



## Clinical trial results:

### Efficacy and Safety of Continuous Subcutaneous Insulin Infusion of Faster-acting Insulin Aspart compared to NovoRapid® in Adults with Type 1 Diabetes

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2010-024054-11    |
| Trial protocol           | NL DE BE FR SI GB |
| Global end of trial date | 21 July 2017      |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 25 July 2018 |
| First version publication date | 25 July 2018 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | NN1218-3854 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | NCT02825251     |
| WHO universal trial number (UTN)   | U1111-1118-2480 |

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                       | 08 February 2018 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 20 June 2017     |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 21 July 2017     |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To confirm the effect of CSII treatment with faster aspart in terms of glycaemic control by comparing it to CSII treatment with NovoRapid®/NovoLog®, in adults with Type 1 Diabetes Mellitus (T1DM), using a non-inferiority approach.

Protection of trial subjects:

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

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable.

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 06 July 2016 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Belgium: 36            |
| Country: Number of subjects enrolled | Canada: 45             |
| Country: Number of subjects enrolled | France: 35             |
| Country: Number of subjects enrolled | Germany: 63            |
| Country: Number of subjects enrolled | Netherlands: 20        |
| Country: Number of subjects enrolled | Russian Federation: 55 |
| Country: Number of subjects enrolled | Slovenia: 33           |
| Country: Number of subjects enrolled | United Kingdom: 27     |
| Country: Number of subjects enrolled | United States: 158     |
| Worldwide total number of subjects   | 472                    |
| EEA total number of subjects         | 214                    |

Notes:

### Subjects enrolled per age group

|  |   |
|--|---|
| In utero                               | 0 |
| Preterm newborn - gestational age < 37 | 0 |

|  |     |
|--|-----|
| wk                                       |     |
| 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)                     | 432 |
| From 65 to 84 years                      | 40  |
| 85 years and over                        | 0   |

## Subject disposition

### Recruitment

Recruitment details:

The trial was conducted at 92 sites in 9 countries as follows: Belgium (7), Canada (8), France (10), Germany (9), Netherlands (9), Russian Federation (11), Slovenia (2), United Kingdom (6), and United States (30). One (1) site in the Netherlands screened, but didn't randomise any subject.

### Pre-assignment

Screening details:

There was a 4-week run-in period primarily for reinforcement of subject training in trial procedures, diabetes education and collecting baseline assessments. Subjects remained on their pre-trial insulin treatment during the run-in period.

### 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                | Investigator, Subject          |

Blinding implementation details:

As the trial was blinded with regard to faster aspart and NovoRapid®, only dispensing unit numbers (DUNs) allocated by the interactive voice/web response system (IV/WRS) were dispensed to the subject. Trial products were packaged in non-subject specific boxes.

### Arms

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

Arm description:

The subjects received faster aspart (basal-bolus regimen) by continuous subcutaneous insulin infusion (CSII) for 16 weeks.

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

Dosage and administration details:

Doses of basal and bolus insulin and timing of bolus dose were individually adjusted and thus no maximum dose of insulin was specified. Basal rate insulin adjustment: The purpose of adjusting the basal rates was to ensure that blood glucose (BG) was kept between 4.0–6.0 mmol/L [71–108 mg/dL] while in a fasting state and during the night. Bolus insulin titration: It was recommended that mealtime bolus insulin was titrated based on carbohydrate-counting using the Bolus Wizard® according to their usual practice and according to instructions from the investigator. Meal-time dosing was defined as bolus infusion initiated 0-2 minutes before a meal.

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

Arm description:

The subjects received insulin aspart (NovoRapid®/NovoLog®: basal-bolus regimen) by CSII for 16 weeks.

|  |                        |
|--|------------------------|
| Arm type                               | Active comparator      |
| Investigational medicinal product name | Insulin aspart         |
| Investigational medicinal product code |                        |
| Other name                             | NovoRapid®, NovoLog®   |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

---

**Dosage and administration details:**

Doses of basal and bolus insulin and timing of bolus dose were individually adjusted and thus no maximum dose of insulin was specified. Basal rate insulin adjustment: The purpose of adjusting the basal rates was to ensure that BG was kept between 4.0–6.0 mmol/L [71–108 mg/dL] while in a fasting state and during the night. Bolus insulin titration: It was recommended that meal-time bolus insulin was titrated based on carbohydrate-counting using the Bolus Wizard® according to their usual practice and according to instructions from the investigator. Meal-time dosing was defined as bolus infusion initiated 0-2 minutes before a meal.

| <b>Number of subjects in period 1</b> | Faster aspart | NovoRapid |
|---------------------------------------|---------------|-----------|
| Started                               | 236           | 236       |
| Completed                             | 233           | 230       |
| Not completed                         | 3             | 6         |
| Consent withdrawn by subject          | 1             | 4         |
| Adverse event, non-fatal              | -             | 1         |
| Unclassified                          | 2             | -         |
| Lost to follow-up                     | -             | 1         |

## Baseline characteristics

### Reporting groups

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

Reporting group description:

The subjects received faster aspart (basal-bolus regimen) by continuous subcutaneous insulin infusion (CSII) for 16 weeks.

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

Reporting group description:

The subjects received insulin aspart (NovoRapid®/NovoLog®: basal-bolus regimen) by CSII for 16 weeks.

| Reporting group values | Faster aspart | NovoRapid | Total |
|------------------------|---------------|-----------|-------|
| Number of subjects     | 236           | 236       | 472   |
| Age Categorical        |               |           |       |
| Units: Subjects        |               |           |       |
| Adults (18-64 years)   | 213           | 219       | 432   |
| From 65-84 years       | 23            | 17        | 40    |
| Age Continuous         |               |           |       |
| Units: years           |               |           |       |
| arithmetic mean        | 43.3          | 43.6      |       |
| standard deviation     | ± 14.8        | ± 14.7    | -     |
| Gender Categorical     |               |           |       |
| Units: Subjects        |               |           |       |
| Female                 | 133           | 136       | 269   |
| Male                   | 103           | 100       | 203   |

## End points

### End points reporting groups

|  |               |
|--|---------------|
| Reporting group title  | Faster aspart |
| Reporting group description:<br>The subjects received faster aspart (basal-bolus regimen) by continuous subcutaneous insulin infusion (CSII) for 16 weeks. |               |
| Reporting group title  | NovoRapid     |
| Reporting group description:<br>The subjects received insulin aspart (NovoRapid®/NovoLog®: basal-bolus regimen) by CSII for 16 weeks.                      |               |

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

|  |  |
|--|--|
| End point title  | Change from baseline in glycosylated haemoglobin (HbA1c) |
| End point description:<br>Change from baseline (week 0) in HbA1c was evaluated 16 weeks after randomisation. The results are based on the last in-trial value, which included the last available measurement in the in-trial period. In-trial period: the observation period from date of randomisation until last trial-related subject-site contact. Results are based on the FAS, which included all randomised subjects. Number of subjects analysed = Number of subjects contributed to the analysis. |  |
| 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          | 236             | 236             |  |  |
| Units: Percentage (%) of HbA1c       |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| Baseline                             | 7.49 (± 0.55)   | 7.49 (± 0.53)   |  |  |
| Change from baseline                 | -0.06 (± 0.50)  | -0.14 (± 0.44)  |  |  |

### Statistical analyses

|  |                                |
|--|--------------------------------|
| Statistical analysis title   | Faster aspart versus 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, strata (use of own continuous glucose monitoring), previous insulin use, and region as factors, and baseline HbA1c as a covariate.<br>Non-inferiority of faster aspart was considered confirmed if the upper limit of the two-sided 95 % CI for the true treatment-difference D (faster aspart minus NovoRapid®) was below 0.4 %. |                                |
| Comparison groups  | Faster aspart v NovoRapid      |

|   |                      |
|---|----------------------|
| Number of subjects included in analysis | 472                  |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | non-inferiority      |
| Parameter estimate                      | Treatment difference |
| Point estimate                          | 0.09                 |
| Confidence interval                     |                      |
| level                                   | 95 %                 |
| sides                                   | 2-sided              |
| lower limit                             | 0.01                 |
| upper limit                             | 0.17                 |

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

|  |  |
|--|--|
| End point title  | Change from baseline in 1-hour PPG increment (meal test) |
| End point description:   |  |
| Change from baseline (week 0) in 1-hour postprandial glucose (PPG) increment was evaluated 16 weeks after randomisation. The results are based on the last in-trial value, which included the last available measurement in the in-trial period. Results are based on the FAS, which included all randomised subjects. Number of subjects analysed (N) = Number of subjects contributed to the analysis. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| 16 weeks after randomisation   |  |

| End point values                     | Faster aspart   | NovoRapid       |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 236             | 236             |  |  |
| Units: mmol/L                        |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| Baseline (N = 235, 235)              | 4.67 (± 3.09)   | 4.62 (± 3.00)   |  |  |
| Change from baseline (N = 228, 227)  | -0.89 (± 3.44)  | 0.05 (± 3.37)   |  |  |

### 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:   |   |
| Change from baseline (week 0) in 1,5-anhydroglucitol was evaluated 16 weeks after randomisation. The results are based on the last in-trial value, which included the last available measurement in the in-trial period. Results are based on the FAS, which included all randomised subjects. Number of subjects analysed (N) = Number of subjects contributed to the analysis. |   |
| End point type   | Secondary                                   |
| End point timeframe:   |   |
| 16 weeks after randomisation   |   |



| End point values                     | Faster aspart   | NovoRapid       |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 236             | 236             |  |  |
| Units: ug/mL                         |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| Baseline (N = 233, 234)              | 4.20 (± 2.34)   | 4.13 (± 2.14)   |  |  |
| Change from baseline (N = 233, 234)  | 0.14 (± 1.48)   | 0.25 (± 1.42)   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline of time spent in low IG ( $\leq 3.9$ mmol/L [70 mg/dL]) during CGM

|   |   |
|---|---|
| End point title   | Change from baseline of time spent in low IG ( $\leq 3.9$ mmol/L [70 mg/dL]) during CGM |
| End point description:  |   |
| Change from baseline (week 0) in low interstitial glucose (IG) ( $\leq 3.9$ mmol/L [70 mg/dL]) during continuous glucose monitoring (CGM) was evaluated 16 weeks after randomisation. The results are based on the last in-trial value, which included the last available measurement in the in-trial period. Results are based on the FAS, which included all randomised subjects. Number of subjects analysed (N) = Number of subjects contributed to the analysis. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| 16 weeks after randomisation  |   |

| End point values                     | Faster aspart   | NovoRapid       |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 236             | 236             |  |  |
| Units: min/day                       |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| Baseline (N = 236, 236)              | 85.42 (± 65.20) | 79.88 (± 60.46) |  |  |
| Change from baseline (N = 234, 231)  | -6.96 (± 55.29) | 2.85 (± 58.56)  |  |  |

### 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. Results are based on the safety analysis set, which included all subjects receiving at least one dose of the investigational medicinal product (IMP; faster aspart) or its comparator (NovoRapid®).

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 20     |

### Reporting groups

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

Reporting group description: -

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

Reporting group description: -

| Serious adverse events                            | Faster aspart   | NovoRapid       |  |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events |                 |                 |  |
| subjects affected / exposed                       | 5 / 236 (2.12%) | 8 / 236 (3.39%) |  |
| number of deaths (all causes)                     | 0               | 0               |  |
| number of deaths resulting from adverse events    | 0               | 0               |  |
| Injury, poisoning and procedural complications    |                 |                 |  |
| Accidental overdose                               |                 |                 |  |
| subjects affected / exposed                       | 0 / 236 (0.00%) | 1 / 236 (0.42%) |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Surgical and medical procedures                   |                 |                 |  |
| Pain management                                   |                 |                 |  |
| subjects affected / exposed                       | 0 / 236 (0.00%) | 1 / 236 (0.42%) |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                          |                 |                 |  |
| Hypoglycaemic seizure                             |                 |                 |  |
| subjects affected / exposed                       | 0 / 236 (0.00%) | 1 / 236 (0.42%) |  |
| occurrences causally related to treatment / all   | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Hypoglycaemic unconsciousness                     |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 236 (0.42%) | 1 / 236 (0.42%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 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 / 236 (0.00%) | 1 / 236 (0.42%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Eye disorders  |                 |                 |  |
| Retinal aneurysm                                     |                 |                 |  |
| subjects affected / exposed                          | 0 / 236 (0.00%) | 1 / 236 (0.42%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                           |                 |                 |  |
| Oesophagitis   |                 |                 |  |
| subjects affected / exposed                          | 1 / 236 (0.42%) | 0 / 236 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders               |                 |                 |  |
| Drug eruption  |                 |                 |  |
| subjects affected / exposed                          | 1 / 236 (0.42%) | 0 / 236 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Neurodermatitis                                      |                 |                 |  |
| subjects affected / exposed                          | 0 / 236 (0.00%) | 1 / 236 (0.42%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Infections and infestations                          |                 |                 |  |
| Adenovirus infection                                 |                 |                 |  |
| subjects affected / exposed                          | 0 / 236 (0.00%) | 1 / 236 (0.42%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Appendicitis   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 236 (0.42%) | 0 / 236 (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 breakage                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 236 (0.00%) | 1 / 236 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Hypoglycaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 236 (0.00%) | 1 / 236 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ketoacidosis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 236 (0.42%) | 0 / 236 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Faster aspart     | NovoRapid         |  |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 84 / 236 (35.59%) | 72 / 236 (30.51%) |  |
| General disorders and administration site conditions  |                   |                   |  |
| Infusion site reaction                                |                   |                   |  |
| subjects affected / exposed                           | 16 / 236 (6.78%)  | 7 / 236 (2.97%)   |  |
| occurrences (all)                                     | 26                | 10                |  |
| Infections and infestations                           |                   |                   |  |
| Gastroenteritis                                       |                   |                   |  |
| subjects affected / exposed                           | 12 / 236 (5.08%)  | 6 / 236 (2.54%)   |  |
| occurrences (all)                                     | 12                | 6                 |  |
| Upper respiratory tract infection                     |                   |                   |  |
| subjects affected / exposed                           | 17 / 236 (7.20%)  | 12 / 236 (5.08%)  |  |
| occurrences (all)                                     | 18                | 12                |  |
| Viral upper respiratory tract infection               |                   |                   |  |

|                             |                   |                   |  |
|-----------------------------|-------------------|-------------------|--|
| subjects affected / exposed | 48 / 236 (20.34%) | 50 / 236 (21.19%) |  |
| occurrences (all)           | 60                | 64                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

---

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28918652>