |  |
| subjects affected / exposed                                         | 1 / 340 (0.29%)  | 0 / 341 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0             |  |
| Adenocarcinoma of colon                                             |                  |                   |  |
| subjects affected / exposed                                         | 0 / 340 (0.00%)  | 1 / 341 (0.29%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0             |  |
| Colorectal adenoma                                                  |                  |                   |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 340 (0.29%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Squamous cell carcinoma of the tongue           |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Squamous cell carcinoma of head and neck        |                 |                 |  |
| subjects affected / exposed                     | 1 / 340 (0.29%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ovarian adenoma                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |
| Deep vein thrombosis                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypertension                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypovolaemic shock                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 340 (0.29%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral arterial occlusive disease           |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Surgical and medical procedures                 |                 |                 |  |

|                                                      |                 |                 |  |
|------------------------------------------------------|-----------------|-----------------|--|
| Cardioversion                                        |                 |                 |  |
| subjects affected / exposed                          | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Chest pain                                           |                 |                 |  |
| subjects affected / exposed                          | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Sudden death                                         |                 |                 |  |
| subjects affected / exposed                          | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 1           |  |
| Reproductive system and breast disorders             |                 |                 |  |
| Prostatitis                                          |                 |                 |  |
| subjects affected / exposed                          | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders      |                 |                 |  |
| Dyspnoea                                             |                 |                 |  |
| subjects affected / exposed                          | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                                   |                 |                 |  |
| subjects affected / exposed                          | 1 / 340 (0.29%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                                |                 |                 |  |
| Depression                                           |                 |                 |  |
| subjects affected / exposed                          | 1 / 340 (0.29%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications       |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Femoral neck fracture                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 340 (0.29%) | 3 / 341 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Femur fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Meniscus injury                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tibia fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 340 (0.29%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Patella fracture                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal column injury                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 340 (0.29%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ulna fracture                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Angina unstable                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina pectoris                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 340 (0.29%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute myocardial infarction                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery disease                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 340 (0.29%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery stenosis                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 340 (0.29%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure chronic                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arteriosclerosis coronary artery                |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Left ventricular failure                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 340 (0.29%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial infarction                           |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ventricular extrasystoles                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ventricular tachycardia                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 340 (0.29%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cerebral infarction                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ischaemic stroke                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Migraine without aura                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| VIth nerve paralysis                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 340 (0.29%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye disorders                                   |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Cataract                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 340 (0.29%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Optic ischaemic neuropathy                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 340 (0.29%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Colon dysplasia                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 340 (0.29%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 340 (0.29%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Food poisoning                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal haemorrhage                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 340 (0.29%) | 0 / 341 (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 / 340 (0.29%) | 0 / 341 (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 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| 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 / 340 (0.29%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Cholecystitis acute                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 340 (0.29%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 340 (0.29%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hydronephrosis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Intervertebral disc protrusion                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lumbar spinal stenosis                          |                 |                 |  |
| subjects affected / exposed                     | 2 / 340 (0.59%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteoarthritis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 340 (0.29%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Abdominal sepsis                                |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Appendicitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Erysipelas                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 340 (0.29%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Otitis media                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Otitis media chronic                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 340 (0.29%) | 2 / 341 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Decreased appetite                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 340 (0.29%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetic ketoacidosis                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 340 (0.00%) | 1 / 341 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ketoacidosis                                    |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 340 (0.29%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lactic acidosis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 340 (0.29%) | 0 / 341 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Type 2 diabetes mellitus                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 340 (0.29%) | 0 / 341 (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        | IcoSema            |  |
|-------------------------------------------------------|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                    |                    |  |
| subjects affected / exposed                           | 159 / 340 (46.76%) | 163 / 341 (47.80%) |  |
| Nervous system disorders                              |                    |                    |  |
| Headache                                              |                    |                    |  |
| subjects affected / exposed                           | 6 / 340 (1.76%)    | 20 / 341 (5.87%)   |  |
| occurrences (all)                                     | 6                  | 25                 |  |
| Eye disorders                                         |                    |                    |  |
| Diabetic retinopathy                                  |                    |                    |  |
| subjects affected / exposed                           | 10 / 340 (2.94%)   | 19 / 341 (5.57%)   |  |
| occurrences (all)                                     | 10                 | 20                 |  |
| Gastrointestinal disorders                            |                    |                    |  |
| Constipation                                          |                    |                    |  |
| subjects affected / exposed                           | 17 / 340 (5.00%)   | 11 / 341 (3.23%)   |  |
| occurrences (all)                                     | 22                 | 14                 |  |
| Diarrhoea                                             |                    |                    |  |
| subjects affected / exposed                           | 41 / 340 (12.06%)  | 38 / 341 (11.14%)  |  |
| occurrences (all)                                     | 82                 | 53                 |  |
| Vomiting                                              |                    |                    |  |
| subjects affected / exposed                           | 22 / 340 (6.47%)   | 17 / 341 (4.99%)   |  |
| occurrences (all)                                     | 48                 | 24                 |  |
| Nausea                                                |                    |                    |  |

|                                                  |                         |                         |  |
|--------------------------------------------------|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all) | 39 / 340 (11.47%)<br>73 | 40 / 341 (11.73%)<br>65 |  |
| Infections and infestations                      |                         |                         |  |
| COVID-19                                         |                         |                         |  |
| subjects affected / exposed                      | 49 / 340 (14.41%)       | 51 / 341 (14.96%)       |  |
| occurrences (all)                                | 53                      | 52                      |  |
| Nasopharyngitis                                  |                         |                         |  |
| subjects affected / exposed                      | 33 / 340 (9.71%)        | 33 / 341 (9.68%)        |  |
| occurrences (all)                                | 45                      | 45                      |  |
| Upper respiratory tract infection                |                         |                         |  |
| subjects affected / exposed                      | 29 / 340 (8.53%)        | 22 / 341 (6.45%)        |  |
| occurrences (all)                                | 34                      | 34                      |  |

## 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