



Clinical trial results:

A trial investigating the pharmacokinetic properties of FIAsp in children, adolescents and adults with type 1 diabetes.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2011-002104-32 |
| Trial protocol | DE |
| Global end of trial date | 24 July 2014 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 16 March 2016 |
| First version publication date | 08 February 2015 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data setNew AE data to be uploaded |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | NN1218-3888 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02035371 |
| WHO universal trial number (UTN) | U1111-1121-1469 |

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? | Yes |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 16 January 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 24 July 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 24 July 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare the total exposure of faster-acting insulin aspart (also known as FIAsp) between children, adolescents and adult subjects with type 1 diabetes.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2008) and ICH Good Clinical Practice (1996) and FDA 21 CFR 312.120.

Background therapy:

Not applicable.

Evidence for comparator:

Not Applicable

| | |
|---|-----------------|
| Actual start date of recruitment | 13 January 2014 |
| 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 | Germany: 40 |
| Worldwide total number of subjects | 40 |
| EEA total number of subjects | 40 |

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) | 12 |
| Adolescents (12-17 years) | 13 |
| Adults (18-64 years) | 15 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This trial was conducted at one site in Germany (single centre study).

Pre-assignment

Screening details:

Not applicable.

Period 1

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

Blinding implementation details:

The trial was randomised, single-centre, double-blind, single-dose, two-period cross-over trial.

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | No |
| Arm title | Faster-acting insulin aspart first, then NovoRapid |

Arm description:

Subjects received faster-acting insulin aspart followed by NovoRapid.

| | |
|--|------------------------------|
| Arm type | crossover assignment |
| Investigational medicinal product name | Faster-acting insulin aspart |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Trial products dose level was 0.2 U/kg body weight. The trial products were administered subcutaneously in the abdomen.

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

Dosage and administration details:

Trial products dose level was 0.2 U/kg body weight. The trial products were administered subcutaneously in the abdomen.

| | |
|------------------|--|
| Arm title | NovoRapid first, then faster-acting insulin aspart |
|------------------|--|

Arm description:

Subjects received NovoRapid first, followed by faster-acting insulin aspart.

| | |
|--|------------------------|
| Arm type | crossover assignment |
| Investigational medicinal product name | NovoRapid |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Trial product dose level was 0.2 U/kg body weight. The trial products were administered subcutaneously

in the abdomen.

| | |
|--|------------------------------|
| Investigational medicinal product name | Faster-acting insulin aspart |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Trial products dose level was 0.2 U/kg body weight. The trial products were administered subcutaneously in the abdomen.

| Number of subjects in period 1 | Faster-acting insulin aspart first, then NovoRapid | NovoRapid first, then faster-acting insulin aspart |
|---|--|--|
| Started | 21 | 19 |
| Completed | 19 | 19 |
| Not completed | 2 | 0 |
| Difficulty in blood sampling in rescheduled visit | 1 | - |
| Protocol deviation | 1 | - |

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | Period 2- completers |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

This was randomised, single- centre, double- blind ,single dose ,two- period cross over trial.

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | NovoRapid first, then faster-acting insulin aspart |

Arm description:

Subjects received NovoRapid first followed by faster-acting insulin aspart.

| | |
|--|------------------------|
| Arm type | crossover assignment |
| Investigational medicinal product name | NovoRapid |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Trial products dose level was 0.2 U/kg body weight. The trial products were administered subcutaneously in the abdomen.

| | |
|--|------------------------------|
| Investigational medicinal product name | Faster-acting insulin aspart |
| Investigational medicinal product code | |
| Other name | |

| | |
|--------------------------|------------------------|
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Trial products dose level was 0.2 U/kg body weight. The trial products were administered subcutaneously in the abdomen.

| | |
|------------------|--|
| Arm title | Faster-acting insulin aspart first, then NovoRapid |
|------------------|--|

Arm description:

Subjects received faster- acting insulin aspart first, followed by NovoRapid.

| | |
|--|------------------------------|
| Arm type | crossover assignment |
| Investigational medicinal product name | Faster-acting insulin aspart |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Trial products dose level was 0.2 U/kg body weight. The trial products were administered subcutaneously in the abdomen.

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

Dosage and administration details:

Trial products dose level were 0.2 U/kg body weight. The trial products were administered subcutaneously in the abdomen.

| Number of subjects in period 2 | NovoRapid first, then faster-acting insulin aspart | Faster-acting insulin aspart first, then NovoRapid |
|--------------------------------|--|--|
| Started | 19 | 19 |
| Completed | 19 | 19 |

| | |
|------------------------------|-------------------------|
| Period 3 | |
| Period 3 title | Period 3 |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

This trial was randomised, double-blind, single centre, single dose, two-period , cross over study.

| | |
|------------------------------|----|
| Arms | |
| Are arms mutually exclusive? | No |

| | |
|---|---|
| Arm title | Faster-acting insulin aspart: Children (6-11 years) |
| Arm description: Subjects received faster-acting Insulin aspart followed by NovoRapid. | |
| Arm type | Experimental |
| Investigational medicinal product name | Faster-acting insulin aspart |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: Trial products dose level was 0.2 U/kg body weight. The trial products were administered subcutaneously in the abdomen. | |
| Arm title | Faster-acting insulin aspart: Adolescents (12-17 years) |
| Arm description: Subjects received faster-acting Insulin aspart followed by NovoRapid. | |
| Arm type | Experimental |
| Investigational medicinal product name | Faster-acting insulin aspart |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: Trial products dose level was 0.2 U/kg body weight. The trial products were administered subcutaneously in the abdomen. | |
| Arm title | Faster-acting insulin aspart: Adults (18-64 years) |
| Arm description: Subjects received faster-acting Insulin aspart followed by NovoRapid. | |
| Arm type | Experimental |
| Investigational medicinal product name | Faster-acting insulin aspart |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: Trial products dose level was 0.2 U/kg body weight. The trial products were administered subcutaneously in the abdomen. | |
| Arm title | NovoRapid: Children (6-11years) |
| Arm description: Subjects received NovoRapid followed by faster-acting Insulin aspart. | |
| Arm type | Active comparator |
| Investigational medicinal product name | NovoRapid |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: Trial product dose level was 0.2 U/kg body weight. The trial products were administered subcutaneously in the abdomen. | |
| Arm title | NovoRapid: Adolescents (12-17 years) |
| Arm description: Subjects received NovoRapid followed by faster-acting Insulin aspart. | |

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

Dosage and administration details:

Trial product, the dose level was 0.2 U/kg body weight. The trial product were administered subcutaneously in the abdomen.

| | |
|------------------|---------------------------------|
| Arm title | NovoRapid: Adults (18-64 years) |
|------------------|---------------------------------|

Arm description:

Subjects received NovoRapid followed by faster-acting insulin aspart.

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

Dosage and administration details:

Trial product dose level was 0.2 U/kg body weight. The trial products were administered subcutaneously in the abdomen.

| Number of subjects in period 3 | Faster-acting insulin aspart: Children (6-11 years) | Faster-acting insulin aspart: Adolescents (12-17 years) | Faster-acting insulin aspart: Adults (18-64 years) |
|---|---|---|--|
| Started | 12 | 13 | 15 |
| Completed | 12 | 13 | 13 |
| Not completed | 0 | 0 | 2 |
| Difficulty in blood sampling in rescheduled visit | - | - | 1 |
| Protocol deviation | - | - | 1 |

| Number of subjects in period 3 | NovoRapid: Children (6-11years) | NovoRapid: Adolescents (12-17 years) | NovoRapid: Adults (18-64 years) |
|---|---------------------------------|--------------------------------------|---------------------------------|
| Started | 12 | 13 | 13 |
| Completed | 12 | 13 | 13 |
| Not completed | 0 | 0 | 0 |
| Difficulty in blood sampling in rescheduled visit | - | - | - |
| Protocol deviation | - | - | - |

Baseline characteristics

Reporting groups

Reporting group title

Period 1

Reporting group description:

Each subject were randomly allocated to a treatment sequence consisting of 2 dosing visits separated by a wash-out period of 3-22 days.

| Reporting group values | Period 1 | Total | |
|---|----------|-------|--|
| Number of subjects | 40 | 40 | |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 12 | 12 | |
| Adolescents (12-17 years) | 13 | 13 | |
| Adults (18-64 years) | 15 | 15 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Gender categorical Units: Subjects | | | |
| Female | 18 | 18 | |
| Male | 22 | 22 | |

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | Faster-acting insulin aspart first, then NovoRapid |
| Reporting group description: Subjects received faster-acting insulin aspart followed by NovoRapid. | |
| Reporting group title | NovoRapid first, then faster-acting insulin aspart |
| Reporting group description: Subjects received NovoRapid first, followed by faster-acting insulin aspart. | |
| Reporting group title | NovoRapid first, then faster-acting insulin aspart |
| Reporting group description: Subjects received NovoRapid first followed by faster-acting insulin aspart. | |
| Reporting group title | Faster-acting insulin aspart first, then NovoRapid |
| Reporting group description: Subjects received faster- acting insulin aspart first, followed by NovoRapid. | |
| Reporting group title | Faster-acting insulin aspart: Children (6-11 years) |
| Reporting group description: Subjects received faster-acting Insulin aspart followed by NovoRapid. | |
| Reporting group title | Faster-acting insulin aspart: Adolescents (12-17 years) |
| Reporting group description: Subjects received faster-acting Insulin aspart followed by NovoRapid. | |
| Reporting group title | Faster-acting insulin aspart: Adults (18-64 years) |
| Reporting group description: Subjects received faster-acting Insulin aspart followed by NovoRapid. | |
| Reporting group title | NovoRapid: Children (6-11years) |
| Reporting group description: Subjects received NovoRapid followed by faster-acting Insulin aspart. | |
| Reporting group title | NovoRapid: Adolescents (12-17 years) |
| Reporting group description: Subjects received NovoRapid followed by faster-acting Insulin aspart. | |
| Reporting group title | NovoRapid: Adults (18-64 years) |
| Reporting group description: Subjects received NovoRapid followed by faster-acting insulin aspart. | |

Primary: AUCIAsp, 0–12h, area under the serum insulin aspart concentration-time curve from 0 to 12 hours

| | |
|---|---|
| End point title | AUCIAsp, 0–12h, area under the serum insulin aspart concentration-time curve from 0 to 12 hours |
| End point description: Area under the serum insulin aspart concentration-time curve. | |
| End point type | Primary |
| End point timeframe: 0-12 hours | |

| End point values | Faster-acting insulin aspart: Children (6-11 years) | Faster-acting insulin aspart: Adolescents (12-17 years) | Faster-acting insulin aspart: Adults (18-64 years) | NovoRapid: Children (6-11years) |
|-------------------------------|---|---|--|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 13 | 15 | 12 |
| Units: pmol h/L | | | | |
| median (full range (min-max)) | 380.45 (308.26 to 562.02) | 504.66 (411.56 to 717.09) | 687.68 (465.16 to 913.32) | 455.59 (250.63 to 539.3) |

| End point values | NovoRapid: Adolescents (12-17 years) | NovoRapid: Adults (18-64 years) | | |
|-------------------------------|--------------------------------------|---------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 13 | | |
| Units: pmol h/L | | | | |
| median (full range (min-max)) | 510.56 (371.26 to 821.21) | 686.89 (500.51 to 861.14) | | |

Statistical analyses

| Statistical analysis title | AUC (0-12h) Faster Aspart : Children/Adults |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

The endpoint was log-transformed and then analysed using a linear mixed model with age-group, treatment, age-group-by-treatment interaction and period as fixed effects and subject as a random effect. The variance of the random effect and the residual variance depend on age.

| | |
|---|--|
| Comparison groups | Faster-acting insulin aspart: Adults (18-64 years) v Faster-acting insulin aspart: Children (6-11 years) |
| Number of subjects included in analysis | 27 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| Method | Mixed models analysis |
| Parameter estimate | Geometric-mean ratio |
| Point estimate | 0.59 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5 |
| upper limit | 0.69 |

Notes:

[1] - Exploratory comparison

| Statistical analysis title | AUC (0-12h) Faster Aspart : Adolescents/Adults |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

The endpoint was log-transformed and then analysed using a linear mixed model with age-group, treatment, age-group-by-treatment interaction and period as fixed effects and subject as a random effect. The variance of the random effect and the residual variance depend on age.

| | |
|---|--|
| Comparison groups | Faster-acting insulin aspart: Adolescents (12-17 years) v Faster-acting insulin aspart: Adults (18-64 years) |
| Number of subjects included in analysis | 28 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| Method | Mixed models analysis |
| Parameter estimate | Geometric-mean ratio |
| Point estimate | 0.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 0.9 |

Notes:

[2] - Exploratory comparison

| | |
|-----------------------------------|---|
| Statistical analysis title | AUC (0-12h) NovoRapid: Children/Adults |
|-----------------------------------|---|

Statistical analysis description:

The endpoint was log-transformed and then analysed using a linear mixed model with age-group, treatment, age-group-by treatment interaction and period as fixed effects and subject as a random effect. The variance of the random effect and the residual variance depend on age.

| | |
|---|---|
| Comparison groups | NovoRapid: Children (6-11years) v NovoRapid: Adults (18-64 years) |
| Number of subjects included in analysis | 25 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| Method | Mixed models analysis |
| Parameter estimate | Geometric-mean ratio |
| Point estimate | 0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.51 |
| upper limit | 0.7 |

Notes:

[3] - Exploratory comparison

| | |
|-----------------------------------|--|
| Statistical analysis title | AUC (0-12h) NovoRapid : Adolescents/Adults |
|-----------------------------------|--|

Statistical analysis description:

The endpoint was log-transformed and then analysed using a linear mixed model with age-group, treatment, age-group-by treatment interaction and period as fixed effects and subject as a random effect. The variance of the random effect and the residual variance depend on age.

| | |
|-------------------|--|
| Comparison groups | NovoRapid: Adolescents (12-17 years) v NovoRapid: Adults (18-64 years) |
|-------------------|--|

| | |
|---|-----------------------|
| Number of subjects included in analysis | 26 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[4] |
| Method | Mixed models analysis |
| Parameter estimate | Geometric-mean ratio |
| Point estimate | 0.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.65 |
| upper limit | 0.87 |

Notes:

[4] - Exploratory comparison

Secondary: Cmax,IAsp,maximum observed serum insulin aspart concentration

| | |
|------------------------|---|
| End point title | Cmax,IAsp,maximum observed serum insulin aspart concentration |
| End point description: | Maximum observed serum insulin aspart concentration. |
| End point type | Secondary |
| End point timeframe: | |
| From 0-12hours | |

| End point values | Faster-acting insulin aspart: Children (6-11 years) | Faster-acting insulin aspart: Adolescents (12-17 years) | Faster-acting insulin aspart: Adults (18-64 years) | NovoRapid: Children (6-11years) |
|-------------------------------|---|---|--|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 13 | 15 | 12 |
| Units: pmol/L | | | | |
| median (full range (min-max)) | 255.1 (160.8 to 380.1) | 276.8 (165 to 458.2) | 257.7 (149.1 to 502.3) | 271.65 (113 to 412.9) |

| End point values | NovoRapid: Adolescents (12-17 years) | NovoRapid: Adults (18-64 years) | | |
|-------------------------------|--------------------------------------|---------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 13 | | |
| Units: pmol/L | | | | |
| median (full range (min-max)) | 261.3 (155.4 to 400.1) | 267.3 (154.2 to 430.3) | | |

Statistical analyses

| | |
|-----------------------------------|--------------------------------------|
| Statistical analysis title | Cmax Faster aspart : Children/Adults |
|-----------------------------------|--------------------------------------|

Statistical analysis description:

The endpoint was log-transformed and then analysed using a linear mixed model with age-group, treatment, age-group-by-treatment interaction and period as fixed effects and subject as a random effect. The variance of the random effect and the residual variance depend on age.

| | |
|---|--|
| Comparison groups | Faster-acting insulin aspart: Children (6-11 years) v Faster-acting insulin aspart: Adults (18-64 years) |
| Number of subjects included in analysis | 27 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[5] |
| Method | Mixed models analysis |
| Parameter estimate | Geometric-mean ratio |
| Point estimate | 0.91 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 1.17 |

Notes:

[5] - Exploratory comparison

| | |
|-----------------------------------|---|
| Statistical analysis title | Cmax Faster aspart : Adolescents/Adults |
|-----------------------------------|---|

Statistical analysis description:

The endpoint was log-transformed and then analysed using a linear mixed model with age-group, treatment, age-group-by-treatment interaction and period as fixed effects and subject as a random effect. The variance of the random effect and the residual variance depend on age.

| | |
|---|--|
| Comparison groups | Faster-acting insulin aspart: Adolescents (12-17 years) v Faster-acting insulin aspart: Adults (18-64 years) |
| Number of subjects included in analysis | 28 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[6] |
| Method | Mixed models analysis |
| Parameter estimate | Geometric-mean ratio |
| Point estimate | 0.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.77 |
| upper limit | 1.26 |

Notes:

[6] - Exploratory comparison

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | Cmax NovoRapid : Children/Adults |
|-----------------------------------|----------------------------------|

Statistical analysis description:

The endpoint was log-transformed and then analysed using a linear mixed model with age-group, treatment, age-group-by-treatment interaction and period as fixed effects and subject as a random effect. The variance of the random effect and the residual variance depend on age.

| | |
|-------------------|--|
| Comparison groups | NovoRapid: Children (6-11years) v NovoRapid: Adults (18-64 |
|-------------------|--|

| | |
|---|-----------------------|
| | years) |
| Number of subjects included in analysis | 25 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[7] |
| Method | Mixed models analysis |
| Parameter estimate | Geometric-mean ratio |
| Point estimate | 0.91 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 1.18 |

Notes:

[7] - Exploratory comparison

| | |
|-----------------------------------|-------------------------------------|
| Statistical analysis title | Cmax NovoRapid : Adolescents/Adults |
|-----------------------------------|-------------------------------------|

Statistical analysis description:

The endpoint was log-transformed and then analysed using a linear mixed model with age-group, treatment, age-group-by-treatment interaction and period as fixed effects and subject as a random effect. The variance of the random effect and the residual variance depend on age.

| | |
|---|--|
| Comparison groups | NovoRapid: Adolescents (12-17 years) v NovoRapid: Adults (18-64 years) |
| Number of subjects included in analysis | 26 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[8] |
| Method | Mixed models analysis |
| Parameter estimate | Geometric-mean ratio |
| Point estimate | 0.91 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1.17 |

Notes:

[8] - Exploratory comparison

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse events were collected at visit 2 (Day 1 and Day 2), visit 3 (Day 1, Day 2, 3-22 days after V2, D2), and Follow-up visit (7-22 days after V3, D2).

Adverse event reporting additional description:

Safety analysis set included all subjects receiving at least one dose of the IMP or its comparator. Subjects in the safety analysis set contributed to the evaluation "as treated".

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Faster-acting insulin aspart: Children (6-11years) |
|-----------------------|--|

Reporting group description:

Subjects received faster-acting insulin aspart followed by NovoRapid.

| | |
|-----------------------|---|
| Reporting group title | Faster-acting insulin aspart: Adolescents (12-17 years) |
|-----------------------|---|

Reporting group description:

Subjects received faster-acting insulin aspart followed by NovoRapid.

| | |
|-----------------------|--|
| Reporting group title | Faster-acting insulin aspart: Adults (18-64 years) |
|-----------------------|--|

Reporting group description:

Subjects received faster-acting insulin aspart followed by NovoRapid.

| | |
|-----------------------|---------------------------------|
| Reporting group title | NovoRapid: Children (6-11years) |
|-----------------------|---------------------------------|

Reporting group description:

Subjects received NovoRapid followed by faster-acting insulin aspart.

| | |
|-----------------------|--------------------------------------|
| Reporting group title | NovoRapid: Adolescents (12-17 years) |
|-----------------------|--------------------------------------|

Reporting group description:

Subjects received NovoRapid followed by faster-acting insulin aspart.

| | |
|-----------------------|---------------------------------|
| Reporting group title | NovoRapid: Adults (18-64 years) |
|-----------------------|---------------------------------|

Reporting group description:

Subjects received NovoRapid followed by faster-acting insulin aspart.

| Serious adverse events | Faster-acting insulin aspart: Children (6-11years) | Faster-acting insulin aspart: Adolescents (12-17 years) | Faster-acting insulin aspart: Adults (18-64 years) |
|---|--|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 13 (0.00%) | 0 / 15 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| Serious adverse events | NovoRapid: Children (6-11years) | NovoRapid: Adolescents (12-17 years) | NovoRapid: Adults (18-64 years) |
|---|---------------------------------|--------------------------------------|---------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 13 (0.00%) | 0 / 13 (0.00%) |

| | | | |
|--|---|---|---|
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

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

| Non-serious adverse events | Faster-acting insulin aspart: Children (6-11years) | Faster-acting insulin aspart: Adolescents (12-17 years) | Faster-acting insulin aspart: Adults (18-64 years) |
|--|--|---|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 2 / 12 (16.67%) | 2 / 13 (15.38%) | 3 / 15 (20.00%) |
| Cardiac disorders Cardiovascular disorder subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 0 / 13 (0.00%) 0 | 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 |
| General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) Catheter site haematoma subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 1 / 15 (6.67%) 1 |
| Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea | 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1 | 1 / 13 (7.69%) 1 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0 |

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 1 / 13 (7.69%) 1 | 0 / 15 (0.00%) 0 |

| Non-serious adverse events | NovoRapid: Children (6-11years) | NovoRapid: Adolescents (12-17 years) | NovoRapid: Adults (18-64 years) |
|---|--|--|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 1 / 12 (8.33%) | 2 / 13 (15.38%) | 2 / 13 (15.38%) |
| Cardiac disorders Cardiovascular disorder subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 13 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 | 0 / 13 (0.00%) 0 0 / 13 (0.00%) 0 | 0 / 13 (0.00%) 0 0 / 13 (0.00%) 0 |
| General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) Catheter site haematoma subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 | 1 / 13 (7.69%) 1 0 / 13 (0.00%) 0 | 0 / 13 (0.00%) 0 0 / 13 (0.00%) 0 |

| | | | | |
|---|-----------------------------|----------------|----------------|----------------|
| Gastrointestinal disorders | Vomiting | | | |
| | subjects affected / exposed | 0 / 12 (0.00%) | 1 / 13 (7.69%) | 0 / 13 (0.00%) |
| | occurrences (all) | 0 | 1 | 0 |
| | Diarrhoea | | | |
| | subjects affected / exposed | 0 / 12 (0.00%) | 0 / 13 (0.00%) | 0 / 13 (0.00%) |
| | occurrences (all) | 0 | 0 | 0 |
| | Nausea | | | |
| | subjects affected / exposed | 0 / 12 (0.00%) | 1 / 13 (7.69%) | 0 / 13 (0.00%) |
| | occurrences (all) | 0 | 1 | 0 |
| Reproductive system and breast disorders | Dysmenorrhoea | | | |
| | subjects affected / exposed | 0 / 12 (0.00%) | 0 / 13 (0.00%) | 1 / 13 (7.69%) |
| | occurrences (all) | 0 | 0 | 1 |
| Respiratory, thoracic and mediastinal disorders | Oropharyngeal pain | | | |
| | subjects affected / exposed | 0 / 12 (0.00%) | 1 / 13 (7.69%) | 0 / 13 (0.00%) |
| | occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | Nasopharyngitis | | | |
| | subjects affected / exposed | 0 / 12 (0.00%) | 0 / 13 (0.00%) | 1 / 13 (7.69%) |
| | occurrences (all) | 0 | 0 | 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 04 April 2014 | <p>One substantial amendment was made to the protocol, and this occurred after first patient first visit. The changes introduced in the amendment were</p> <p>1. Extension of the maximum time allowed between visits in order to provide more flexibility in the scheduling of patients to attend visits From 3–21 days to 3–22 days between the screening visit (V1) and the first dosing visit (V2). From 3–12 days to 3–22 days between dosing visits (V2 and V3). From 7–21 days to 7–22 days between the second dosing visit (V3) and the follow-up visit (V4)</p> <p>2. The timing of the fundoscopy assessment at the screening visit (V1) was extended to allow assessment up until the day before the first dosing visit (V2), day 1 to provide more flexibility in the screening of subjects.</p> <p>3. Addition of dose to the information collected for concomitant medication, in order to be consistent with the concomitant medication form.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Not applicable

Notes: