



## Clinical trial results:

**A randomised, double-blind, cross-over trial comparing the safety and efficacy of insulin degludec and insulin glargine, both with insulin aspart as mealtime insulin in subjects with type 1 diabetes**

### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2012-001930-32  |
| Trial protocol           | PL              |
| Global end of trial date | 12 January 2016 |

### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 27 January 2017 |
| First version publication date | 27 January 2017 |

### Trial information

#### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | NN1250-3995 |
|-----------------------|-------------|

#### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | NCT02034513     |
| WHO universal trial number (UTN)   | U1111-1129-9668 |

Notes:

### Sponsors

|                              |                                                                                        |
|------------------------------|----------------------------------------------------------------------------------------|
| Sponsor organisation name    | Novo Nordisk A/S                                                                       |
| Sponsor organisation address | Novo Allé, Bagsvaerd, Denmark, 2880                                                    |
| Public contact               | Global Clinical Registry (GCR, 1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com |
| Scientific contact           | Global Clinical Registry (GCR, 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:

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**Results analysis stage**

|                                                      |                 |
|------------------------------------------------------|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 03 June 2016    |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 12 January 2016 |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 12 January 2016 |
| Was the trial ended prematurely?                     | No              |

Notes:

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**General information about the trial**

Main objective of the trial:

To compare the rates of severe or BG (blood glucose) confirmed symptomatic hypoglycaemia of IDeg once daily (OD) + IAsp to IGlax OD + IAsp, by demonstrating that the upper limit of the 95% confidence interval of the rate ratio is below or equal to a non-inferiority margin of 1.10, and if confirmed, to a superiority limit of 1.00.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki, ICH Good Clinical Practice, and 21 CFR 312.120.

Background therapy:

Insulin aspart (IAsp; bolus insulin) was titrated individually based on either carbohydrate counting or by using sliding scale based on the lowest of three pre-meal or bedtime self-measured plasma glucose (SMPG) values.

Evidence for comparator:

Not applicable.

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment                          | 06 January 2014 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Poland: 43         |
| Country: Number of subjects enrolled | United States: 458 |
| Worldwide total number of subjects   | 501                |
| EEA total number of subjects         | 43                 |

Notes:

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**Subjects enrolled per age group**

|                                           |   |
|-------------------------------------------|---|
| 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) | 448 |
| From 65 to 84 years  | 53  |
| 85 years and over    | 0   |

## Subject disposition

### Recruitment

Recruitment details:

The trial was conducted at 90 sites in 2 countries, as follows: the United States (US): 84 sites, Poland: 6 sites.

### Pre-assignment

Screening details:

Not applicable.

### Period 1

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

### Arms

|                              |                                                |
|------------------------------|------------------------------------------------|
| Are arms mutually exclusive? | Yes                                            |
| <b>Arm title</b>             | Insulin degludec/insulin glargine (IDeg/IGlar) |

Arm description:

Subjects received insulin degludec (IDeg) in treatment period 1 and insulin glargine (IGlar) in treatment period 2. Each treatment period consisted of a 16-week titration period and a 16-week maintenance period (total 32 weeks for each treatment period).

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Cross-over             |
| Investigational medicinal product name | Insulin glargine       |
| Investigational medicinal product code |                        |
| Other name                             | Lantus®                |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

Subjects received IGlar for a total of 32 weeks (16-week titration period and a 16-week maintenance period). IGlar was administered s.c. in the morning (from waking up to breakfast) or in the evening (from main evening meal to bedtime), as per randomisation and were to be taken OD at the same time of day throughout the trial. To prevent an increased risk of hypoglycaemia in the first treatment month, the overall daily doses of IGlar were reduced by 20% at the start of both the treatment periods. Doses of IGlar were titrated individually. Titration of the dose was performed once weekly based on the lowest of 3 pre-breakfast SMPG values measured on 3 consecutive days immediately prior to titration (fasting glycaemic target of 4.0-5.0 mmol/L).

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

Dosage and administration details:

Subjects received IDeg for a total of 32 weeks (16-week titration period and a 16-week maintenance period). IDeg was administered subcutaneously (s.c.; under the skin) in the morning (from waking up to breakfast) or in the evening (from main evening meal to bedtime), as per randomisation and was to be taken once daily (OD) at the same time of day throughout the trial. To prevent an increased risk of hypoglycaemia in the first treatment month, the overall daily doses of IDeg were reduced by 20% at the start of both the treatment periods. Doses of IDeg were titrated individually. Titration of the dose was performed once weekly based on the lowest of 3 pre-breakfast self measured plasma glucose (SMPG) values measured on 3 consecutive days immediately prior to titration (fasting glycaemic target of 4.0-5.0 mmol/L).

|                  |                                                |
|------------------|------------------------------------------------|
| <b>Arm title</b> | Insulin glargine/insulin degludec (IGlar/IDeg) |
|------------------|------------------------------------------------|

#### Arm description:

Subjects received IGLar in treatment period 1 and IDeg in treatment period 2. Each treatment period consisted of a 16-week titration period and a 16-week maintenance period (total 32 weeks for each treatment period).

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Cross-over             |
| Investigational medicinal product name | Insulin glargine       |
| Investigational medicinal product code |                        |
| Other name                             | Lantus®                |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

#### Dosage and administration details:

Subjects received IGLar for a total of 32 weeks (16-week titration period and a 16-week maintenance period). IGLar was administered s.c. in the morning (from waking up to breakfast) or in the evening (from main evening meal to bedtime), as per randomisation and were to be taken OD at the same time of day throughout the trial. To prevent an increased risk of hypoglycaemia in the first treatment month, the overall daily doses of IGLar were reduced by 20% at the start of both the treatment periods. Doses of IGLar were titrated individually. Titration of the dose was performed once weekly based on the lowest of 3 pre-breakfast SMPG values measured on 3 consecutive days immediately prior to titration (fasting glycaemic target of 4.0-5.0 mmol/L).

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

#### Dosage and administration details:

Subjects received IDeg for a total of 32 weeks (16-week titration period and a 16-week maintenance period). IDeg was administered s.c. in the morning (from waking up to breakfast) or in the evening (from main evening meal to bedtime), as per randomisation and was to be taken OD at the same time of day throughout the trial. To prevent an increased risk of hypoglycaemia in the first treatment month, the overall daily doses of IDeg were reduced by 20% at the start of both the treatment periods. Doses of IDeg were titrated individually. Titration of the dose was performed once weekly based on the lowest of 3 pre-breakfast SMPG values measured on 3 consecutive days immediately prior to titration (fasting glycaemic target of 4.0-5.0 mmol/L).

| <b>Number of subjects in period 1</b> | <b>Insulin degludec/insulin glargine (IDeg/IGlar)</b> | <b>Insulin glargine/insulin degludec (IGlar/IDeg)</b> |
|---------------------------------------|-------------------------------------------------------|-------------------------------------------------------|
| Started                               | 249                                                   | 252                                                   |
| Exposed                               | 249                                                   | 251                                                   |
| Completed                             | 200                                                   | 195                                                   |
| Not completed                         | 49                                                    | 57                                                    |
| Consent withdrawn by subject          | 25                                                    | 25                                                    |
| Adverse event, non-fatal              | 11                                                    | 10                                                    |
| Pregnancy                             | -                                                     | 3                                                     |
| Unclassified                          | -                                                     | 1                                                     |
| Lost to follow-up                     | 6                                                     | 7                                                     |
| Protocol deviation                    | 7                                                     | 10                                                    |
| Lack of efficacy                      | -                                                     | 1                                                     |



## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                                                                |                                                |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                          | Insulin degludec/insulin glargine (IDeg/IGlar) |
| Reporting group description:<br>Subjects received insulin degludec (IDeg) in treatment period 1 and insulin glargine (IGlar) in treatment period 2. Each treatment period consisted of a 16-week titration period and a 16-week maintenance period (total 32 weeks for each treatment period). |                                                |
| Reporting group title                                                                                                                                                                                                                                                                          | Insulin glargine/insulin degludec (IGlar/IDeg) |
| Reporting group description:<br>Subjects received IGlar in treatment period 1 and IDeg in treatment period 2. Each treatment period consisted of a 16-week titration period and a 16-week maintenance period (total 32 weeks for each treatment period).                                       |                                                |

| Reporting group values                                                      | Insulin degludec/insulin glargine (IDeg/IGlar) | Insulin glargine/insulin degludec (IGlar/IDeg) | Total |
|-----------------------------------------------------------------------------|------------------------------------------------|------------------------------------------------|-------|
| Number of subjects                                                          | 249                                            | 252                                            | 501   |
| Age categorical<br>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)                                                        | 223                                            | 225                                            | 448   |
| From 65-84 years                                                            | 26                                             | 27                                             | 53    |
| 85 years and over                                                           | 0                                              | 0                                              | 0     |
| Age Continuous<br>Units: years                                              |                                                |                                                |       |
| arithmetic mean                                                             | 45.4                                           | 46.4                                           | -     |
| standard deviation                                                          | ± 13.7                                         | ± 14.6                                         | -     |
| Gender, Male/Female<br>Units: Subjects                                      |                                                |                                                |       |
| Female                                                                      | 123                                            | 109                                            | 232   |
| Male                                                                        | 126                                            | 143                                            | 269   |
| Study Specific Characteristic   Glycosylated hemoglobin (HbA1c)             |                                                |                                                |       |
| Number of subjects analyzed=248 for IDeg/IGlar arm, 252 for IGlar/IDeg arm. |                                                |                                                |       |
| Units: Percentage of HbA1c                                                  |                                                |                                                |       |
| arithmetic mean                                                             | 7.7                                            | 7.5                                            | -     |
| standard deviation                                                          | ± 1                                            | ± 1                                            | -     |
| Study Specific Characteristic   Fasting plasma glucose (FPG)                |                                                |                                                |       |
| Number of subjects analyzed=248 for IDeg/IGlar arm, 252 for IGlar/IDeg arm. |                                                |                                                |       |
| Units: mg/dL                                                                |                                                |                                                |       |
| arithmetic mean                                                             | 165.1                                          | 174.4                                          | -     |
| standard deviation                                                          | ± 77.3                                         | ± 81.7                                         | -     |



## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Insulin degludec/insulin glargine (IDeg/IGlar) |
| Reporting group description:<br>Subjects received insulin degludec (IDeg) in treatment period 1 and insulin glargine (IGlar) in treatment period 2. Each treatment period consisted of a 16-week titration period and a 16-week maintenance period (total 32 weeks for each treatment period).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Insulin glargine/insulin degludec (IGlar/IDeg) |
| Reporting group description:<br>Subjects received IGlar in treatment period 1 and IDeg in treatment period 2. Each treatment period consisted of a 16-week titration period and a 16-week maintenance period (total 32 weeks for each treatment period).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Insulin degludec (IDeg)                        |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Full analysis                                  |
| Subject analysis set description:<br>Subjects received IDeg in treatment period 1 (from treatment sequence IDeg/IGlar) and in treatment period 2 (from treatment sequence IGlar/IDeg). Each treatment period consisted of a 16-week titration period and a 16-week maintenance period (total 32 weeks for each treatment period). IDeg was administered s.c. in the morning (from waking up to breakfast) or in the evening (from main evening meal to bedtime), as per randomisation and was to be taken OD at the same time of day throughout the trial. To prevent an increased risk of hypoglycaemia in the first treatment month, the overall daily doses of IDeg were reduced by 20% at the start of both the treatment periods. Doses of IDeg were titrated individually. Titration of the dose was performed once weekly based on the lowest of 3 pre-breakfast SMPG values measured on 3 consecutive days immediately prior to titration.     |                                                |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Insulin glargine (IGlar)                       |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Full analysis                                  |
| Subject analysis set description:<br>Subjects received IGlar in treatment period 1 (from treatment sequence IGlar/IDeg) and in treatment period 2 (from treatment sequence IDeg/IGlar). Each treatment period consisted of a 16-week titration period and a 16-week maintenance period (total 32 weeks for each treatment period). IGlar was administered s.c. in the morning (from waking up to breakfast) or in the evening (from main evening meal to bedtime), as per randomisation and was to be taken OD at the same time of day throughout the trial. To prevent an increased risk of hypoglycaemia in the first treatment month, the overall daily doses of IGlar were reduced by 20% at the start of both the treatment periods. Doses of IGlar were titrated individually. Titration of the dose was performed once weekly based on the lowest of 3 pre-breakfast SMPG values measured on 3 consecutive days immediately prior to titration. |                                                |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Insulin degludec (IDeg)                        |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Safety analysis                                |
| Subject analysis set description:<br>Subjects received IDeg in treatment period 1 (from treatment sequence IDeg/IGlar) and in treatment period 2 (from treatment sequence IGlar/IDeg). Each treatment period consisted of a 16-week titration period and a 16-week maintenance period (total 32 weeks for each treatment period). IDeg was administered s.c. in the morning (from waking up to breakfast) or in the evening (from main evening meal to bedtime), as per randomisation and was to be taken OD at the same time of day throughout the trial. To prevent an increased risk of hypoglycaemia in the first treatment month, the overall daily doses of IDeg were reduced by 20% at the start of both the treatment periods. Doses of IDeg were titrated individually. Titration of the dose was performed once weekly based on the lowest of 3 pre-breakfast SMPG values measured on 3 consecutive days immediately prior to titration.     |                                                |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Insulin glargine (IGlar)                       |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Safety analysis                                |
| Subject analysis set description:<br>Subjects received IGlar in treatment period 1 (from treatment sequence IGlar/IDeg) and in treatment period 2 (from treatment sequence IDeg/IGlar). Each treatment period consisted of a 16-week titration period and a 16-week maintenance period (total 32 weeks for each treatment period). IGlar was administered s.c. in the morning (from waking up to breakfast) or in the evening (from main evening meal to bedtime), as per randomisation and was to be taken OD at the same time of day throughout the trial. To prevent an increased risk of hypoglycaemia in the first treatment month, the overall daily doses of IGlar were reduced by 20% at the start of both the treatment periods. Doses of IGlar were titrated individually. Titration of the dose was performed once weekly based on the lowest of 3 pre-breakfast                                                                            |                                                |

# **Primary: Number of treatment emergent severe or BG (blood glucose) confirmed symptomatic hypoglycaemic episodes during the maintenance period**

|                 |                                                                                                                                      |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of treatment emergent severe or BG (blood glucose) confirmed symptomatic hypoglycaemic episodes during the maintenance period |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------|

## End point description:

Severe or blood glucose (BG) confirmed symptomatic hypoglycaemic episodes were defined as episodes that were severe and/or BG confirmed by a plasma glucose value of <3.1 mmol/L (56 mg/dL), with symptoms consistent with hypoglycaemia. Treatment emergent hypoglycaemic episode was defined as an event with onset date on or after the first day of exposure to randomised treatment and no later than the last day of randomised treatment. The trial followed a cross over design. Descriptive analysis was based on the safety analysis set (SAS: subjects receiving at least 1 dose of the investigational product, IDeg or its comparator, IGLar; number of subjects (N)=500). Number of subjects analysed=subjects with available data for the endpoint as per individual trial product. Statistical analysis was based on the subjects in the full analysis set (FAS: included all randomised subjects (N=501)), who were exposed in at least one maintenance period (i.e., N=437).

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

## End point timeframe:

After 16 weeks of treatment, in each treatment period (Week 16-32 and Week 48-64).

| End point values            | Insulin degludec (IDeg) | Insulin glargine (IGlar) |  |  |
|-----------------------------|-------------------------|--------------------------|--|--|
| Subject group type          | Subject analysis set    | Subject analysis set     |  |  |
| Number of subjects analysed | 418                     | 422                      |  |  |
| Units: Event                | 2772                    | 3126                     |  |  |

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

## Statistical analysis description:

Stepwise hierarchical testing procedure was applied for confirmatory endpoints: Step 1: Number of treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the maintenance period. Due to cross-over design of the study, the following "number of subjects included in analysis" is being erroneously displayed as 840. Actual "number of subjects included in analysis" is 437.

|                                         |                                                    |
|-----------------------------------------|----------------------------------------------------|
| Comparison groups                       | Insulin degludec (IDeg) v Insulin glargine (IGlar) |
| Number of subjects included in analysis | 840                                                |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | non-inferiority <sup>[1]</sup>                     |
| P-value                                 | < 0.0001                                           |
| Method                                  | Poisson                                            |
| Parameter estimate                      | Treatment ratio                                    |
| Point estimate                          | 0.89                                               |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.85    |
| upper limit         | 0.94    |

Notes:

[1] - Non-inferiority was considered confirmed if the 95% confidence interval for the rate ratio (IDeg/IGlar) was  $\leq 1.10$  or equivalently if the p-value for the 1-sided test of  $H_0: RR > 1.10$  against  $H_A: RR \leq 1.10$  was less than 2.5%, where RR is the estimated rate ratio IDeg/IGlar. If non-inferiority was confirmed the superiority of IDeg/IGlar was investigated outside of the test hierarchy. Superiority was considered confirmed if the upper bound of the 2-sided 95% confidence interval was  $< 1.00$ .

## Secondary: Number of treatment emergent severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes during the maintenance period

|                 |                                                                                                                                |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of treatment emergent severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes during the maintenance period |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------|

End point description:

Severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes were defined as episodes that were severe and/or BG confirmed by a plasma glucose value of  $< 3.1$  mmol/L (56 mg/dL), with symptoms consistent with hypoglycaemia and with time of onset between 00:01 and 05:59 a.m., both inclusive. Treatment emergent hypoglycaemic episode was defined as an event with onset date on or after the first day of exposure to randomised treatment and no later than the last day of randomised treatment. The trial followed a cross over design. Descriptive analysis was based on the SAS (N=500). Number of subjects analysed=subjects with available data for the endpoint as per individual trial product. Statistical analysis was based on the subjects in the FAS (N=501), who were exposed in at least one maintenance period (i.e., N=437).

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

End point timeframe:

After 16 weeks of treatment, in each treatment period (Week 16-32 and Week 48-64)

| End point values            | Insulin degludec (IDeg) | Insulin glargine (IGlar) |  |  |
|-----------------------------|-------------------------|--------------------------|--|--|
| Subject group type          | Subject analysis set    | Subject analysis set     |  |  |
| Number of subjects analysed | 418                     | 422                      |  |  |
| Units: Event                | 349                     | 544                      |  |  |

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Stepwise hierarchical testing procedure was applied for confirmatory endpoints: Step 2: Number of treatment-emergent severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes during the maintenance period. Due to cross-over design of the study, the following "number of subjects included in analysis" is being erroneously displayed as 840. Actual "number of subjects included in analysis" is 437.

|                   |                                                    |
|-------------------|----------------------------------------------------|
| Comparison groups | Insulin degludec (IDeg) v Insulin glargine (IGlar) |
|-------------------|----------------------------------------------------|

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 840                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority <sup>[2]</sup> |
| P-value                                 | < 0.0001                       |
| Method                                  | Poisson                        |
| Parameter estimate                      | Treatment ratio                |
| Point estimate                          | 0.64                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 0.56                           |
| upper limit                             | 0.73                           |

Notes:

[2] - Non-inferiority was considered confirmed if the 95% confidence interval for the rate ratio (IDeg/IGlar) was  $\leq 1.10$  or equivalently if the p-value for the 1-sided test of  $H_0: RR > 1.10$  against  $H_A: RR \leq 1.10$  was less than 2.5%, where RR is the estimated rate ratio IDeg/IGlar. If non-inferiority was confirmed the superiority of IDeg/IGlar was investigated outside of the test hierarchy. Superiority was considered confirmed if the upper bound of the 2-sided 95% confidence interval was  $< 1.00$ .

## Secondary: Proportion of subjects with one or more severe hypoglycaemic episodes during the maintenance period

|                 |                                                                                                     |
|-----------------|-----------------------------------------------------------------------------------------------------|
| End point title | Proportion of subjects with one or more severe hypoglycaemic episodes during the maintenance period |
|-----------------|-----------------------------------------------------------------------------------------------------|

End point description:

Percentage of subjects who experienced one or more severe hypoglycaemic episodes during the maintenance period. Severe hypoglycaemia (according to the American Diabetes Association 2013 definition): A hypoglycaemic episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose values may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration. The trial followed a cross over design. Descriptive analysis was based on the SAS (N=500). Number of subjects analysed=subjects with available data for the endpoint as per individual trial product. Statistical analysis was based on the subjects in the FAS (N=501) who were exposed in both the maintenance periods (i.e., N=403).

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

End point timeframe:

After 16 weeks of treatment, in each treatment period (Week 16-32 and Week 48-64)

| End point values              | Insulin degludec (IDeg) | Insulin glargine (IGlar) |  |  |
|-------------------------------|-------------------------|--------------------------|--|--|
| Subject group type            | Subject analysis set    | Subject analysis set     |  |  |
| Number of subjects analysed   | 418                     | 422                      |  |  |
| Units: Percentage of subjects |                         |                          |  |  |
| number (not applicable)       | 10.3                    | 17.1                     |  |  |

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Stepwise hierarchical testing procedure was applied for confirmatory endpoints: Step 3: Proportion of subjects with one or more severe hypoglycaemic episodes during the maintenance period. Due to cross-

over design of the study, the following "number of subjects included in analysis" is being erroneously displayed as 840. Actual "number of subjects included in analysis" is 403.

|                                         |                                                    |
|-----------------------------------------|----------------------------------------------------|
| Comparison groups                       | Insulin degludec (IDeg) v Insulin glargine (IGlar) |
| Number of subjects included in analysis | 840                                                |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority <sup>[3]</sup>                         |
| P-value                                 | = 0.0016                                           |
| Method                                  | McNemar                                            |

Notes:

[3] - Superiority was confirmed if the p-value was less than 0.025.

## Secondary: Incidence of treatment emergent adverse events

|                                                                                                                                                                                                                                                                                                                                                                    |                                                |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                    | Incidence of treatment emergent adverse events |
| End point description:<br>Treatment emergent adverse event was defined as an event with onset date on or after the first day of exposure to randomised treatment and no later than the last day of randomised treatment. The trial followed a cross over design. Results are based on the SAS (N=500). Total "number of subjects analysed" for this endpoint: 500. |                                                |
| End point type                                                                                                                                                                                                                                                                                                                                                     | Secondary                                      |
| End point timeframe:<br>During 32 weeks of treatment for each treatment period                                                                                                                                                                                                                                                                                     |                                                |

| End point values            | Insulin degludec (IDeg) | Insulin glargine (IGlar) |  |  |
|-----------------------------|-------------------------|--------------------------|--|--|
| Subject group type          | Subject analysis set    | Subject analysis set     |  |  |
| Number of subjects analysed | 454                     | 460                      |  |  |
| Units: Event                | 925                     | 937                      |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in HbA1c (glycosylated haemoglobin)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                          |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Change from baseline in HbA1c (glycosylated haemoglobin) |
| End point description:<br>Change from baseline in HbA1c (glycosylated haemoglobin) at week 32 (treatment period 1) and at week 64 (treatment period 2). Week 32 HbA1c absolute values were considered as baseline for calculating change from baseline in HbA1c at week 64. Week 32 HbA1c absolute values: mean (standard deviation) = 6.9% (0.9) and 6.8% (0.8) for IDeg/IGlar and IGlar/IDeg treatment groups, respectively. Both descriptive analysis and statistical analysis were based on the FAS (n=501). Here, 'n' specifies the number of subjects with available data at specified time-point. |                                                          |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Secondary                                                |
| End point timeframe:<br>Week 32, Week 64                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                          |

| End point values                              | Insulin degludec/insulin glargine (IDeg/IGlar) | Insulin glargine/insulin degludec (IGlar/IDeg) |  |  |
|-----------------------------------------------|------------------------------------------------|------------------------------------------------|--|--|
| Subject group type                            | Reporting group                                | Reporting group                                |  |  |
| Number of subjects analysed                   | 249                                            | 252                                            |  |  |
| Units: Percentage of glycosylated haemoglobin |                                                |                                                |  |  |
| arithmetic mean (standard deviation)          |                                                |                                                |  |  |
| week 32 (n=209, 205)                          | -0.73 (± 0.89)                                 | -0.66 (± 0.76)                                 |  |  |
| week 64 (n=203, 199)                          | 0.04 (± 0.51)                                  | 0.17 (± 0.64)                                  |  |  |

## Statistical analyses

| Statistical analysis title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Statistical Analysis 1                                                                          |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Statistical analysis description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                 |
| Change from baseline in HbA1c at week 32 (treatment period 1). Before testing the primary endpoint, the secondary supportive efficacy endpoint "Change from baseline in HbA1c after 32 weeks of treatment" was tested for non-inferiority as a prerequisite for testing the primary endpoint. Analysis was based on mixed model for repeated measurement (MMRM); treatment, sex, region, pre-trial insulin treatment regimen, visit and dosing time were fixed effects, and age and baseline HbA1c were covariates. |                                                                                                 |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Insulin degludec/insulin glargine (IDeg/IGlar) v Insulin glargine/insulin degludec (IGlar/IDeg) |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 501                                                                                             |
| Analysis specification                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Pre-specified                                                                                   |
| Analysis type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | non-inferiority <sup>[4]</sup>                                                                  |
| Parameter estimate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Treatment contrast                                                                              |
| Point estimate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 0.03                                                                                            |
| Confidence interval                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                 |
| level                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 95 %                                                                                            |
| sides                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 2-sided                                                                                         |
| lower limit                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | -0.1                                                                                            |
| upper limit                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 0.15                                                                                            |

Notes:

[4] - Non-inferiority was considered confirmed if the upper bound of the two-sided 95% confidence interval was below or equal to 0.40%. The above comparison groups should be read as: "IDeg versus IGlar". Due to cross-over design of the study, the above "number of subjects included in analysis" is being erroneously displayed as 501. Actual "number of subjects included in analysis" is 437 (n=220 for IDeg and n=217 for IGlar).

| Statistical analysis title                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Statistical Analysis 2                                                                          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Statistical analysis description:                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                 |
| Change from baseline in HbA1c at week 64 (treatment period 2). Before the primary endpoint was tested, the secondary supportive efficacy endpoint "Change from baseline in HbA1c after 32 weeks of treatment" was tested for non-inferiority as prerequisite for testing the primary endpoint. Analysis was based on MMRM; treatment, sex, region, pre-trial insulin treatment regimen, visit and dosing time were fixed effects, and age and baseline HbA1c were covariates. |                                                                                                 |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Insulin degludec/insulin glargine (IDeg/IGlar) v Insulin glargine/insulin degludec (IGlar/IDeg) |

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 501                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority <sup>[5]</sup> |
| Parameter estimate                      | Treatment contrast             |
| Point estimate                          | 0.11                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 0                              |
| upper limit                             | 0.23                           |

Notes:

[5] - For this analysis, Week 32 HbA1c absolute values were considered as baseline. Non-inferiority was considered confirmed if the upper bound of the two-sided 95% confidence interval was below or equal to 0.40%. The above comparison groups should be read as: "IDeg versus IGlär". Due to cross-over design of the study, the above "number of subjects included in analysis" is being erroneously displayed as 501. Actual "number of subjects included in analysis" is 410 (n=202 for IDeg and n=208 for IGlär).

## Secondary: FPG (Fasting plasma glucose)

|                                                                                                                                                                                     |                              |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| End point title                                                                                                                                                                     | FPG (Fasting plasma glucose) |
| End point description:                                                                                                                                                              |                              |
| Fasting plasma glucose values at week 32 and week 64. Results are based on the FAS (N=501). Here, 'n' specifies the number of subjects with available data at specified time-point. |                              |
| End point type                                                                                                                                                                      | Secondary                    |
| End point timeframe:                                                                                                                                                                |                              |
| Week 32, Week 64                                                                                                                                                                    |                              |

| End point values                     | Insulin<br>degludec/insulin<br>glargine<br>(IDeg/IGlar) | Insulin<br>glargine/insulin<br>degludec<br>(IGlar/IDeg) |  |  |
|--------------------------------------|---------------------------------------------------------|---------------------------------------------------------|--|--|
| Subject group type                   | Reporting group                                         | Reporting group                                         |  |  |
| Number of subjects analysed          | 249                                                     | 252                                                     |  |  |
| Units: mmol/L                        |                                                         |                                                         |  |  |
| arithmetic mean (standard deviation) |                                                         |                                                         |  |  |
| week 32 (n=208, 204)                 | 7.45 (± 3.57)                                           | 8.12 (± 3.56)                                           |  |  |
| week 64 (n=203, 201)                 | 8.62 (± 4.24)                                           | 7.54 (± 3.68)                                           |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first day of exposure to randomised treatment and no later than the last day of randomised treatment (64 weeks).

Adverse event reporting additional description:

The trial followed a cross over design. Subjects in the SAS (N=500) contributed to the evaluation of adverse events. Treatment emergent adverse event was defined as an event that has onset date on or after the first day of exposure to randomised treatment and no later than the last day of randomised treatment.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 18.1   |

### Reporting groups

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Insulin glargine (IGlar) |
|-----------------------|--------------------------|

Reporting group description:

Subjects received IGlar in treatment period 1 (from treatment sequence IGlar/IDeg) and in treatment period 2 (from treatment sequence IDeg/IGlar). Each treatment period consisted of a 16-week titration period and a 16-week maintenance period (total 32 weeks for each treatment period).

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Insulin degludec (IDeg) |
|-----------------------|-------------------------|

Reporting group description:

Subjects received IDeg in treatment period 1 (from treatment sequence IDeg/IGlar) and in treatment period 2 (from treatment sequence IGlar/IDeg). Each treatment period consisted of a 16-week titration period and a 16-week maintenance period (total 32 weeks for each treatment period).

| Serious adverse events                                              | Insulin glargine (IGlar) | Insulin degludec (IDeg) |  |
|---------------------------------------------------------------------|--------------------------|-------------------------|--|
| Total subjects affected by serious adverse events                   |                          |                         |  |
| subjects affected / exposed                                         | 70 / 460 (15.22%)        | 58 / 454 (12.78%)       |  |
| number of deaths (all causes)                                       | 2                        | 1                       |  |
| number of deaths resulting from adverse events                      | 0                        | 0                       |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                          |                         |  |
| Breast cancer in situ                                               |                          |                         |  |
| subjects affected / exposed                                         | 0 / 460 (0.00%)          | 1 / 454 (0.22%)         |  |
| occurrences causally related to treatment / all                     | 0 / 0                    | 0 / 1                   |  |
| deaths causally related to treatment / all                          | 0 / 0                    | 0 / 0                   |  |
| Papillary thyroid cancer                                            |                          |                         |  |
| subjects affected / exposed                                         | 0 / 460 (0.00%)          | 1 / 454 (0.22%)         |  |
| occurrences causally related to treatment / all                     | 0 / 0                    | 0 / 1                   |  |
| deaths causally related to treatment / all                          | 0 / 0                    | 0 / 0                   |  |
| Uterine leiomyoma                                                   |                          |                         |  |

|                                                      |                 |                 |  |
|------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 460 (0.00%) | 2 / 454 (0.44%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Vascular disorders                                   |                 |                 |  |
| Haematoma                                            |                 |                 |  |
| subjects affected / exposed                          | 0 / 460 (0.00%) | 1 / 454 (0.22%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Surgical and medical procedures                      |                 |                 |  |
| Pancreas transplant                                  |                 |                 |  |
| subjects affected / exposed                          | 0 / 460 (0.00%) | 1 / 454 (0.22%) |  |
| 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 |                 |                 |  |
| Non-cardiac chest pain                               |                 |                 |  |
| subjects affected / exposed                          | 0 / 460 (0.00%) | 1 / 454 (0.22%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Pyrexia                                              |                 |                 |  |
| subjects affected / exposed                          | 1 / 460 (0.22%) | 0 / 454 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders      |                 |                 |  |
| Pneumothorax                                         |                 |                 |  |
| subjects affected / exposed                          | 0 / 460 (0.00%) | 1 / 454 (0.22%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                                |                 |                 |  |
| Mental status changes                                |                 |                 |  |
| subjects affected / exposed                          | 1 / 460 (0.22%) | 0 / 454 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Schizophrenia                                        |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 460 (0.00%) | 1 / 454 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Accidental overdose                             |                 |                 |  |
| subjects affected / exposed                     | 3 / 460 (0.65%) | 2 / 454 (0.44%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fall                                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 460 (0.00%) | 2 / 454 (0.44%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gun shot wound                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 460 (0.00%) | 1 / 454 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Overdose                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 460 (0.22%) | 0 / 454 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pelvic fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 460 (0.22%) | 0 / 454 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory fume inhalation disorder            |                 |                 |  |
| subjects affected / exposed                     | 0 / 460 (0.00%) | 1 / 454 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Road traffic accident                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 460 (0.22%) | 0 / 454 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tibia fracture                                  |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 460 (0.00%) | 1 / 454 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Cardiac disorders</b>                        |                 |                 |  |
| Acute coronary syndrome                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 460 (0.22%) | 0 / 454 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Acute myocardial infarction                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 460 (0.22%) | 1 / 454 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Supraventricular tachycardia                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 460 (0.22%) | 0 / 454 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ventricular tachycardia                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 460 (0.00%) | 1 / 454 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wolff-Parkinson-White syndrome                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 460 (0.22%) | 0 / 454 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Nervous system disorders</b>                 |                 |                 |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 460 (0.00%) | 1 / 454 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dizziness                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 460 (0.22%) | 0 / 454 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Headache                                        |                 |                 |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 460 (0.22%)  | 0 / 454 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoglycaemic coma                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 460 (0.22%)  | 0 / 454 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoglycaemic seizure                           |                  |                  |  |
| subjects affected / exposed                     | 5 / 460 (1.09%)  | 3 / 454 (0.66%)  |  |
| occurrences causally related to treatment / all | 3 / 5            | 5 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoglycaemic unconsciousness                   |                  |                  |  |
| subjects affected / exposed                     | 19 / 460 (4.13%) | 18 / 454 (3.96%) |  |
| occurrences causally related to treatment / all | 17 / 24          | 18 / 23          |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Loss of consciousness                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 460 (0.22%)  | 0 / 454 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Multiple sclerosis                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 460 (0.22%)  | 0 / 454 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Optic neuritis                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 460 (0.22%)  | 0 / 454 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Syncope                                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 460 (0.22%)  | 0 / 454 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Eye disorders                                   |                  |                  |  |
| Optic ischaemic neuropathy                      |                  |                  |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 460 (0.22%) | 0 / 454 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Gastrointestinal disorders</b>               |                 |                 |  |
| <b>Abdominal pain</b>                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 460 (0.22%) | 0 / 454 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Ascites</b>                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 460 (0.22%) | 0 / 454 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Colitis</b>                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 460 (0.22%) | 0 / 454 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Constipation</b>                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 460 (0.22%) | 0 / 454 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Gastrointestinal haemorrhage</b>             |                 |                 |  |
| subjects affected / exposed                     | 0 / 460 (0.00%) | 1 / 454 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Ileus</b>                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 460 (0.22%) | 0 / 454 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Impaired gastric emptying</b>                |                 |                 |  |
| subjects affected / exposed                     | 1 / 460 (0.22%) | 1 / 454 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Large intestine polyp</b>                    |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 460 (0.00%) | 1 / 454 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 460 (0.22%) | 0 / 454 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting                                        |                 |                 |  |
| subjects affected / exposed                     | 2 / 460 (0.43%) | 1 / 454 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Biliary dyskinesia                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 460 (0.00%) | 1 / 454 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholelithiasis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 460 (0.00%) | 1 / 454 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Calculus ureteric                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 460 (0.22%) | 0 / 454 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Intervertebral disc degeneration                |                 |                 |  |
| subjects affected / exposed                     | 1 / 460 (0.22%) | 0 / 454 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intervertebral disc displacement                |                 |                 |  |
| subjects affected / exposed                     | 1 / 460 (0.22%) | 0 / 454 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Lumbar spinal stenosis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 460 (0.00%) | 1 / 454 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rhabdomyolysis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 460 (0.22%) | 0 / 454 (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                     |                 |                 |  |
| Bacterial sepsis                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 460 (0.00%) | 1 / 454 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 460 (0.00%) | 2 / 454 (0.44%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridium difficile colitis                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 460 (0.00%) | 1 / 454 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fungal skin infection                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 460 (0.22%) | 0 / 454 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Influenza                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 460 (0.00%) | 1 / 454 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteomyelitis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 460 (0.22%) | 1 / 454 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 460 (0.65%)  | 2 / 454 (0.44%)  |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Pneumonia bacterial                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 460 (0.00%)  | 1 / 454 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sepsis                                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 460 (0.00%)  | 1 / 454 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metabolism and nutrition disorders              |                  |                  |  |
| Dehydration                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 460 (0.22%)  | 0 / 454 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic ketoacidosis                           |                  |                  |  |
| subjects affected / exposed                     | 3 / 460 (0.65%)  | 2 / 454 (0.44%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoglycaemia                                   |                  |                  |  |
| subjects affected / exposed                     | 33 / 460 (7.17%) | 17 / 454 (3.74%) |  |
| occurrences causally related to treatment / all | 34 / 47          | 23 / 32          |  |
| 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>                     | Insulin glargine (IGlar) | Insulin degludec (IDeg) |  |
|-------------------------------------------------------|--------------------------|-------------------------|--|
| Total subjects affected by non-serious adverse events |                          |                         |  |
| subjects affected / exposed                           | 97 / 460 (21.09%)        | 97 / 454 (21.37%)       |  |
| Infections and infestations                           |                          |                         |  |
| Nasopharyngitis                                       |                          |                         |  |
| subjects affected / exposed                           | 61 / 460 (13.26%)        | 68 / 454 (14.98%)       |  |
| occurrences (all)                                     | 73                       | 92                      |  |

|                                                                                       |                        |                        |  |
|---------------------------------------------------------------------------------------|------------------------|------------------------|--|
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 39 / 460 (8.48%)<br>41 | 29 / 454 (6.39%)<br>34 |  |
|---------------------------------------------------------------------------------------|------------------------|------------------------|--|

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 12 August 2014    | Amendment-1: Due to major challenges in recruiting the population described in protocol version 5.0 dated 22-Oct-2013, a broadening of inclusion criteria was needed. This amendment was prepared in order to broaden the inclusion criteria to include subjects using continuous subcutaneous insulin infusion (CSII), to increase the upper limit of HbA1c to $\leq 10\%$ and to increase the upper limit of BMI to $\leq 45$ kg/m <sup>2</sup> . Exclusion criterion 4 was altered to allow short-term use of IGLar prior to screening. Short term use ( $\leq 2$ weeks) before the last 4 weeks prior to inclusion is not believed to bias the study as this would not require subjects to adapt their lifestyle to a specific insulin profile. Finally, a note has been added to exclusion criterion 2, allowing subjects that were screening failures due to inclusion criteria 5, 6 and 7 and exclusion criterion 4 in protocol version 5.0 dated 22-Oct-2013 to be re-screened according to this protocol amendment. A EudraCT number has been added as Poland was added to the trial. |
| 18 September 2014 | Amendment-2: This amendment was created to clarify that bolus insulin may include both rapid acting and fast acting insulin. This amendment also clarifies that review of patient reported outcome (PRO) questionnaires for adverse events and/or change in overall health and concomitant medication could be done by any medically qualified site staff delegated by the investigator.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 01 December 2015  | Amendment-3: The analysis of HbA1c specified in protocol version 7.0 dated 25-Jul-2014 was not in alignment with Novo Nordisk's response to FDA's comments to the Special Protocol Assessment on this study. This protocol amendment was created to reflect the response to the FDA, as the analysis is a prerequisite for performing the primary analysis.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported