# Clinical trial results:
# A 52-Week, Multinational, Multi-Centre, Open-Labelled Extension Trial of Insulin Detemir in Children and Adolescents 3-17 years with Type 1 Diabetes on a Basal-Bolus Regimen with Insulin Aspart as Bolus Insulin
# Trial Phase: 3

## Summary

| | |
|---|---|
| EudraCT number | 2006-002478-23 |
| Trial protocol | GB FI DK HU CZ FR BG |
| Global end of trial date | 07 September 2009 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 15 March 2016 |
| First version publication date | 31 July 2015 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | NN304-1690 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00623194 |
| WHO universal trial number (UTN) | - |

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) | Yes |
| EMA paediatric investigation plan number(s) | EMEA-000412-PIP01-08 |
| 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 | 17 February 2010 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 07 September 2009 |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 September 2009 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To study the development of insulin detemir-insulin aspart cross-reacting antibodies following a 104 week-period (52 weeks in NN304-1689 and 52 weeks in NN304-1690) of insulin detemir treatment in children and adolescents.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (October 2000, amended 2002 and 2004) and ICH Good Clinical Practice (01-May-1996).

Background therapy:

The subjects were treated with insulin detemir and completed 52 weeks of treatment in the NN304-1689 trial.

Evidence for comparator:

Not applicable

| | |
|---|---|
| Actual start date of recruitment | 19 February 2008 |
| 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: 20 |
| Country: Number of subjects enrolled | United Kingdom: 2 |
| Country: Number of subjects enrolled | Bulgaria: 19 |
| Country: Number of subjects enrolled | Czech Republic: 18 |
| Country: Number of subjects enrolled | Denmark: 6 |
| Country: Number of subjects enrolled | Finland: 7 |
| Country: Number of subjects enrolled | France: 2 |
| Country: Number of subjects enrolled | Hungary: 10 |
| Country: Number of subjects enrolled | Macedonia, the former Yugoslav Republic of: 11 |
| Country: Number of subjects enrolled | Russian Federation: 40 |
| Country: Number of subjects enrolled | Turkey: 11 |
| Worldwide total number of subjects | 146 |
| EEA total number of subjects | 84 |

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) | 88 |
| Adolescents (12-17 years) | 58 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The trial sites included 29 sites in 11 countries: Bulgaria (3 sites), Czech Republic (3 sites), Denmark (2 sites), Finland (4 sites), France (1 site), Hungary (2 sites), Macedonia (1 site), Poland (4 sites), Russian Federation (4 sites), Turkey (4 sites) and United Kingdom (1 site).

### Pre-assignment

Screening details:

At entry subjects had finalised 52-weeks treatment with insulin detemir (Trial NN304-1689, NCT00435019).The subjects continued treatment with insulin detemir and insulin aspart doses used in Trial NN304-1689.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| **Arm title** | Insulin Detemir |

Arm description:

Subjects received insulin detemir up to twice daily plus insulin aspart at larger meals. Doses were adjusted individually (treatment up to 104 weeks).

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

Dosage and administration details:

Insulin detemir was administered subcutaneously once or twice daily at the same time of the day as in Trial NN304-1689. All subjects also received insulin aspart as bolus insulin immediately before or after main meals. The dose of insulin was continuously and individually adjusted based on plasmaglucose (PG) measurements according to the NN304-1689 Titration Guideline.

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

Dosage and administration details:

All subjects received insulin aspart as bolus insulin immediately before or after main meals. The dose of insulin was continuously and individually adjusted based on plasmaglucose (PG) measurements according to the NN304-1689 Titration Guideline.

| **Number of subjects in period 1** | Insulin Detemir |
|---|---|
| Started | 146 |
| Completed | 141 |
| Not completed | 5 |
| protocol violation | 3 |
| unclassified | 1 |
| Lack of efficacy | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Overall Study |
| Reporting group description: | |
| Insulin detemir up to twice daily plus insulin aspart at larger meals, doses are adjusted individually (treatment up to 104 weeks) | |

| Reporting group values | Overall Study | Total | |
|---|---|---|---|
| Number of subjects | 146 | 146 | |
| Age categorical | | | |
| Units: Subjects | | | |
| 2 to 5 years | 37 | 37 | |
| 6 to 12 years | 59 | 59 | |
| 13 to 16 years | 50 | 50 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 10.1 | | |
| standard deviation | ± 4.2 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 77 | 77 | |
| Male | 69 | 69 | |
| Race | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 0 | 0 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 0 | 0 | |
| White | 144 | 144 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 2 | 2 | |
| Pubertal Status | | | |
| Units: Subjects | | | |
| Tanner grade 1 | 83 | 83 | |
| Tanner grade 2+ | 63 | 63 | |
| Height | | | |
| Units: meters | | | |
| arithmetic mean | 1.39 | | |
| standard deviation | ± 0.26 | - | |
| BMI | | | |
| Units: kg/m^2 | | | |
| arithmetic mean | 18.14 | | |
| standard deviation | ± 2.81 | - | |

## End points

### End points reporting groups

| Reporting group title | Insulin Detemir |
|---|---|

Reporting group description:

Subjects received insulin detemir up to twice daily plus insulin aspart at larger meals. Doses were adjusted individually (treatment up to 104 weeks).

### Primary: Insulin detemir-insulin aspart cross-reacting antibodies.

| End point title | Insulin detemir-insulin aspart cross-reacting antibodies.[1] |
|---|---|

End point description:

Estimated amount of bound antibodies in percent of total antibodies. The primary analysis of cross-reacting antibodies included results from blood samples taken before insulin detemir and less than 3 hours after insulin aspart injection. In addition, an analysis was done including results from samples taken before insulin detemir and less than 2.5 hours after insulin aspart injection. For all subjects the difference between the individual subject's antibody measurements at Visit 10 and Visit 1 exension were calculated. This individual difference was used to adjust the antibody measurements. These corrected values were used for all analyses

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

End point timeframe:

week 0, 52 and 104.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: In order to clarify if the antibody measurements stabilised or decreased the parameter of interest was the estimated slope of the model. No other statistical analysis was provided for Insulin Detemir-insulin Aspart Cross-reacting Antibodies.

| End point values | Insulin Detemir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 146 | | | |
| Units: Percent bound of total | | | | |
| least squares mean (standard error) | | | | |
| Week 0 (3 hours) | 31.11 (± 1.25) | | | |
| Week 52 (3 hours) | 43.99 (± 1.02) | | | |
| Week 104 (3 hours) | 35.96 (± 1.14) | | | |
| Week 0 (2.5 hours) | 31.22 (± 1.23) | | | |
| Week 52 (2.5 hours) | 44.09 (± 1.01) | | | |
| Week 104 (2.5 hours) | 35.92 (± 1.13) | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Development of insulin detemir specific antibodies and insulin aspart specific antibodies

| End point title | Development of insulin detemir specific antibodies and insulin aspart specific antibodies |
|---|---|

End point description:

Amount of insulin detemir and insulin aspart specific antibodies in percent of total antibodies after 0, 52 and 104 weeks. The blood samples analysed were taken before insulin detemir and less than 3 hours after insulin aspart injection.

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

End point timeframe:

At 0, 52 and 104 weeks

| **End point values** | Insulin Detemir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 146 | | | |
| Units: Percent bound of total | | | | |
| least squares mean (standard error) | | | | |
| Insulin Detemir specific, week 0 | 2.81 (± 1.28) | | | |
| Insulin Detemir specific, week 52 | 4.4 (± 1.27) | | | |
| Insulin Detemir specific, week 104 | 3.05 (± 1.27) | | | |
| Insulin Aspart specific, week 0 | 1.32 (± 0.67) | | | |
| Insulin Aspart specific, week 52 | 2.79 (± 0.64) | | | |
| Insulin Aspart specific, week 104 | 1.99 (± 0.65) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: BMI (Body Mass Index)

| End point title | BMI (Body Mass Index) |
|---|---|

End point description:

BMI (Body Mass Index) after 104 weeks.

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

End point timeframe:

At 104 weeks

| **End point values** | Insulin Detemir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 144 | | | |
| Units: kg/m^2 | | | | |
| arithmetic mean (standard deviation) | 18.88 (± 3.19) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: SD-score (Z-score) for Body Weight

| End point title | SD-score (Z-score) for Body Weight |
|---|---|

End point description:

Standard deviation-score (SD-score or z-score) after 104 weeks. The SD-score for weight was calculated based on a British reference population from 1990. To estimate the growth of children, standardised mean weight values were calculated for each month of age and for each sex. Thus, a child with a weight equal to the mean value for its age and sex has an SD score of 0, while a child with a weight 2 SDs above the mean value for its age and sex has an SD score of +2.

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

End point timeframe:

At 104 weeks

| **End point values** | Insulin Detemir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 144 | | | |
| Units: SD-scores | | | | |
| arithmetic mean (standard deviation) | 0.13 (± 0.97) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Occurrence of ketoacidosis requiring hospitalisation during treatment

| End point title | Occurrence of ketoacidosis requiring hospitalisation during treatment |
|---|---|

End point description:

Number of diabetic ketoacidosis events requiring hospitalisation.

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

End point timeframe:

At 104 weeks

| **End point values** | Insulin Detemir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 146 | | | |
| Units: Number | 3 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Insulin Dose

| End point title | Insulin Dose |
|---|---|

End point description:

Daily insulin doses (basal (Insulin Detemir) and bolus (Insulin Aspart)) at week 104.

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

End point timeframe:

At 104 weeks

| End point values | Insulin Detemir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 144 | | | |
| Units: U/kg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Insulin Detemir dose (Basal)<br>Insulin Aspart dose (Bolus) | 0.66 (± 0.29)<br>0.51 (± 0.19) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Laboratory safety parameters: Biochemistry - Albumin Serum (g/dL)

| End point title | Laboratory safety parameters: Biochemistry - Albumin Serum (g/dL) |
|---|---|

End point description:

Albumin Serum after 104 weeks.

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

End point timeframe:

At 104 weeks

| End point values | Insulin Detemir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 144 | | | |
| Units: g/dL | | | | |
| arithmetic mean (standard deviation) | 4.32 (± 0.25) | | | |

### Statistical analyses

No statistical analyses for this end point

| Secondary: Laboratory safety parameters: Biochemistry- Creatinine Serum umol/L | |
|---|---|
| End point title | Laboratory safety parameters: Biochemistry- Creatinine Serum umol/L |
| End point description:<br>Creatine serum after 104 weeks. | |
| End point type | Secondary |
| End point timeframe:<br>At 104 weeks | |

| End point values | Insulin Detemir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 144 | | | |
| Units: umol/L | | | | |
| arithmetic mean (standard deviation) | 51.08 (± 13.55) | | | |

## Statistical analyses

No statistical analyses for this end point

| Secondary: Laboratory safety parameters: Biochemistry - Sodium Serum (mmol/L) | |
|---|---|
| End point title | Laboratory safety parameters: Biochemistry - Sodium Serum (mmol/L) |
| End point description:<br>Sodium Serum, Potassium Serum and Haemoglobin after 104 weeks. | |
| End point type | Secondary |
| End point timeframe:<br>At 104 weeks | |

| End point values | Insulin Detemir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 144 | | | |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | 141.6 (± 3.11) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Laboratory safety parameters: Biochemistry- Alkaline Phosphatase Serum (U/L)

| End point title | Laboratory safety parameters: Biochemistry- Alkaline Phosphatase Serum (U/L) |
|---|---|

End point description:

Alkaline phosphatase serum after 104 weeks.

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

End point timeframe:

At 104 weeks

| **End point values** | Insulin Detemir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 144 | | | |
| Units: U/L | | | | |
| arithmetic mean (standard deviation) | 226.7 (± 197.1) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Laboratory safety parameters: Haematology - Leukocytes

| End point title | Laboratory safety parameters: Haematology - Leukocytes |
|---|---|

End point description:

Leukocytes after 104 weeks.

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

End point timeframe:

At 104 weeks

| **End point values** | Insulin Detemir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 144 | | | |
| Units: 10^9/L | | | | |
| arithmetic mean (standard deviation) | 6.72 (± 1.85) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Laboratory safety parameters: Fundoscopy/Fundus Photography

| End point title | Laboratory safety parameters: Fundoscopy/Fundus |
|---|---|

| | |
|---|---|
| | Photography |

End point description:

Fundoscopy after 104 weeks. Abn. CS = Abnormal, clinically significant; Abn. NCS = Abnormal, Not clinically significant; Abn. CS = Abnormal, clinically significant; Abn. NCS = Abnormal, Not clinically significant.

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

End point timeframe:

At 52 weeks and at 104 weeks

| **End point values** | Insulin Detemir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 146 | | | |
| Units: participants | | | | |
| Abnormal, clinically significant | 1 | | | |
| Abnormal, not clinically significant | 8 | | | |
| Normal | 131 | | | |
| Missing | 6 | | | |
| Abn CS baseline and 104 weeks | 1 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Vital Signs: Blood Pressure

| | |
|---|---|
| End point title | Vital Signs: Blood Pressure |

End point description:

Blood pressure (Systolic and Diastolic) after 104 weeks.

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

End point timeframe:

At 104 weeks

| **End point values** | Insulin Detemir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 143 | | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Systolic Blood Pressure | 109.5 (± 13.6) | | | |
| Diastolic Blood Pressure | 66.6 (± 8.9) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Vital Signs: Pulse

| End point title | Vital Signs: Pulse |
|---|---|

End point description:

Pulse at week 104, measured after resting in a sitting position for 5 minutes.

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

End point timeframe:

At 104 weeks

| End point values | Insulin Detemir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 141 | | | |
| Units: beats/minute | | | | |
| arithmetic mean (standard deviation) | 82.6 (± 9) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Incidence of hypoglycaemia (mild, moderate, severe and biochemical)

| End point title | Incidence of hypoglycaemia (mild, moderate, severe and biochemical) |
|---|---|

End point description:

Incidence of hypoglycaemia (mild, moderate, severe and biochemical) – total, daytime and night time during treatment.
Mild: signs/symptoms but able to treat him/herself. Moderate: signs/symptoms not able to treat him/herself. Responds to oral treatment. Severe: signs/symptoms and unable to treat him/herself. semiconscious/unconscious/in coma +/- convulsion and may require parenteral treatment. Biochemical: Plasma glucose < 3.6mmol/L with no signs or symptoms.

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

End point timeframe:

Weeks 0 - 104

| End point values | Insulin Detemir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 146 | | | |
| Units: Episodes | | | | |
| Total hypoglycaemic episodes | 16074 | | | |
| Total hypoglycaemic episodes, daytime | 13605 | | | |
| Total hypoglycaemic episodes, night-time | 2469 | | | |
| Daytime, Mild | 9080 | | | |
| Daytime, Moderate | 396 | | | |

| | | | | |
|---|---|---|---|---|
| Daytime, Severe | 3 | | | |
| Daytime, Biochemical | 4122 | | | |
| Daytime, Unclassified | 4 | | | |
| Night-time, Mild | 1450 | | | |
| Night-time, Moderate | 54 | | | |
| Night-time, Severe | 4 | | | |
| Night-time, Biochemical | 958 | | | |
| Night-time, unclassified | 3 | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Adverse events during treatment

| End point title | Adverse events during treatment |
|---|---|

End point description:

Adverse events during the treatment period expressed as number of events per 100 exposure years.

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

End point timeframe:

Adverse events from the first day on trial product (Visit 1 + 1 day) to one week after last day on trial product (Visit 5Ext + 7 days at most).

| **End point values** | Insulin Detemir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 146 | | | |
| Units: Number of events per 100 exposure years | | | | |
| number (not applicable) | 246.9 | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Laboratory safety parameters: Biochemistry - Total protein serum (g/dL)

| End point title | Laboratory safety parameters: Biochemistry - Total protein serum (g/dL) |
|---|---|

End point description:

Total protein serum after 104 weeks.

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

End point timeframe:

At 104 weeks

| End point values | Insulin Detemir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 144 | | | |
| Units: g/dL | | | | |
| arithmetic mean (standard deviation) | 7.09 (± 0.45) | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Laboratory safety parameters: Biochemistry - Pottassium Serum (mmol/L)

| End point title | Laboratory safety parameters: Biochemistry - Pottassium Serum (mmol/L) |
|---|---|
| End point description: | |
| Potassium Serum after 104 weeks. | |
| End point type | Secondary |
| End point timeframe: | |
| At 104 weeks | |

| End point values | Insulin Detemir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 137 | | | |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | 4.38 (± 0.5) | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Laboratory safety parameters: Haematology - Haemoglobin (mmol/L)

| End point title | Laboratory safety parameters: Haematology - Haemoglobin (mmol/L) |
|---|---|
| End point description: | |
| Haemoglobin after 104 weeks | |
| End point type | Secondary |
| End point timeframe: | |
| At 104 weeks | |

| End point values | Insulin Detemir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 144 | | | |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | 8.28 (± 0.65) | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Laboratory safety parameters: Biochemistry -Alanine Aminotransferase Serum (U/L)

| End point title | Laboratory safety parameters: Biochemistry -Alanine Aminotransferase Serum (U/L) |
|---|---|
| End point description: | |
| Alanine Aminotransferase serum after 104 weeks. | |
| End point type | Secondary |
| End point timeframe: | |
| At 104 weeks | |

| End point values | Insulin Detemir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 144 | | | |
| Units: U/L | | | | |
| arithmetic mean (standard deviation) | 19 (± 8.26) | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Laboratory safety parameters: Biochemistry - Lactate Dehydrogenase Serum (U/L)

| End point title | Laboratory safety parameters: Biochemistry - Lactate Dehydrogenase Serum (U/L) |
|---|---|
| End point description: | |
| Lactate Dehydrogenase serum after 104 weeks. | |
| End point type | Secondary |
| End point timeframe: | |
| At 104 weeks | |

| End point values | Insulin Detemir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 137 | | | |
| Units: U/L | | | | |
| arithmetic mean (standard deviation) | 199.6 (± 40.34) | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Laboratory safety parameters: Haematology - Thrombocytes

| End point title | Laboratory safety parameters: Haematology - Thrombocytes |
|---|---|
| End point description:<br>Thrombocytes after 104 weeks. | |
| End point type | Secondary |
| End point timeframe:<br>At 104 weeks | |

| End point values | Insulin Detemir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 144 | | | |
| Units: 10^9/L | | | | |
| arithmetic mean (standard deviation) | 301.9 (± 76.55) | | | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The adverse events were collected over a period of 104 weeks.

Adverse event reporting additional description:

The safety analysis set is all subjects exposed to at least one dose of trial drug.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 11.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Insulin Detemir |

Reporting group description:

Insulin detemir up to twice daily plus insulin aspart at larger meals, doses are adjusted individually (treatment up to 104 weeks)

| **Serious adverse events** | Insulin Detemir | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 12 / 146 (8.22%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Burns second degrees | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 146 (1.37%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abscess limb | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis shigella | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 146 (0.68%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Influenza | | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Otitis media acute | | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Soft tissue infection | | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Viral infection | | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Metabolism and nutrition disorders | | | | |
| Diabetic ketoacidosis | | | | |
| subjects affected / exposed | 3 / 146 (2.05%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypoglycaemia | | | | |
| subjects affected / exposed | 2 / 146 (1.37%) | | | |
| occurrences causally related to treatment / all | 3 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diabetes mellitus inadequate control | | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypoglycaemia unconsciousness | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 146 (0.68%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Insulin Detemir | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 106 / 146 (72.60%) | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 25 / 146 (17.12%) | | |
| occurrences (all) | 84 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 8 / 146 (5.48%) | | |
| occurrences (all) | 13 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 9 / 146 (6.16%) | | |
| occurrences (all) | 10 | | |
| Vomiting | | | |
| subjects affected / exposed | 10 / 146 (6.85%) | | |
| occurrences (all) | 10 | | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 71 / 146 (48.63%) | | |
| occurrences (all) | 164 | | |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 21 / 146 (14.38%) | | |
| occurrences (all) | 44 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 20 / 146 (13.70%) | | |
| occurrences (all) | 41 | | |
| Influenza | | | |
| subjects affected / exposed | 17 / 146 (11.64%) | | |
| occurrences (all) | 38 | | |

| | | | |
|---|---|---|---|
| Gastroenteritis | | | |
| subjects affected / exposed | 15 / 146 (10.27%) | | |
| occurrences (all) | 21 | | |
| Bronchitis | | | |
| subjects affected / exposed | 9 / 146 (6.16%) | | |
| occurrences (all) | 16 | | |
| Viral infection | | | |
| subjects affected / exposed | 10 / 146 (6.85%) | | |
| occurrences (all) | 12 | | |
| Rhinitis | | | |
| subjects affected / exposed | 9 / 146 (6.16%) | | |
| occurrences (all) | 11 | | |
| Acute Tonsilliitis | | | |
| subjects affected / exposed | 8 / 146 (5.48%) | | |
| occurrences (all) | 8 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 29 February 2008 | Substantial amendment no. 1, dated 28 January 2008, was prepared to implement the decision to use a paper-based diary in the trial. |

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: