



## Clinical trial results:

### **Efficacy and safety of fast-acting Insulin Aspart compared to NovoRapid® both in combination with Insulin Degludec with or without metformin in adults with type 2 diabetes (onset® 9)**

#### **Summary**

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2016-000878-38       |
| Trial protocol           | BG CZ ES GR DE HR IT |
| Global end of trial date | 29 January 2019      |

#### **Results information**

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 13 February 2020 |
| First version publication date | 13 February 2020 |

#### **Trial information**

##### **Trial identification**

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | NN1218-4113 |
|-----------------------|-------------|

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

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | NCT03268005     |
| WHO universal trial number (UTN)   | U1111-1180-0636 |

Notes:

##### **Sponsors**

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

Notes:

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

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

Notes:

## Results analysis stage

|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 20 June 2019    |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 07 January 2019 |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 29 January 2019 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To confirm the effect in terms of glycaemic control of treatment with fast-acting insulin aspart compared to NovoRapid® both in combination with insulin degludec with or without metformin in adults with type 2 diabetes treated with a basal-bolus regimen, using a non-inferiority approach.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator:

Not applicable

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 19 September 2017 |
| Long term follow-up planned                               | No                |
| Independent data monitoring committee (IDMC) involvement? | No                |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 40          |
| Country: Number of subjects enrolled | Bulgaria: 41           |
| Country: Number of subjects enrolled | Canada: 49             |
| Country: Number of subjects enrolled | Czech Republic: 25     |
| Country: Number of subjects enrolled | Germany: 32            |
| Country: Number of subjects enrolled | Spain: 70              |
| Country: Number of subjects enrolled | Greece: 57             |
| Country: Number of subjects enrolled | Croatia: 25            |
| Country: Number of subjects enrolled | Italy: 38              |
| Country: Number of subjects enrolled | Korea, Republic of: 58 |
| Country: Number of subjects enrolled | Poland: 60             |
| Country: Number of subjects enrolled | Romania: 44            |
| Country: Number of subjects enrolled | Russian Federation: 64 |
| Country: Number of subjects enrolled | Serbia: 75             |
| Country: Number of subjects enrolled | Slovakia: 42           |
| Country: Number of subjects enrolled | Ukraine: 51            |
| Country: Number of subjects enrolled | United States: 320     |
| Worldwide total number of subjects   | 1091                   |
| EEA total number of subjects         | 434                    |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 625 |
| From 65 to 84 years                       | 461 |
| 85 years and over                         | 5   |

## Subject disposition

### Recruitment

Recruitment details:

The trial was conducted at 165 sites in 17 countries as follows: Argentina-3, Bulgaria-4, Canada-10, Croatia-4, Czech Republic-4, Germany-6, Greece-8, Italy-4, Poland-6, Republic of Korea-10, Romania-6, Russia-8, Serbia-9, Slovakia-5, Spain-8, Ukraine-6 and United States (US)-62. Two sites in the US screened but didn't randomise any subject.

### Pre-assignment

Screening details:

There was a 12-week run-in period primarily for optimisation of the basal insulin and reinforcement of subject training in trial procedures, diabetes education and dietary training. During the run-in period, the investigator focused on optimising the basal insulin treatment using a treat-to-target approach.

### 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>             | Faster aspart |

Arm description:

Subjects received faster aspart along with insulin degludec (basal-bolus regimen) with or without metformin for 16 weeks. Before the treatment period was a 12-week run-in period in which the investigator optimised basal insulin dose.

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Faster aspart    |
| Investigational medicinal product code |                  |
| Other name                             | Fiasp®           |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

Dosage and administration details:

Insulin degludec dose was adjusted weekly by the investigator in the run-in period based on the mean of three pre-breakfast SMPG values measured on the last two days prior to and on the day of contact. If one of the SMPG values were below target ( $< 4.0$  mmol/L or 71 mg/dL) then the insulin degludec dose was adjusted according to the titration guideline specified in the protocol. Faster aspart was titrated from randomisation (week 0) and onwards, twice weekly to reach the glycaemic target of pre-prandial and bedtime PG between 4.0-6.0 mmol/L (71 - 108 mg/dL) in a treat-to-target fashion. Insulin degludec was administered once daily, at any time of the day but preferably the same time every day, into the thigh or upper arm. Faster aspart was injected 0-2 minutes prior to meals, into the abdominal wall.

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

Arm description:

Subjects received insulin aspart (NovoRapid®/NovoLog®: basal-bolus regimen) with or without metformin for 16 weeks. Before the treatment period was a 12-week run-in period in which the investigator optimised basal insulin dose.

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Insulin aspart   |
| Investigational medicinal product code |                  |
| Other name                             | NovoLog®         |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

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**Dosage and administration details:**

Insulin degludec dose was adjusted weekly by the investigator in the run-in period based on the mean of three pre-breakfast SMPG values measured on the last two days prior to and on the day of contact. If one of the SMPG values were below target (< 4.0 mmol/L or 71 mg/dL) then the insulin degludec dose was adjusted according to the titration guideline specified in the protocol. NovoRapid was titrated from randomisation (week 0) and onwards, twice weekly to reach the glycaemic target of pre-prandial and bedtime PG between 4.0-6.0 mmol/L (71 - 108 mg/dL) in a treat-to-target fashion. Insulin degludec was administered once daily, at any time of the day but preferably the same time every day, into the thigh or upper arm. NovoRapid was injected 0-2 minutes prior to meals, into the abdominal wall.

| <b>Number of subjects in period 1</b> | Faster aspart | NovoRapid |
|---------------------------------------|---------------|-----------|
| Started                               | 546           | 545       |
| Completed                             | 531           | 531       |
| Not completed                         | 15            | 14        |
| Adverse event, serious fatal          | 2             | 1         |
| Consent withdrawn by subject          | 11            | 11        |
| Lost to follow-up                     | 2             | 2         |

## Baseline characteristics

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Faster aspart |
|-----------------------|---------------|

Reporting group description:

Subjects received faster aspart along with insulin degludec (basal-bolus regimen) with or without metformin for 16 weeks. Before the treatment period was a 12-week run-in period in which the investigator optimised basal insulin dose.

|                       |           |
|-----------------------|-----------|
| Reporting group title | NovoRapid |
|-----------------------|-----------|

Reporting group description:

Subjects received insulin aspart (NovoRapid®/NovoLog®: basal-bolus regimen) with or without metformin for 16 weeks. Before the treatment period was a 12-week run-in period in which the investigator optimised basal insulin dose.

| Reporting group values   | Faster aspart | NovoRapid | Total |
|--------------------------|---------------|-----------|-------|
| Number of subjects       | 546           | 545       | 1091  |
| Age categorical          |               |           |       |
| Units: Subjects          |               |           |       |
| Adults (18-64 years)     | 301           | 324       | 625   |
| From 65-84 years         | 240           | 221       | 461   |
| 85 years and over        | 5             | 0         | 5     |
| Age Continuous           |               |           |       |
| Units: Years             |               |           |       |
| arithmetic mean          | 62.6          | 62.1      |       |
| standard deviation       | ± 8.6         | ± 8.8     | -     |
| Sex: Female, Male        |               |           |       |
| Gender Categorical       |               |           |       |
| Units: Participants      |               |           |       |
| Male                     | 265           | 289       | 554   |
| Female                   | 281           | 256       | 537   |
| HbA1c                    |               |           |       |
| Glycosylated haemoglobin |               |           |       |
| Units: %-points          |               |           |       |
| arithmetic mean          | 7.15          | 7.05      |       |
| standard deviation       | ± 0.77        | ± 0.70    | -     |

## End points

### End points reporting groups

|   |               |
|---|---------------|
| Reporting group title   | Faster aspart |
| Reporting group description:<br>Subjects received faster aspart along with insulin degludec (basal-bolus regimen) with or without metformin for 16 weeks. Before the treatment period was a 12-week run-in period in which the investigator optimised basal insulin dose. |               |
| Reporting group title   | NovoRapid     |
| Reporting group description:<br>Subjects received insulin aspart (NovoRapid®/NovoLog®: basal-bolus regimen) with or without metformin for 16 weeks. Before the treatment period was a 12-week run-in period in which the investigator optimised basal insulin dose.       |               |

### Primary: Change from baseline in HbA1c

|  |                               |
|--|-------------------------------|
| End point title  | Change from baseline in HbA1c |
| End point description:<br>Change from baseline (week 0) in glycosylated haemoglobin (HbA1c) was evaluated at week 16. The endpoint was evaluated based on data from the in-trial observation period. In-trial observation period was from date of randomisation and until last trial-related participant-site contact. |                               |
| End point type   | Primary                       |
| End point timeframe:<br>16 weeks after randomisation   |                               |

| End point values                     | Faster aspart   | NovoRapid       |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 544             | 539             |  |  |
| Units: Percentage of HbA1c           |                 |                 |  |  |
| arithmetic mean (standard deviation) | -0.15 (± 0.62)  | -0.09 (± 0.60)  |  |  |

### Statistical analyses

|   |                            |
|---|----------------------------|
| Statistical analysis title  | Faster aspart vs NovoRapid |
| Statistical analysis description:<br>Change from baseline in HbA1c was analysed using an analysis of variance model after multiple imputation assuming treatment according to randomisation. The model included treatment, region and metformin use at baseline (Yes/No) as factors, and baseline HbA1c as a covariate. |                            |
| Comparison groups   | Faster aspart v NovoRapid  |
| Number of subjects included in analysis   | 1083                       |
| Analysis specification  | Pre-specified              |
| Analysis type   |                            |
| P-value   | = 0.31                     |
| Method  | ANOVA                      |
| Parameter estimate  | Treatment difference       |
| Point estimate  | -0.04                      |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -0.11   |
| upper limit         | 0.03    |

### Secondary: Change from baseline in 1-hour postprandial glucose increment (meal test)

|   |   |
|---|---|
| End point title   | Change from baseline in 1-hour postprandial glucose increment (meal test) |
| End point description:<br>Change from baseline (week 0) in 1-hour postprandial glucose (PPG) increment was evaluated after 16 weeks of randomisation. The results are based on the last in-trial value, which included the last available measurement in the in-trial period. In trial observation period was from date of randomisation and until last trial-related participant-site contact. |   |
| End point type  | Secondary   |
| End point timeframe:<br>16 weeks after randomisation  |   |

| End point values                     | Faster aspart   | NovoRapid       |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 519             | 523             |  |  |
| Units: mmol/L                        |                 |                 |  |  |
| arithmetic mean (standard deviation) | -0.43 (± 2.45)  | 0.08 (± 2.65)   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in 1,5-anhydroglucitol

|   |   |
|---|---|
| End point title   | Change from baseline in 1,5-anhydroglucitol |
| End point description:<br>Change from baseline (week 0) in 1,5-anhydroglucitol was evaluated after 16 weeks of randomisation. The results are based on the last in-trial value, which included the last available measurement in the in-trial period. In trial observation period was from date of randomisation and until last trial-related participant-site contact. |   |
| End point type  | Secondary                                   |
| End point timeframe:<br>16 weeks after randomisation  |   |

|                                      |                 |                 |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>              | Faster aspart   | NovoRapid       |  |  |
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 534             | 531             |  |  |
| Units: mmol/L                        |                 |                 |  |  |
| arithmetic mean (standard deviation) | 1.38 (± 3.10)   | 0.89 (± 3.31)   |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Week 0 to Week 16 + 7 days. All reported AEs are treatment emergent (i.e., TEAE).

Adverse event reporting additional description:

Results are based on the SAS. All presented AEs are TEAEs which were recorded during the exposure to trial products. AEs with onset during the on-treatment observation period were considered treatment-emergent. Number of deaths causally related to treatment is the data considered to present under 'total number of deaths resulting from AEs.

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 21 |
|--------------------|----|

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Faster aspart |
|-----------------------|---------------|

Reporting group description:

Subjects received Faster aspart along with insulin degludec (basal-bolus regimen) with or without metformin for 16 weeks. Before the treatment period was a 12-week run-in period in which the investigator optimised basal insulin dose. Insulin degludec dose was adjusted weekly by the investigator in the run-in period based on the mean of three pre-breakfast SMPG values measured on the last two days prior to and on the day of contact. If one of the SMPG values were below target ( $< 4.0$  mmol/L or 71 mg/dL) then the insulin degludec dose was adjusted according to the titration guideline specified in the protocol. Faster aspart was titrated from randomisation (week 0) and onwards, twice weekly to reach the glycaemic target of pre-prandial and bedtime PG between 4.0-6.0 mmol/L (71 - 108 mg/dL) in a treat-to-target fashion.

|                       |           |
|-----------------------|-----------|
| Reporting group title | NovoRapid |
|-----------------------|-----------|

Reporting group description:

Subjects received insulin aspart (NovoRapid®/NovoLog®: basal-bolus regimen) with or without metformin for 16 weeks. Before the treatment period was a 12-week run-in period in which the investigator optimised basal insulin dose. Insulin degludec dose was adjusted weekly by the investigator in the run-in period based on the mean of three pre-breakfast SMPG values measured on the last two days prior to and on the day of contact. If one of the SMPG values were below target ( $< 4.0$  mmol/L or 71 mg/dL) then the insulin degludec dose was adjusted according to the titration guideline specified in the protocol. NovoRapid was titrated from randomisation (week 0) and onwards, twice weekly to reach the glycaemic target of pre-prandial and bedtime PG between 4.0-6.0 mmol/L (71 - 108 mg/dL) in a treat-to-target fashion.

| Serious adverse events  | Faster aspart    | NovoRapid        |  |
|---|------------------|------------------|--|
| Total subjects affected by serious adverse events                   |                  |                  |  |
| subjects affected / exposed   | 38 / 544 (6.99%) | 40 / 544 (7.35%) |  |
| number of deaths (all causes)                                       | 2                | 1                |  |
| number of deaths resulting from adverse events                      | 1                | 0                |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                  |  |
| Adenocarcinoma of colon   |                  |                  |  |
| subjects affected / exposed   | 1 / 544 (0.18%)  | 0 / 544 (0.00%)  |  |
| occurrences causally related to treatment / all                     | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0            |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Hepatocellular carcinoma                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Invasive ductal breast carcinoma                |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung neoplasm malignant                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatic carcinoma metastatic                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |
| Aortic aneurysm                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Deep vein thrombosis                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypotension                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral vascular disorder                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subclavian vein occlusion                       |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Varicose ulceration                                  |                 |                 |  |
| subjects affected / exposed                          | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Surgical and medical procedures                      |                 |                 |  |
| Aortic valve replacement                             |                 |                 |  |
| subjects affected / exposed                          | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Carpal tunnel decompression                          |                 |                 |  |
| subjects affected / exposed                          | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Rehabilitation therapy                               |                 |                 |  |
| subjects affected / exposed                          | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Vitrectomy   |                 |                 |  |
| subjects affected / exposed                          | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Chest pain   |                 |                 |  |
| subjects affected / exposed                          | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Pain   |                 |                 |  |
| subjects affected / exposed                          | 1 / 544 (0.18%) | 0 / 544 (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 |                 |                 |  |
| Chronic obstructive pulmonary disease           |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 2 / 544 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary oedema                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Delusion  |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rapid eye movements sleep abnormal              |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Product issues                                  |                 |                 |  |
| Device malfunction                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Cardiac stress test abnormal                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Accidental overdose                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 544 (0.37%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Contusion                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fall  |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fibula fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Humerus fracture                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Road traffic accident                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wrong product administered                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Acute coronary syndrome                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 544 (0.37%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Acute myocardial infarction                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina pectoris                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 2 / 544 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina unstable                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arteriosclerosis coronary artery                |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bradycardia                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure                                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 544 (0.37%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure congestive                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 2 / 544 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery disease                         |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 544 (0.00%) | 2 / 544 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Left ventricular failure                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mitral valve incompetence                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Cerebellar infarction                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetic neuropathy                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dizziness                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 2 / 544 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Encephalopathy                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhagic stroke                             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Headache  |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycaemic unconsciousness                   |                 |                 |  |
| subjects affected / exposed                     | 3 / 544 (0.55%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transient ischaemic attack                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 544 (0.37%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular parkinsonism                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Haemorrhagic anaemia                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Iron deficiency anaemia                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye disorders                                   |                 |                 |  |
| Vitreous haemorrhage                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Colitis   |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cyclic vomiting syndrome                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal ulcer                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastritis erosive                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Obstructive pancreatitis                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Small intestinal obstruction                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Bile duct obstruction                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Arthritis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (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 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal pain                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Trigger finger                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Bronchitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related sepsis                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Gangrene  |                 |                 |  |
| subjects affected / exposed                                   | 0 / 544 (0.00%) | 2 / 544 (0.37%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Gastroenteritis viral   |                 |                 |  |
| subjects affected / exposed                                   | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Infective exacerbation of chronic obstructive airways disease |                 |                 |  |
| subjects affected / exposed                                   | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Lower respiratory tract infection                             |                 |                 |  |
| subjects affected / exposed                                   | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Orchitis  |                 |                 |  |
| subjects affected / exposed                                   | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Osteomyelitis   |                 |                 |  |
| subjects affected / exposed                                   | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Pneumonia   |                 |                 |  |
| subjects affected / exposed                                   | 2 / 544 (0.37%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all               | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Respiratory tract infection                                   |                 |                 |  |
| subjects affected / exposed                                   | 0 / 544 (0.00%) | 2 / 544 (0.37%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Upper respiratory tract infection                             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 544 (0.18%) | 0 / 544 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperglycaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 544 (0.00%) | 1 / 544 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 4 / 544 (0.74%) | 3 / 544 (0.55%) |  |
| occurrences causally related to treatment / all | 2 / 4           | 1 / 3           |  |
| 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>                     | Faster aspart    | NovoRapid        |  |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                  |                  |  |
| subjects affected / exposed                           | 32 / 544 (5.88%) | 33 / 544 (6.07%) |  |
| Infections and infestations                           |                  |                  |  |
| Nasopharyngitis                                       |                  |                  |  |
| subjects affected / exposed                           | 32 / 544 (5.88%) | 33 / 544 (6.07%) |  |
| occurrences (all)                                     | 35               | 36               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 20 June 2017     | Criteria for premature discontinuation of trial products was updated with 2 additional criteria: Lack of efficacy Unacceptable adverse event (including toxicity) The master agreement for amendment form was updated to version 2 to include the title of the original protocol and not only the title of the amendment. Both version 1 and 2 was used to document agreement of amendment 1.   |
| 28 February 2018 | Replacement of eDiary requirements with paper diary requirements including change of trial BGM. Throughout the protocol "eDiary" was replaced with "diary". Clarification to titration guideline section Information was provided to investigators in a memo dated 30-Nov-2017 to make it clear that insulin degludec titration was based on SMPGs two days prior to and on day of contact instead of three days prior to contact SI/IC updated with information regarding Personal Data Protection. Minor clarifying updates to protocol text. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Not applicable

Notes: