# EU Clinical Trials Register

## Clinical trial results:
## Efficacy and Safety of FIAsp compared to insulin aspart both in Combination with insulin detemir in Adults with Type 1 Diabetes

### Summary

| | |
|---|---|
| EudraCT number | 2010-024049-53 |
| Trial protocol | BE HU CZ GB DE PL FI |
| Global end of trial date | 11 June 2015 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 26 June 2016 |
| First version publication date | 26 June 2016 |

### Trial information

#### Trial identification

| | |
|---|---|
| Sponsor protocol code | NN1218-3852 |

#### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01831765 |
| WHO universal trial number (UTN) | U1111-1118-2442 |

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:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 25 January 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 11 June 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 11 June 2015 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To confirm efficacy of treatment with meal time faster-acting insulin aspart (FIAsp) in terms of glycaemic control measured by change from baseline in glycosylated haemoglobin (HbA1c) after 26 weeks of randomised treatment by comparing it to meal time insulin aspart both in combination with insulin detemir, using a non-inferiority approach.

Protection of trial subjects:

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

Background therapy:

Insulin detemir, a long-acting insulin analogue was used as part of a basal−bolus insulin regimen. During run-in, insulin detemir was titrated in a treat-to-target fashion on a weekly basis to the prebreakfast glycaemic target of 4.0−5.0 mmol/L (71−90 mg/dL) and the predinner glycaemic target of 4.0−6.0 mmol/L (71−108 mg/dL) if the subject was on a twice daily regimen, in accordance with the titration guideline. When needed, dose adjustments of basal insulin were allowed after the run-in period at the discretion of the investigator. However, changing the dose frequency after randomisation was not allowed.

Evidence for comparator:

Not applicable

| | |
|---|---|
| Actual start date of recruitment | 26 August 2013 |
| 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 | Poland: 66 |
| Country: Number of subjects enrolled | United Kingdom: 60 |
| Country: Number of subjects enrolled | Belgium: 27 |
| Country: Number of subjects enrolled | Czech Republic: 48 |
| Country: Number of subjects enrolled | Finland: 28 |
| Country: Number of subjects enrolled | Germany: 193 |
| Country: Number of subjects enrolled | Hungary: 46 |
| Country: Number of subjects enrolled | United States: 603 |
| Country: Number of subjects enrolled | Canada: 72 |
| Worldwide total number of subjects | 1143 |
| EEA total number of subjects | 468 |

Notes:

## 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) | 1057 |
| From 65 to 84 years | 86 |
| 85 years and over | 0 |

# Subject disposition

## Recruitment

Recruitment details:

The trial was conducted at 165 sites in 9 countries, as follows: Belgium: 5 sites, Canada: 12 sites, Czech Republic: 5 sites; Finland: 6 sites; Germany: 25 sites; Hungary: 5 sites; Poland: 6 sites; United Kingdom: 9 sites; United States: 92 sites.

## Pre-assignment

Screening details:

Screening visit was within 2 weeks prior to run-in visit to assess subject's eligibility.Visit 2(week -8),subjects confirmed eligible enrolled in 8-week run-in period during which basal insulin treatment was optimised using treat-to-target approach.All subjects received once/twice daily insulin detemir and NovoRapid®/NovoLog® during 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 | Subject, Investigator |

Blinding implementation details:

The treatment was double-blinded for the mealtime faster aspart and NovoRapid®/NovoLog® arms and open-labelled for the postmeal faster aspart arm all in combination with open label insulin detemir. In case safety committee recommended unblinding of any data, an independent adhoc group was established to maintain the blinding.

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Faster aspart (meal) |

Arm description:

The subjects in this arm were administered mealtime faster aspart in combination with once or twice daily insulin detemir in a basal−bolus regimen. Mealtime faster aspart was administered subcutaneously 0−2 minutes before each main meal. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Faster-acting insulin aspart |
| Investigational medicinal product code | |
| Other name | Insulin aspart |
| Pharmaceutical forms | Suspension for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Faster aspart, 100 U/mL solution for subcutaneous injection was provided in a prefilled 3 mL PDS290 peninjector (blinded for the mealtime arm). Insulin detemir (Levemir®), 100 U/mL solution for subcutaneous injection was provided in a 3 mL FlexPen®. The dose of faster aspart was titrated to the premeal or bedtime glycaemic target of 4.0−6.0 mmol/L (71−108 mg/dL) using either predefined bolus-dosing algorithm or using principles of flexible dosing based on the meal carbohydrate content. Bolus titration took place twice weekly for subjects who followed the pre-defined bolus dosing algorithms. At the scheduled visit, the investigator titrated based on the previous 3 or 4 days and the subject titrated based on the remaining data as appropriate between scheduled visit as instructed by the investigator. Subjects using the principles of flexible dosing based on the meal carbohydrate content continued to do so, and adjusted the dose several times daily.

| | |
|---|---|
| **Arm title** | Faster aspart (post) |

Arm description:

The subjects in this arm were administered postmeal faster aspart in combination with once or twice daily insulin detemir in a basal−bolus regimen.Postmeal faster aspart was administered subcutaneously 20 minutes after the start of the meal. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation.

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | Faster-acting insulin aspart |
| Investigational medicinal product code | |
| Other name | Insulin aspart |
| Pharmaceutical forms | Suspension for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Faster aspart, 100 U/mL solution for subcutaneous injection was provided in a prefilled 3 mL PDS290 peninjector (open-label for the postmeal arm). Insulin detemir (Levemir®), 100 U/mL solution for subcutaneous injection was provided in a 3 mL FlexPen®. The dose of faster aspart was titrated to the premeal or bedtime glycaemic target of 4.0−6.0 mmol/L (71−108 mg/dL) using either using a predefined bolus-dosing algorithm or using the principles of flexible dosing based on the meal carbohydrate content. Bolus titration took place twice weekly for subjects who followed the pre-defined bolus dosing algorithms. At the scheduled visit, the investigator titrated based on the last 3 or 4 previous days and the subject titrated based on the remaining data as appropriate between scheduled visit as instructed by the investigator. Subjects using the principles of flexible dosing based on the meal carbohydrate content continued to do so, and adjusted the dose several times daily.

| **Arm title** | NovoRapid (meal) |
|---|---|

Arm description:

The subjects in this arm were administered mealtime NovoRapid®/NovoLog® in combination with once or twice daily insulin detemir in a basal-bolus regimen. Mealtime NovoRapid®/NovoLog® was administered subcutaneously 0−2 minutes before each main meal. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation.

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

Dosage and administration details:

NovoRapid®/NovoLog®, 100 U/mL solution for subcutaneous injection was provided in a prefilled 3 mL PDS290 pen-injector. Insulin detemir (Levemir®), 100 U/mL solution for subcutaneous injection was provided in a 3 mL FlexPen®. The dose of NovoRapid®/NovoLog® was titrated to the premeal or bedtime glycaemic target of 4.0−6.0 mmol/L (71−108 mg/dL) using either using a predefined bolus-dosing algorithm or using the principles of flexible dosing based on the meal carbohydrate content. Bolus titration took place twice weekly for subjects who followed the pre-defined bolus dosing algorithms. At the scheduled visit, the investigator titrated based on the previous 3 or 4 days and the subject titrated based on the remaining data as appropriate between scheduled visit as instructed by the investigator. Subjects using the principles of flexible dosing based on the meal carbohydrate content continued to do so, and adjusted the dose several times daily.

| Number of subjects in period 1 | Faster aspart (meal) | Faster aspart (post) | NovoRapid (meal) |
|---|---|---|---|
| Started | 381 | 382 | 380 |
| Completed 26 weeks | 351 | 355 | 356 |
| Completed 52 weeks | 337 | 0 [1] | 338 |
| Completed | 337 | 355 | 338 |
| Not completed | 44 | 27 | 42 |
|     Adverse event, serious fatal | - | 1 | 1 |
|     Consent withdrawn by subject | 22 | 7 | 17 |
|     Other, sponsor and PI decided to close site | 1 | 1 | - |
|     Adverse event, non-fatal | 5 | 3 | 3 |
|     Withdrawal criteria | 12 | 10 | 16 |
|     Pregnancy | 1 | 1 | 2 |
|     Lost to follow-up | 2 | 3 | 3 |
|     Other, sponsor withdrew subject | - | 1 | - |
|     Lack of efficacy | 1 | - | - |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This group did not continue in the study after 26 weeks. The completed subjects for this group represents the treatment period till 26 weeks, while completed for other groups represents treatment period till 52 weeks.

## Baseline characteristics

### Reporting groups

| Reporting group title | Faster aspart (meal) |
|---|---|

Reporting group description:

The subjects in this arm were administered mealtime faster aspart in combination with once or twice daily insulin detemir in a basal−bolus regimen. Mealtime faster aspart was administered subcutaneously 0−2 minutes before each main meal. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation.

| Reporting group title | Faster aspart (post) |
|---|---|

Reporting group description:

The subjects in this arm were administered postmeal faster aspart in combination with once or twice daily insulin detemir in a basal−bolus regimen.Postmeal faster aspart was administered subcutaneously 20 minutes after the start of the meal. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation.

| Reporting group title | NovoRapid (meal) |
|---|---|

Reporting group description:

The subjects in this arm were administered mealtime NovoRapid®/NovoLog® in combination with once or twice daily insulin detemir in a basal-bolus regimen. Mealtime NovoRapid®/NovoLog® was administered subcutaneously 0−2 minutes before each main meal. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation.

| Reporting group values | Faster aspart (meal) | Faster aspart (post) | NovoRapid (meal) |
|---|---|---|---|
| Number of subjects | 381 | 382 | 380 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 346 | 359 | 352 |
| From 65-84 years | 35 | 23 | 28 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 46.1 | 43.5 | 43.7 |
| standard deviation | ± 13.8 | ± 13.7 | ± 14 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 166 | 163 | 142 |
| Male | 215 | 219 | 238 |
| Body weight | | | |
| Units: kg | | | |
| arithmetic mean | 78.56 | 80.49 | 80.15 |
| standard deviation | ± 14.89 | ± 15.93 | ± 15.21 |
| HbA1c | | | |
| Units: % of haemoglobin | | | |
| arithmetic mean | 7.62 | 7.63 | 7.58 |

| | | | |
|---|---|---|---|
| standard deviation | ± 0.71 | ± 0.72 | ± 0.68 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 1143 | | |
| Age categorical<br>Units: Subjects | | | |
|     Adults (18-64 years) | 1057 | | |
|     From 65-84 years | 86 | | |
| Age continuous<br>Units: years<br>    arithmetic mean<br>    standard deviation | <br><br><br>- | | |
| Gender categorical<br>Units: Subjects | | | |
|     Female | 471 | | |
|     Male | 672 | | |
| Body weight<br>Units: kg<br>    arithmetic mean<br>    standard deviation | <br><br><br>- | | |
| HbA1c<br>Units: % of haemoglobin<br>    arithmetic mean<br>    standard deviation | <br><br><br>- | | |

# End points

## End points reporting groups

| Reporting group title | Faster aspart (meal) |
|---|---|

Reporting group description:

The subjects in this arm were administered mealtime faster aspart in combination with once or twice daily insulin detemir in a basal−bolus regimen. Mealtime faster aspart was administered subcutaneously 0−2 minutes before each main meal. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation.

| Reporting group title | Faster aspart (post) |
|---|---|

Reporting group description:

The subjects in this arm were administered postmeal faster aspart in combination with once or twice daily insulin detemir in a basal−bolus regimen.Postmeal faster aspart was administered subcutaneously 20 minutes after the start of the meal. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation.

| Reporting group title | NovoRapid (meal) |
|---|---|

Reporting group description:

The subjects in this arm were administered mealtime NovoRapid®/NovoLog® in combination with once or twice daily insulin detemir in a basal-bolus regimen. Mealtime NovoRapid®/NovoLog® was administered subcutaneously 0−2 minutes before each main meal. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation.

| Subject analysis set title | Faster aspart (meal)-as treated |
|---|---|
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The subjects in this arm were administered mealtime faster aspart in combination with once or twice daily insulin detemir in basal−bolus regimen. Mealtime faster aspart was administered subcutaneously 0−2 minutes before each main meal. Subjects who prior to screening had used principles of flexible dosing based on meal carbohydrate content, and who were assessed by investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during treatment period. All other subjects were to use predefined bolus-dosing algorithm to adjust bolus dose during treatment period. Additional bolus dosing was allowed at investigator's recommendation. A total of 5 subjects were randomised to the postmeal faster aspart arm but had consistently throughout the trial taken their bolus insulin before the meal, hence were included as treated in the safety analysis set for this arm (number of subjects: 386).

| Subject analysis set title | Faster aspart (post)-as treated |
|---|---|
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The subjects in this arm were administered postmeal faster aspart in combination with once or twice daily insulin detemir in basal−bolus regimen. Postmeal faster aspart was administered subcutaneously 20 minutes after start of meal. Subjects who prior to screening had used principles of flexible dosing based on meal carbohydrate content, and who were assessed by investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during treatment period. All other subjects were to use predefined bolus-dosing algorithm to adjust bolus dose during treatment period. Additional bolus dosing was allowed at investigator's recommendation. A total of 5 subjects were randomised to the postmeal faster aspart arm but had consistently throughout the trial taken their bolus insulin before the meal, hence were included as treated and included in the mealtime faster aspart arm instead (number of subjects: 377).

| Subject analysis set title | NovoRapid (meal)-as treated |
|---|---|
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The subjects in this arm were administered mealtime NovoRapid®/NovoLog® in combination with once or twice daily insulin detemir in a basal-bolus regimen. Mealtime NovoRapid®/NovoLog® was administered subcutaneously 0−2 minutes before each main meal. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation.  Number of subjects in this arm: 380.

## Primary: Change from baseline in HbA1c

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

End point description:

Change from baseline in HbA1c after 26 weeks of randomised treatment.
The analysis of this efficacy endpoint was based on the full analysis set (FAS). FAS included all randomised subjects. The statistical evaluation of the FAS was to follow the intention-to-treat (ITT) principle and subjects contributed to the evaluation 'as randomised'. For this endpoint,  baseline and week 26 have been presented, where week 26 data is end of trial containing last available measurement.

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

End point timeframe:

After 26 weeks of randomised treatment

| End point values | Faster aspart (meal) | Faster aspart (post) | NovoRapid (meal) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 381 | 382 | 380 | |
| Units: percentage | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 7.62 (± 0.71) | 7.63 (± 0.72) | 7.58 (± 0.68) | |
| Week 26 | 7.31 (± 0.77) | 7.51 (± 0.77) | 7.42 (± 0.78) | |

## Statistical analyses

| Statistical analysis title | Primary statistical analysis |
|---|---|

Statistical analysis description:

Change from baseline in HbA1c analysed using a mixed-effect model for repeated measurements including visit 14, 18, 22, 26, 30, 34 and 36. The model included treatment, region and strata (combination of bolus adjusting method, basal treatment regimen and continuous glucose monitoring (CGM) and frequently sampled meal test subgroup) as fixed effects, subject as random effect, baseline HbA1c as covariate and interaction between all fixed effects and visit, and between the covariate and visit.

| Comparison groups | Faster aspart (meal) v NovoRapid (meal) |
|---|---|
| Number of subjects included in analysis | 761 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[1] |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.15 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.23 |
| upper limit | -0.07 |

Notes:

[1] - Noninferiority was considered confirmed if the upper boundary of the two-sided 95% CI was below or equal to 0.4% or equivalent if the p-value for noninferiority for the one-sided test of null hypothesis (H0): D >0.4% against the alternative hypothesis (HA): D ≤0.4%, was less than or equal to 2.5%, where D is the mean treatment difference (mealtime faster aspart minus NovoRapid®/NovoLog®).

| **Statistical analysis title** | Primary statistical analysis |
|---|---|

Statistical analysis description:

Change from baseline in HbA1c analysed using a mixed-effect model for repeated measurements including visit 14, 18, 22, 26, 30, 34 and 36. The model included treatment, region and strata (combination of bolus adjusting method, basal treatment regimen and continuous glucose monitoring (CGM) and frequently sampled meal test subgroup) as fixed effects, subject as random effect, baseline HbA1c as covariate and interaction between all fixed effects and visit, and between the covariate and visit.

| Comparison groups | Faster aspart (post) v NovoRapid (meal) |
|---|---|
| Number of subjects included in analysis | 762 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[2] |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.04 |
| upper limit | 0.12 |

Notes:

[2] - Noninferiority was considered confirmed if the upper boundary of the two-sided 95% CI was below or equal to 0.4% or equivalent if the p-value for noninferiority for the one-sided test of null hypothesis (H0): D >0.4% against the alternative hypothesis (HA): D ≤0.4%, was less than or equal to 2.5%, where D is the mean treatment difference (postmeal faster aspart minus NovoRapid®/NovoLog®).

## Secondary: Change from baseline in 2-hour PPG increment (meal test)

| End point title | Change from baseline in 2-hour PPG increment (meal test) |
|---|---|

End point description:

Change from baseline in 2-hour PPG increments after 26 weeks of randomised treatment (meal test). The analysis of this efficacy endpoint was based on FAS. FAS included all randomised subjects. For this endpoint, baseline and week 26 have been presented, where week 26 data is end of trial containing last available measurement. Here, 'n' specifies the number of subjects with data available for 2-hour PPG increment at baseline (Faster aspart (meal) = 379, Faster aspart (post) = 377 and NovoRapid (meal) = 375) and at week 26 ( Faster aspart (meal) = 381, Faster aspart (post) = 382 and NovoRapid (meal) = 380).

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

End point timeframe:

After 26 weeks of randomised treatment

| End point values | Faster aspart (meal) | Faster aspart (post) | NovoRapid (meal) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 381 | 382 | 380 | |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n = 379, 377, 375) | 6.06 (± 5.16) | 6.06 (± 4.9) | 6.24 (± 4.81) | |
| Week 26 (n = 381, 382, 380) | 5.88 (± 4.67) | 6.73 (± 4.67) | 6.55 (± 4.78) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in HbA1c (post meal arm)

| End point title | Change from baseline in HbA1c (post meal arm)[3] |
|---|---|

End point description:

Change from baseline in HbA1c (post meal arm) after 26 weeks of randomised treatment.
This endpoint was summarised using the FAS. FAS included all randomised subjects. For this endpoint, baseline and week 26 have been presented, where week 26 data is end of trial containing last available measurement.

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

End point timeframe:

After 26 weeks of randomised treatment

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The change from baseline in HbA1c was analysed here for the postmeal faster aspart versus NovoRapid®/NovoLog® and hence the data is provided for the faster aspart (post) and the NovoRapid (meal) arm.

| End point values | Faster aspart (post) | NovoRapid (meal) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 382 | 380 | | |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 7.63 (± 0.72) | 7.58 (± 0.68) | | |
| Week 26 | 7.51 (± 0.77) | 7.42 (± 0.78) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of treatment emergent confirmed hypoglycaemic episodes

| End point title | Number of treatment emergent confirmed hypoglycaemic episodes |
|---|---|

End point description:

Number of treatment-emergent severe or BG confirmed hypoglycaemic episodes from baseline until week 26. A hypoglycaemic episode was defined as treatment-emergent if the onset of the episode was

on or after the first day of exposure to randomised treatment and no later than 1 day after the last day of randomised treatment. Severe or BG confirmed is an episode that is severe according to the American Diabetes Association (ADA) classification (an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions) or BG confirmed by a PG value <3.1 mmol/L (56 mg/dL) with or without symptoms consistent with hypoglycaemia. This endpoint was summarized using the safety analysis set.

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

End point timeframe:

From baseline until 26 weeks of randomised treatment

| **End point values** | Faster aspart (meal)-as treated | Faster aspart (post)-as treated | NovoRapid (meal)-as treated | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 386 | 377 | 380 | |
| Units: Number of episodes | | | | |
| Severe or BG confirmed | 5899 | 5443 | 5865 | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in body weight

| End point title | Change from baseline in body weight |
|---|---|

End point description:

Change from baseline in body weight after 26 weeks of randomised treatment.
This endpoint was summarised using the FAS. FAS included all randomised subjects. For this endpoint baseline, and week 26 have been presented, where week 26 data is end of trial containing last available measurement. Here, 'n' specifies the number of subjects with data available for body weight at baseline (Faster aspart (meal) = 381, Faster aspart (post) = 382 and NovoRapid (meal) = 378) and at week 26 (Faster aspart (meal) = 381, Faster aspart (post) = 382 and NovoRapid (meal) = 380).

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

End point timeframe:

After 26 weeks of randomised treatment

| **End point values** | Faster aspart (meal) | Faster aspart (post) | NovoRapid (meal) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 381 | 382 | 380 | |
| Units: kg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=381, 382, 378) | 78.56 (± 14.89) | 80.49 (± 15.93) | 80.21 (± 15.21) | |
| Week 26 (n=381, 382, 380) | 79.21 (± 15.25) | 81.17 (± 16.45) | 80.69 (± 15.44) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Adverse events

| End point title | Adverse events |
|---|---|

End point description:

All treatment emergent adverse events (TEAEs) from baseline until 52 weeks of randomised treatment. A TEAE was defined as an event that had an onset date on or after the first day of exposure to randomised treatment, and no later than 7 days after the last day of randomised treatment.

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

End point timeframe:

From the first day of exposure to randomised treatment and until 26 +1 weeks [faster aspart (post)] or until 26+26+1 weeks [faster aspart (meal) and NovoRapid®/NovoLog® (meal)].

| End point values | Faster aspart (meal)-as treated | Faster aspart (post)-as treated | NovoRapid (meal)-as treated | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 386 | 377 | 380 | |
| Units: event rate/100 patient yrs of exposure | | | | |
| number (not applicable) | 445.8 | 441 | 411 | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: HbA1c

| End point title | HbA1c[4] |
|---|---|

End point description:

Change from baseline in HbA1c (%) after 52 weeks of randomised treatment.
This endpoint was summarised using the FAS. FAS included all randomised subjects. The statistical evaluation of the FAS was to follow the ITT principle and subjects contributed to the evaluation 'as randomised'. For this endpoint, baseline and week 52 have been presented, where week 52 data is the end of trial containing last available measurement.

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

End point timeframe:

After 52 weeks of randomised treatment

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The change from baseline in HbA1c after 52 weeks of randomised treatment is reported

here. The  subjects in the postmeal arm did not enter the additional 26-week treatment period and hence the data is provided for the faster aspart (meal) and the NovoRapid (meal) arm.

| End point values | Faster aspart (meal) | NovoRapid (meal) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 381 | 380 | | |
| Units: percentage | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 7.62 (± 0.71) | 7.58 (± 0.68) | | |
| Week 52 | 7.51 (± 0.83) | 7.58 (± 0.86) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Postprandial glucose (PPG)

| End point title | Postprandial glucose (PPG)[5] |
|---|---|

End point description:

Change from baseline in PPG and PPG increment (meal test) after 52 weeks of randomised treatment. This endpoint was summarised using the FAS. FAS included all randomised subjects. For this endpoint, baseline and week 52 have been presented, where week 52 data is the end of trial containing last available measurement. Here, 'n' specifies the number of subjects with data available for PPG at baseline [Faster aspart (meal) =379 and NovoRapid (meal) =379] and at week 52 [Faster aspart (meal) =380 and NovoRapid (meal) =380].
The number of subjects with data available for PPG increment at 120 mins at baseline [Faster aspart (meal) =379 and NovoRapid (meal) =379] and at week 52 [Faster aspart (meal) =380 and NovoRapid (meal) =380] is also presented.

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

End point timeframe:

After 52 weeks of randomised treatment

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The change from baseline in PPG and PPG increment (meal test) for mealtime faster aspart group and the NovoRapid®/NovoLog® group after 52 weeks of randomised treatment is reported here. The  subjects in the postmeal arm did not enter the additional 26-week treatment period and hence the data is provided for the faster aspart (meal) and the NovoRapid (meal) arm.

| End point values | Faster aspart (meal) | NovoRapid (meal) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 381 | 380 | | |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| PPG at 120 minutes (Baseline) (n=379,379) | 14.51 (± 6.09) | 14.14 (± 5.69) | | |
| PPG at 120 minutes (Week 52) (n=380,380) | 14.26 (± 5.76) | 14.51 (± 6.02) | | |
| PPG increment at 120 mins (Baseline) (n=379,375) | 6.06 (± 5.16) | 6.24 (± 4.81) | | |
| PPG increment at 120 mins(Week 52) (n=381,380) | 5.71 (± 4.92) | 6.14 (± 4.86) | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Until 52 (26+26) weeks of treatment + 1 week of follow-up for faster aspart (meal) and NovoRapid®/NovoLog®(meal) or until 26 weeks of treatment + 1 week of follow-up for faster aspart (post).

Adverse event reporting additional description:

All TEAEs are summarised.A TEAE defined as an event that had an onset date on or after first day of exposure to randomised treatment,and no later than 7 days after the last day of randomised treatment.Note:number of deaths causally related to treatment is the data considered to present under 'total number of deaths resulting from adverse events'.

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

### Dictionary used

| Dictionary name | MedDRA |
|---|---|
| Dictionary version | 17 |

### Reporting groups

| Reporting group title | Faster aspart (meal)-as treated |
|---|---|

Reporting group description:

The subjects in this arm were administered mealtime faster aspart in combination with once or twice daily insulin detemir in a basal−bolus regimen. Mealtime faster aspart was administered subcutaneously 0−2 minutes before each main meal for 52 weeks. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation. A total of 5 subjects were randomised to the postmeal faster aspart arm but had consistently throughout the trial taken their bolus insulin before the meal, hence were included as treated in the safety analysis set for this arm (number of subjects: 386)

| Reporting group title | Faster aspart (post)-as treated |
|---|---|

Reporting group description:

The subjects in this arm were administered postmeal faster aspart in combination with once or twice daily insulin detemir in a basal−bolus regimen.Postmeal faster aspart was administered subcutaneously 20 minutes after the start of the meal for 26 weeks.Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period.All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation.A total of 5 subjects were randomised to the postmeal faster aspart arm but had consistently throughout the trial taken their bolus insulin before the meal, hence were included as treated and included in the mealtime faster aspart arm instead(number of subjects:377).

| Reporting group title | NovoRapid (meal)-as treated |
|---|---|

Reporting group description:

The subjects in this arm were administered mealtime NovoRapid®/NovoLog® in combination with once or twice daily insulin detemir in a basal−bolus regimen. Mealtime NovoRapid®/NovoLog® was administered subcutaneously 0−2 minutes before each main meal for 52 weeks. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation. Number of subjects in this arm: 380.

| Serious adverse events | Faster aspart (meal)-as treated | Faster aspart (post)-as treated | NovoRapid (meal)-as treated |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 35 / 386 (9.07%) | 28 / 377 (7.43%) | 33 / 380 (8.68%) |
| number of deaths (all causes) | 0 | 1 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 1 / 377 (0.27%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 1 / 386 (0.26%) | 0 / 377 (0.00%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Papillary thyroid cancer | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 0 / 377 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Aneurysm | | | |
| subjects affected / exposed | 1 / 386 (0.26%) | 0 / 377 (0.00%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 1 / 386 (0.26%) | 0 / 377 (0.00%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 386 (0.26%) | 0 / 377 (0.00%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Coronary arterial stent insertion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 386 (0.26%) | 0 / 377 (0.00%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary revascularisation | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 1 / 377 (0.27%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Uterine polyp | | | |
| subjects affected / exposed | 1 / 386 (0.26%) | 0 / 377 (0.00%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Nasal septum deviation | | | |
| subjects affected / exposed | 1 / 386 (0.26%) | 0 / 377 (0.00%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Mental status changes | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 0 / 377 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Blood glucose decreased | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 0 / 377 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiovascular evaluation | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 0 / 377 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |

|  | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 386 (0.26%) | 1 / 377 (0.27%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Fall** | | | |
| subjects affected / exposed | 2 / 386 (0.52%) | 0 / 377 (0.00%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Lower limb fracture** | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 1 / 377 (0.27%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Lumbar vertebral fracture** | | | |
| subjects affected / exposed | 1 / 386 (0.26%) | 0 / 377 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Overdose** | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 1 / 377 (0.27%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Radius fracture** | | | |
| subjects affected / exposed | 1 / 386 (0.26%) | 0 / 377 (0.00%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Road traffic accident** | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 1 / 377 (0.27%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Subdural haematoma** | | | |
| subjects affected / exposed | 1 / 386 (0.26%) | 0 / 377 (0.00%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Tendon rupture** | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 386 (0.26%) | 0 / 377 (0.00%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Wrong drug administered** | | | |
| subjects affected / exposed | 1 / 386 (0.26%) | 1 / 377 (0.27%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Cardiac disorders** | | | |
| **Angina pectoris** | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 1 / 377 (0.27%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Arrhythmia** | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 1 / 377 (0.27%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| **Arteriosclerosis coronary artery** | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 1 / 377 (0.27%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Cardiac failure congestive** | | | |
| subjects affected / exposed | 1 / 386 (0.26%) | 0 / 377 (0.00%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Cardiac ventricular thrombosis** | | | |
| subjects affected / exposed | 1 / 386 (0.26%) | 0 / 377 (0.00%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Coronary artery disease** | | | |
| subjects affected / exposed | 1 / 386 (0.26%) | 1 / 377 (0.27%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Myocardial infarction** | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 386 (0.00%) | 0 / 377 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| **Nervous system disorders** | | | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 1 / 377 (0.27%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemic seizure | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 1 / 377 (0.27%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemic unconsciousness | | | |
| subjects affected / exposed | 5 / 386 (1.30%) | 3 / 377 (0.80%) | 4 / 380 (1.05%) |
| occurrences causally related to treatment / all | 7 / 8 | 3 / 3 | 3 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 0 / 377 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 1 / 386 (0.26%) | 0 / 377 (0.00%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 386 (0.26%) | 0 / 377 (0.00%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Eye disorders** | | | |
| Diabetic retinopathy | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 0 / 377 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Gastrointestinal disorders** | | | |

| Abdominal pain | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 386 (0.00%) | 0 / 377 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Anal fistula** | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 0 / 377 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Colitis microscopic** | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 0 / 377 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Diarrhoea** | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 1 / 377 (0.27%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Nausea** | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 1 / 377 (0.27%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Pancreatitis** | | | |
| subjects affected / exposed | 1 / 386 (0.26%) | 0 / 377 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Peritoneal fibrosis** | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 1 / 377 (0.27%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Vomiting** | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 1 / 377 (0.27%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Musculoskeletal and connective tissue disorders** | | | |

| | | | |
|---|---|---|---|
| **Compartment syndrome** | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 0 / 377 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Joint stiffness** | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 0 / 377 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Meniscal degeneration** | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 0 / 377 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Musculoskeletal pain** | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 0 / 377 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Infections and infestations** | | | |
| **Appendicitis** | | | |
| subjects affected / exposed | 1 / 386 (0.26%) | 0 / 377 (0.00%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Bronchitis** | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 0 / 377 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Cellulitis** | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 0 / 377 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Gastroenteritis** | | | |
| subjects affected / exposed | 1 / 386 (0.26%) | 0 / 377 (0.00%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Osteomyelitis** | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 386 (0.00%) | 1 / 377 (0.27%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Peritonsillar abscess** | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 0 / 377 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Pharyngitis** | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 0 / 377 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Pilonidal cyst** | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 1 / 377 (0.27%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Pneumonia staphylococcal** | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 1 / 377 (0.27%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Pyelonephritis** | | | |
| subjects affected / exposed | 1 / 386 (0.26%) | 1 / 377 (0.27%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Vestibular neuronitis** | | | |
| subjects affected / exposed | 1 / 386 (0.26%) | 0 / 377 (0.00%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Viral infection** | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 0 / 377 (0.00%) | 1 / 380 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Metabolism and nutrition disorders** | | | |
| Diabetic ketoacidosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 386 (0.26%) | 0 / 377 (0.00%) | 2 / 380 (0.53%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 12 / 386 (3.11%) | 11 / 377 (2.92%) | 10 / 380 (2.63%) |
| occurrences causally related to treatment / all | 10 / 16 | 7 / 11 | 8 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lactic acidosis | | | |
| subjects affected / exposed | 0 / 386 (0.00%) | 1 / 377 (0.27%) | 0 / 380 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Faster aspart (meal)-as treated | Faster aspart (post)-as treated | NovoRapid (meal)-as treated |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 252 / 386 (65.28%) | 189 / 377 (50.13%) | 236 / 380 (62.11%) |
| Injury, poisoning and procedural complications | | | |
| Wrong drug administered | | | |
| subjects affected / exposed | 22 / 386 (5.70%) | 18 / 377 (4.77%) | 23 / 380 (6.05%) |
| occurrences (all) | 31 | 20 | 28 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 37 / 386 (9.59%) | 26 / 377 (6.90%) | 45 / 380 (11.84%) |
| occurrences (all) | 70 | 41 | 79 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 27 / 386 (6.99%) | 11 / 377 (2.92%) | 27 / 380 (7.11%) |
| occurrences (all) | 34 | 11 | 33 |
| Nausea | | | |
| subjects affected / exposed | 28 / 386 (7.25%) | 18 / 377 (4.77%) | 23 / 380 (6.05%) |
| occurrences (all) | 36 | 29 | 34 |
| Vomiting | | | |
| subjects affected / exposed | 19 / 386 (4.92%) | 15 / 377 (3.98%) | 25 / 380 (6.58%) |
| occurrences (all) | 23 | 16 | 30 |

| | | | |
|---|---|---|---|
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Cough | | | |
| subjects affected / exposed | 17 / 386 (4.40%) | 12 / 377 (3.18%) | 20 / 380 (5.26%) |
| occurrences (all) | 21 | 13 | 21 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 17 / 386 (4.40%) | 16 / 377 (4.24%) | 23 / 380 (6.05%) |
| occurrences (all) | 22 | 21 | 30 |
| **Musculoskeletal and connective tissue disorders** | | | |
| Back pain | | | |
| subjects affected / exposed | 28 / 386 (7.25%) | 15 / 377 (3.98%) | 20 / 380 (5.26%) |
| occurrences (all) | 36 | 17 | 22 |
| **Infections and infestations** | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 20 / 386 (5.18%) | 8 / 377 (2.12%) | 17 / 380 (4.47%) |
| occurrences (all) | 25 | 8 | 21 |
| Influenza | | | |
| subjects affected / exposed | 22 / 386 (5.70%) | 11 / 377 (2.92%) | 37 / 380 (9.74%) |
| occurrences (all) | 30 | 12 | 54 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 128 / 386 (33.16%) | 90 / 377 (23.87%) | 120 / 380 (31.58%) |
| occurrences (all) | 214 | 111 | 174 |
| Sinusitis | | | |
| subjects affected / exposed | 19 / 386 (4.92%) | 7 / 377 (1.86%) | 28 / 380 (7.37%) |
| occurrences (all) | 21 | 7 | 37 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 56 / 386 (14.51%) | 28 / 377 (7.43%) | 40 / 380 (10.53%) |
| occurrences (all) | 75 | 31 | 61 |
| Urinary tract infection | | | |
| subjects affected / exposed | 20 / 386 (5.18%) | 15 / 377 (3.98%) | 18 / 380 (4.74%) |
| occurrences (all) | 25 | 20 | 29 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol?  Yes

| Date | Amendment |
|---|---|
| 26 July 2013 | A 30-day follow-up period was introduced in order to collect information on potential major cardiovascular events (MACE) to support cardiovascular risk assessment. Furthermore, collection of smoking history (to support cardiovascular risk analysis) and new diabetes treatment after end of trial treatment was introduced for all subjects at randomisation. The continuous glucose monitoring (CGM) data collection period was increased from 3−7 days to 10−14 days with the simultaneous decrease from 180 to 90 subjects in the CGM and frequently sampled meal test subgroup. This was done in order to improve data quality by having more CGM data from individual subjects at fewer clinical sites. The ADA classification of hypoglycaemia was updated to reflect the latest ADA classification. France was replaced by Finland. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial?  No

## Limitations and caveats

None reported