



## Clinical trial results:

**A clinical trial comparing glycaemic control and safety of insulin degludec/liraglutide (IDegLira) versus insulin glargine (IGlar) as add-on therapy to SGLT2i in subjects with type 2 diabetes mellitus.**

### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2015-001596-48  |
| Trial protocol           | SI FI HU ES SK  |
| Global end of trial date | 23 October 2017 |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 08 November 2018 |
| First version publication date | 08 November 2018 |

### Trial information

#### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | nn9068-4229 |
|-----------------------|-------------|

#### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | NCT02773368     |
| WHO universal trial number (UTN)   | U1111-1168-9343 |

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                       | 29 March 2018     |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 26 September 2017 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 23 October 2017   |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

To confirm the effect of insulin degludec/liraglutide (IDegLira) in terms of glycaemic control in subjects with type 2 diabetes mellitus (T2DM) on previous treatment with sodium-glucose co-transporter 2 inhibitors (SGLT2i) ± oral anti-diabetic drug (OAD) therapy. This is done by comparing the difference in change from baseline in HbA1c after 26 weeks to a non-inferiority margin of 0.3% for IDegLira versus insulin glargine (IGlar), both in combination with SGLT2i ± OAD.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (64th WMA Assembly, October 2013) and ICH Good Clinical Practice, including archiving of essential documents (June 1996) and 21 CFR 312.120.

Background therapy:

Subjects on pre-trial OAD treatment with stable daily dose of SGLT2i either as monotherapy or in combination with metformin ± dipeptidyl peptidase-4 inhibitors (DPP4i) ± pioglitazone according to locally approved label for at least 90 days prior to screening. Subjects on DPP4i before the trial had to be discontinued at randomisation.

Evidence for comparator:

Not applicable

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 23 May 2016 |
| Long term follow-up planned                               | No          |
| Independent data monitoring committee (IDMC) involvement? | No          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 45          |
| Country: Number of subjects enrolled | Canada: 30             |
| Country: Number of subjects enrolled | Finland: 25            |
| Country: Number of subjects enrolled | Hungary: 37            |
| Country: Number of subjects enrolled | India: 58              |
| Country: Number of subjects enrolled | Russian Federation: 49 |
| Country: Number of subjects enrolled | Slovakia: 38           |
| Country: Number of subjects enrolled | Slovenia: 24           |
| Country: Number of subjects enrolled | Spain: 47              |
| Country: Number of subjects enrolled | Switzerland: 8         |
| Country: Number of subjects enrolled | United States: 59      |
| Worldwide total number of subjects   | 420                    |
| EEA total number of subjects         | 171                    |

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)                      | 322 |
| From 65 to 84 years                       | 98  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

The trial was conducted at 74 sites in 11 countries as follows: Argentina (3), Canada (5), Finland (6), Hungary (5), India (8), Russian Federation (7), Slovakia (5), Slovenia (4), Spain (6), Switzerland (5) and United States (20).

### Pre-assignment

Screening details:

Eligible subjects with type 2 diabetes mellitus on OAD therapy with stable daily dose of SGLT2i either as monotherapy or in combination with metformin  $\pm$  DPP4i  $\pm$  pioglitazone as per locally approved label for at least 90 days prior to screening. Subjects on DPP4i before the trial had to discontinue at randomisation.

### Period 1

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

Blinding implementation details:

Not applicable

### Arms

|                              |          |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes      |
| <b>Arm title</b>             | IDegLira |

Arm description:

Subjects were administered with insulin degludec/liraglutide (IDegLira: 100 U/3.6 mg per mL) once daily for a duration of 26 weeks. IDegLira treatment was initiated at starting dose of 10 dose steps. The dose of IDegLira was adjusted individually twice weekly according to a predefined titration algorithm with a maximum daily dose of 50 dose steps. Pre-trial OAD treatments were continued according to current local label. The randomised subjects would be on either SGLT2i monotherapy or SGLT2i  $\pm$  metformin  $\pm$  pioglitazone excluding DPP4i. This treatment was to be unchanged throughout the trial, unless there was a safety concern.

|  |                              |
|--|------------------------------|
| Arm type                               | Experimental                 |
| Investigational medicinal product name | Insulin degludec liraglutide |
| Investigational medicinal product code |                              |
| Other name                             | Xultophy®                    |
| Pharmaceutical forms                   | Solution for injection       |
| Routes of administration               | Subcutaneous use             |

Dosage and administration details:

IDegLira was supplied in a 3 mL prefilled PDS290 pen-injector with a fixed IDeg/liraglutide ratio of 100 units/3.6 mg per mL solution subcutaneously in the thigh, upper arm (deltoid) or abdomen approximately at the same time every day throughout the trial. IDegLira treatment was initiated at 10 dose steps (containing 10 units IDeg /0.36 mg liraglutide). Dose was adjusted individually twice weekly on fixed days based on the mean of three pre-breakfast self-measured plasma glucose (SMPG) values measured on the days of the titration and the two days prior to the titration (target SMPG: 4.0-5.0 mmol/L [72- 90 mg/dL]). The maximum daily dose for IDegLira was 50 dose steps.

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

Arm description:

Subjects were administered with insulin glargine (IGlar: 100 U/mL) once daily for a duration of 26 weeks. IGlar treatment was initiated with the starting dose of 10 U and adjusted individually twice weekly according to a predefined titration algorithm. Pre-trial OAD treatments were continued according to current local label. The randomised subjects would be on either SGLT2i monotherapy or SGLT2i  $\pm$  metformin  $\pm$  pioglitazone excluding DPP4i. This treatment was to be unchanged throughout the trial, unless there was a safety concern.

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

|  |                        |
|--|------------------------|
| Investigational medicinal product name | Insulin Glargine       |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

IGlar was supplied in a 3 mL pre-filled Solostar® pen at 100 U/mL solution and administered subcutaneously according to the local labelling. Dose adjustment was based on the mean of three pre-breakfast self-measured plasma glucose (SMPG) values measured individually on the days of the titration and two days prior to the titration (target SMPG: 4.0-5.0 mmol/L [72 - 90 mg/dL]). There was no maximum dose specified for IGlar.

| <b>Number of subjects in period 1</b> | IDegLira | IGlar |
|---------------------------------------|----------|-------|
| Started                               | 210      | 210   |
| Exposed                               | 209      | 210   |
| Completed                             | 200      | 206   |
| Not completed                         | 10       | 4     |
| Consent withdrawn by subject          | 5        | 1     |
| Unclassified                          | 1        | 1     |
| Lost to follow-up                     | 4        | 1     |
| Missing                               | -        | 1     |

## Baseline characteristics

### Reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | IDegLira |
|-----------------------|----------|

#### Reporting group description:

Subjects were administered with insulin degludec/liraglutide (IDegLira: 100 U/3.6 mg per mL) once daily for a duration of 26 weeks. IDegLira treatment was initiated at starting dose of 10 dose steps. The dose of IDegLira was adjusted individually twice weekly according to a predefined titration algorithm with a maximum daily dose of 50 dose steps. Pre-trial OAD treatments were continued according to current local label. The randomised subjects would be on either SGLT2i monotherapy or SGLT2i ± metformin ± pioglitazone excluding DPP4i. This treatment was to be unchanged throughout the trial, unless there was a safety concern.

|                       |       |
|-----------------------|-------|
| Reporting group title | IGlar |
|-----------------------|-------|

#### Reporting group description:

Subjects were administered with insulin glargine (IGlar: 100 U/mL) once daily for a duration of 26 weeks. IGlar treatment was initiated with the starting dose of 10 U and adjusted individually twice weekly according to a predefined titration algorithm. Pre-trial OAD treatments were continued according to current local label. The randomised subjects would be on either SGLT2i monotherapy or SGLT2i ± metformin ± pioglitazone excluding DPP4i. This treatment was to be unchanged throughout the trial, unless there was a safety concern.

| Reporting group values   | IDegLira | IGlar  | Total |
|--|----------|--------|-------|
| Number of subjects   | 210      | 210    | 420   |
| Age Categorical<br>Units: Subjects   |          |        |       |
| In utero   | 0        | 0      | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks)                                | 0        | 0      | 0     |
| Newborns (0-27 days)   | 0        | 0      | 0     |
| Infants and toddlers (28 days-23<br>months)  | 0        | 0      | 0     |
| Children (2-11 years)  | 0        | 0      | 0     |
| Adolescents (12-17 years)  | 0        | 0      | 0     |
| Adults (18-64 years)   | 160      | 162    | 322   |
| From 65-84 years   | 50       | 48     | 98    |
| 85 years and over  | 0        | 0      | 0     |
| Age Continuous<br>Units: years   |          |        |       |
| arithmetic mean  | 56.1     | 57.2   | -     |
| standard deviation   | ± 10.4   | ± 10.2 | -     |
| Gender Categorical<br>Units: Subjects  |          |        |       |
| Female   | 89       | 84     | 173   |
| Male   | 121      | 126    | 247   |
| Glycosylated haemoglobin (HbA1c)<br>Units: percentage of glycosylated<br>haemoglobin |          |        |       |
| arithmetic mean  | 8.20     | 8.36   | -     |
| standard deviation   | ± 0.93   | ± 1.08 | -     |
| Body Weight<br>Units: kg   |          |        |       |
| arithmetic mean  | 89.3     | 87.2   | -     |
| standard deviation   | ± 17.6   | ± 17.2 | -     |

|                              |        |        |   |
|------------------------------|--------|--------|---|
| Fasting plasma glucose (FPG) |        |        |   |
| Units: mmol/L                |        |        |   |
| arithmetic mean              | 9.51   | 9.57   |   |
| standard deviation           | ± 2.69 | ± 2.40 | - |

## End points

### End points reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | IDegLira |
|-----------------------|----------|

Reporting group description:

Subjects were administered with insulin degludec/liraglutide (IDegLira: 100 U/3.6 mg per mL) once daily for a duration of 26 weeks. IDegLira treatment was initiated at starting dose of 10 dose steps. The dose of IDegLira was adjusted individually twice weekly according to a predefined titration algorithm with a maximum daily dose of 50 dose steps. Pre-trial OAD treatments were continued according to current local label. The randomised subjects would be on either SGLT2i monotherapy or SGLT2i ± metformin ± pioglitazone excluding DPP4i. This treatment was to be unchanged throughout the trial, unless there was a safety concern.

|                       |       |
|-----------------------|-------|
| Reporting group title | IGlar |
|-----------------------|-------|

Reporting group description:

Subjects were administered with insulin glargine (IGlar: 100 U/mL) once daily for a duration of 26 weeks. IGlar treatment was initiated with the starting dose of 10 U and adjusted individually twice weekly according to a predefined titration algorithm. Pre-trial OAD treatments were continued according to current local label. The randomised subjects would be on either SGLT2i monotherapy or SGLT2i ± metformin ± pioglitazone excluding DPP4i. This treatment was to be unchanged throughout the trial, unless there was a safety concern.

### Primary: Change from baseline in HbA1c

|                 |                               |
|-----------------|-------------------------------|
| End point title | Change from baseline in HbA1c |
|-----------------|-------------------------------|

End point description:

The mean change from baseline (week 0) in HbA1c values evaluated after 26 weeks of randomised treatment. The full analysis set (FAS) included all randomised subjects. The statistical evaluation of the FAS followed the intent-to-treat (ITT) principle and subjects contributed to the evaluation "as randomised". Number analysed = Number of subjects contributed to the analysis at week 26. The results presented included retrieved data at week 26 for subjects who prematurely discontinued the trial product.

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

End point timeframe:

After 26 weeks

| End point values                              | IDegLira        | IGlar           |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                            | Reporting group | Reporting group |  |  |
| Number of subjects analysed                   | 197             | 202             |  |  |
| Units: Percentage of glycosylated haemoglobin |                 |                 |  |  |
| arithmetic mean (standard deviation)          |                 |                 |  |  |
| HbA1c (%) change from baseline to week 26     | -1.94 (± 0.95)  | -1.68 (± 1.05)  |  |  |

### Statistical analyses

|                            |                                      |
|----------------------------|--------------------------------------|
| Statistical analysis title | Analysis 1: Non-inferiority Analysis |
|----------------------------|--------------------------------------|

Statistical analysis description:

Analysis was based on ANCOVA model with treatment, pre-trial OAD, region as factors and baseline



HbA1c as covariate. Missing data were imputed using unconditional reference based multiple imputation including data obtained after premature treatment discontinuation. The non-inferiority margin of 0.3 % was added to the end-of-treatment value for prematurely discontinued and withdrawn from trial IDegLira subjects. Number of subjects contributed to the analysis included all randomised subjects (420)

|   |                                |
|---|--------------------------------|
| Comparison groups                       | IDegLira v IGLar               |
| Number of subjects included in analysis | 399                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority <sup>[1]</sup> |
| Method                                  | ANCOVA                         |
| Parameter estimate                      | Treatment Contrast             |
| Point estimate                          | -0.34                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.48                          |
| upper limit                             | -0.2                           |

Notes:

[1] - Non-inferiority of IDegLira was considered confirmed if the upper limit of the two-sided 95% confidence interval (CI) for mean treatment difference (IDegLira minus IGLar) was strictly below 0.3%.

|                                   |                                  |
|-----------------------------------|----------------------------------|
| <b>Statistical analysis title</b> | Analysis 2: Superiority analysis |
|-----------------------------------|----------------------------------|

Statistical analysis description:

This endpoint was analysed using an ANCOVA model with treatment, pre-trial OAD and region as factors and corresponding baseline value as covariate. Data obtained after premature treatment discontinuation were included in the analysis. Missing data were imputed using unconditional reference based multiple imputation including data obtained after premature treatment discontinuation. Number of subjects contributed to the analysis included all randomised subjects (420).

|   |                            |
|---|----------------------------|
| Comparison groups                       | IDegLira v IGLar           |
| Number of subjects included in analysis | 399                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[2]</sup> |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | Treatment Contrast         |
| Point estimate                          | -0.36                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -0.5                       |
| upper limit                             | -0.21                      |

Notes:

[2] - Superiority of IDegLira was considered confirmed if the test procedure was not stopped (i.e. non-inferiority of IDegLira was confirmed for change from baseline in HbA1c; and superiority of IDegLira was confirmed for weight change and the number of treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes) and if the upper limit of the two-sided 95% CI for the mean treatment difference (IDegLira minus IGLar) in change from baseline in HbA1c was strictly below 0%.

## Secondary: Change from baseline in body weight

|   |                                     |
|---|-------------------------------------|
| End point title   | Change from baseline in body weight |
| End point description:  |                                     |
| The mean change from baseline (week 0) in body weight evaluated after 26 weeks of randomised treatment. The FAS included all randomised subjects. The statistical evaluation of the FAS followed the intent-to-treat (ITT) principle and subjects contributed to the evaluation "as randomised". Number analysed = Number of subjects contributed to the analysis at week 26. The results presented included retrieved data at week 26 for subjects who prematurely discontinued the trial product. |                                     |
| End point type  | Secondary                           |

End point timeframe:

After 26 weeks

| End point values                                 | IDegLira        | IGlar           |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                               | Reporting group | Reporting group |  |  |
| Number of subjects analysed                      | 199             | 204             |  |  |
| Units: kg  |                 |                 |  |  |
| arithmetic mean (standard deviation)             |                 |                 |  |  |
| Body weight (kg) change from baseline to week 26 | -0.0 (± 3.8)    | 2.0 (± 3.9)     |  |  |

## Statistical analyses

| Statistical analysis title | Analysis 1: Superiority analysis |
|----------------------------|----------------------------------|
|----------------------------|----------------------------------|

Statistical analysis description:

This endpoint was analysed using an ANCOVA model with treatment, pre-trial OAD and region as factors and corresponding baseline weight as covariate. Data obtained after premature treatment discontinuation were included in the analysis. Missing data were imputed using unconditional reference based multiple imputation including data obtained after premature treatment discontinuation. Number of subjects contributed to the analysis included all randomised subjects (420).

|   |                            |
|---|----------------------------|
| Comparison groups                       | IDegLira v IGlar           |
| Number of subjects included in analysis | 403                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[3]</sup> |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | Treatment Contrast         |
| Point estimate                          | -1.92                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -2.64                      |
| upper limit                             | -1.19                      |

Notes:

[3] - Superiority of IDegLira was considered confirmed if the test procedure was not stopped (i.e. non-inferiority of IDegLira was confirmed for change from baseline in HbA1c) and if the upper limit of the two-sided 95% CI for the mean treatment difference (IDegLira minus IGlar) in change from baseline in body weight was strictly below 0 kg.

## Secondary: Number of treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes

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

End point description:

Severe or BG confirmed symptomatic hypoglycaemic episodes were defined as episodes that were severe (subjects who were not able to self-treat) and/or BG confirmed by a plasma glucose values <3.1 mmol/L (56 mg/dL) with accompanied symptoms consistent with hypoglycaemia. The safety analysis set (SAS) included all subjects who received at least one dose of the investigational product or comparator.

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

End point timeframe:

During 26 weeks

| End point values            | IDegLira        | IGlar           |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 209             | 210             |  |  |
| Units: Number of episodes   | 38              | 95              |  |  |

## Statistical analyses

| Statistical analysis title  | Analysis 1: Superiority analysis   |
|---|------------------------------------|
| Statistical analysis description:   |                                    |
| This endpoint was analysed using a negative binomial regression model with a log link and the logarithm of the exposure time as offset. The model included treatment and pre-trial OAD as fixed factors. Missing data were imputed using multiple imputations (conditioning on expected event rate before premature treatment discontinuation or withdrawal from trial as if treated with IGlar). |                                    |
| Comparison groups   | IDegLira v IGlar                   |
| Number of subjects included in analysis   | 419                                |
| Analysis specification  | Pre-specified                      |
| Analysis type   | superiority <sup>[4]</sup>         |
| Method  | Negative binomial regression model |
| Parameter estimate  | Treatment Ratio                    |
| Point estimate  | 0.42                               |
| Confidence interval   |                                    |
| level   | 95 %                               |
| sides   | 2-sided                            |
| lower limit   | 0.23                               |
| upper limit   | 0.75                               |

Notes:

[4] - Superiority of IDegLira was considered confirmed if the test procedure was not stopped (i.e. non-inferiority of IDegLira was confirmed for change from baseline in HbA1c and superiority of IDegLira was confirmed for change from baseline in body weight) and if the upper limit of the two-sided 95% CI for the rate ratio (IDegLira over IGlar) of rate of treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes was strictly below 1.

## Secondary: Insulin dose, total daily dose (U)

| End point title   | Insulin dose, total daily dose (U) |
|---|------------------------------------|
| End point description:  |                                    |
| Actual daily total insulin dose (Units) was evaluated after 26 weeks of randomised treatment. The results presented included retrieved data at week 26 for subjects who prematurely discontinued the trial product. The FAS included all randomised subjects. The statistical evaluation of the FAS followed the intent-to-treat (ITT) principle and subjects contributed to the evaluation "as randomised". Number analysed = Number of subjects contributed to the analysis at week 26. |                                    |
| End point type  | Secondary                          |
| End point timeframe:  |                                    |
| After 26 weeks  |                                    |

| End point values                     | IDegLira        | IGlar           |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 196             | 201             |  |  |
| Units: Units (U)                     |                 |                 |  |  |
| arithmetic mean (standard deviation) | 36.2 (± 13.4)   | 53.5 (± 26.1)   |  |  |

## Statistical analyses

| Statistical analysis title | Analysis 1: Superiority analysis |
|----------------------------|----------------------------------|
|----------------------------|----------------------------------|

Statistical analysis description:

The endpoint was analysed using an ANCOVA model with treatment, pre-trial OAD and region as factors and corresponding baseline HbA1c as covariate. Missing data were imputed using unconditional reference based multiple imputation including data obtained after premature treatment discontinuation. Number of subjects contributed to the analysis included all randomised subjects receiving at least one dose of the investigational product or comparator (419).

|   |                            |
|---|----------------------------|
| Comparison groups                       | IDegLira v IGlar           |
| Number of subjects included in analysis | 397                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[5]</sup> |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | Treatment Contrast         |
| Point estimate                          | -15.37                     |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -19.6                      |
| upper limit                             | -11.13                     |

Notes:

[5] - Superiority of IDegLira was considered confirmed if the test procedure was not stopped (i.e. non-inferiority of IDegLira was confirmed for change from baseline in HbA1c; and superiority of IDegLira was confirmed for weight change, number of treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes and change in HbA1c) and if the upper limit of the two-sided 95% CI for the mean treatment difference (IDegLira minus IGlar) in insulin dose after 26 weeks was strictly below 0 U.

## Secondary: Responder (Yes/No) for HbA1c < 7.0%

|                 |                                     |
|-----------------|-------------------------------------|
| End point title | Responder (Yes/No) for HbA1c < 7.0% |
|-----------------|-------------------------------------|

End point description:

The proportion of subjects achieving pre-defined HbA1c targets <7.0% after 26 weeks of randomised treatment. The FAS included all randomised subjects. The statistical evaluation of the FAS followed the intent-to-treat (ITT) principle and subjects contributed to the evaluation "as randomised". Number analysed = Number of subjects contributed to the analysis at week 26. The results presented included retrieved data at week 26 for subjects who prematurely discontinued the trial product.

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

End point timeframe:

After 26 weeks

| End point values              | IDegLira        | IGlar           |  |  |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type            | Reporting group | Reporting group |  |  |
| Number of subjects analysed   | 197             | 202             |  |  |
| Units: Number of participants |                 |                 |  |  |
| Yes                           | 167             | 144             |  |  |
| No                            | 30              | 58              |  |  |

## Statistical analyses

No statistical analyses for this end point

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

|                 |  |
|-----------------|--|
| End point title | Change from baseline in fasting plasma glucose (FPG) |
|-----------------|--|

End point description:

Change from baseline (week 0) in FPG was evaluated after 26 weeks of randomised treatment. The FAS included all randomised subjects. The statistical evaluation of the FAS followed the intent-to-treat (ITT) principle and subjects contributed to the evaluation "as randomised". Number analysed = Number of subjects contributed to the analysis at week 26.

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

End point timeframe:

After 26 weeks

| End point values                             | IDegLira        | IGlar           |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                           | Reporting group | Reporting group |  |  |
| Number of subjects analysed                  | 189             | 195             |  |  |
| Units: mmol/L                                |                 |                 |  |  |
| arithmetic mean (standard deviation)         |                 |                 |  |  |
| FPG (mmol/L) change from baseline to week 26 | -3.72 (± 2.89)  | -3.50 (± 2.43)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of treatment-emergent adverse events

|                 |   |
|-----------------|---|
| End point title | Number of treatment-emergent adverse events |
|-----------------|---|

End point description:

Treatment emergent adverse events (TEAEs) were recorded from week 0-week 26. A TEAE was defined as an event that had onset date on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment. If the event had onset date before the first day of exposure on randomised treatment and increased in severity during the treatment period and until 7 days after the last drug date, then this event should also be considered as a TEAE. Major cardiovascular events (MACEs) were considered treatment-emergent until 30 calendar days after the last day of randomised treatment. The safety analysis set included all subjects who received at least one dose of the investigational product or comparator.

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

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End point timeframe:

During 26 weeks

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| <b>End point values</b>     | IDegLira        | IGlar           |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 209             | 210             |  |  |
| Units: Number of events     | 450             | 386             |  |  |

### **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 first day of exposure until the end of treatment (week 0 to week 26) plus 7 days after last dose of trial product or 30 days for major cardiovascular events.

Adverse event reporting additional description:

TEAE: An event that had onset date on or after the first day of exposure to randomised treatment and no later than 7 days (30 days for MACEs) after the last day of randomised treatment (or an event that increased in severity during this period but had an onset date before first day of exposure).

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

### Dictionary used

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

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

### Reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | IDegLira |
|-----------------------|----------|

Reporting group description:

Subjects were administered with insulin degludec/liraglutide (IDegLira: 100 U/3.6 mg per mL) once daily for a duration of 26 weeks. IDegLira treatment was initiated at starting dose of 10 dose steps. The dose of IDegLira was adjusted individually twice weekly according to a predefined titration algorithm with a maximum daily dose of 50 dose steps. Pre-trial OAD treatments were continued according to current local label. The randomised subjects would be on either SGLT2i monotherapy or SGLT2i ± metformin ± pioglitazone excluding DPP4i. This treatment was to be unchanged throughout the trial, unless there was a safety concern.

|                       |       |
|-----------------------|-------|
| Reporting group title | IGlar |
|-----------------------|-------|

Reporting group description:

Subjects were administered with insulin glargine (IGlar: 100 U/mL) once daily for a duration of 26 weeks. IGlar treatment was initiated with the starting dose of 10 U and adjusted individually twice weekly according to a predefined titration algorithm. Pre-trial OAD treatments were continued according to current local label. The randomised subjects would be on either SGLT2i monotherapy or SGLT2i ± metformin ± pioglitazone excluding DPP4i. This treatment was to be unchanged throughout the trial, unless there was a safety concern.

| Serious adverse events                            | IDegLira        | IGlar           |  |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events |                 |                 |  |
| subjects affected / exposed                       | 6 / 209 (2.87%) | 7 / 210 (3.33%) |  |
| number of deaths (all causes)                     | 0               | 0               |  |
| number of deaths resulting from adverse events    | 0               | 0               |  |
| Investigations                                    |                 |                 |  |
| Blood potassium increased                         |                 |                 |  |
| subjects affected / exposed                       | 1 / 209 (0.48%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Cardiovascular evaluation                         |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed   | 1 / 209 (0.48%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                 |  |
| Gastrointestinal stromal tumour                                     |                 |                 |  |
| subjects affected / exposed   | 0 / 209 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Cardiac disorders   |                 |                 |  |
| Cardiac failure chronic   |                 |                 |  |
| subjects affected / exposed   | 0 / 209 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Coronary artery disease   |                 |                 |  |
| subjects affected / exposed   | 0 / 209 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Myocardial infarction   |                 |                 |  |
| subjects affected / exposed   | 1 / 209 (0.48%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all                     | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Nervous system disorders  |                 |                 |  |
| Haemorrhagic stroke   |                 |                 |  |
| subjects affected / exposed   | 1 / 209 (0.48%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders  |                 |                 |  |
| Abdominal pain  |                 |                 |  |
| subjects affected / exposed   | 0 / 209 (0.00%) | 1 / 210 (0.48%) |  |
| 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 / 209 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic kidney disease                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Product issues                                  |                 |                 |  |
| Device failure                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 209 (0.48%) | 0 / 210 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Infected skin ulcer                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 209 (0.96%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 209 (0.00%) | 1 / 210 (0.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| 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>                     | IDegLira          | IGlar             |  |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 49 / 209 (23.44%) | 45 / 210 (21.43%) |  |
| Investigations  |                   |                   |  |
| Lipase increased                                      |                   |                   |  |
| subjects affected / exposed                           | 12 / 209 (5.74%)  | 3 / 210 (1.43%)   |  |
| occurrences (all)                                     | 15                | 3                 |  |

|  |                        |                         |  |
|--|------------------------|-------------------------|--|
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)                                   | 18 / 209 (8.61%)<br>35 | 19 / 210 (9.05%)<br>27  |  |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)                                   | 12 / 209 (5.74%)<br>22 | 1 / 210 (0.48%)<br>2    |  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all)           | 11 / 209 (5.26%)<br>12 | 9 / 210 (4.29%)<br>15   |  |
| Infections and infestations<br>Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 16 / 209 (7.66%)<br>22 | 22 / 210 (10.48%)<br>24 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 20 January 2017 | Update of section 18 with 'Acute Gallstone disease' in accordance with IDegLira minimum mandatory safety text.<br>Update of procedures and minor administrative corrections and typographical errors. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported