# Clinical trial results:
# A Phase 3, Multicenter, Randomized, Parallel-Design, Open-Label Study to Evaluate the Efficacy and Safety of LY3209590 as a Weekly Basal Insulin Compared with Insulin Degludec in Participants with Type 1 Diabetes Treated with Multiple Daily Injection Therapy

## Summary

| | |
|---|---|
| EudraCT number | 2021-005892-38 |
| Trial protocol | SK PL |
| Global end of trial date | 07 May 2024 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 22 May 2025 |
| First version publication date | 22 May 2025 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | I8H-MC-BDCY |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT05463744 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Trial Number: 18263 |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Eli Lilly and Company |
| Sponsor organisation address | Lilly Corporate Center, Indianapolis, United States, 46285 |
| Public contact | Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877-CTLilly, |
| Scientific contact | Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877-285-4559, |

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 | 07 May 2024 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 07 May 2024 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

A Study of Insulin Efsitora Alfa (LY3209590) Compared with Insulin Degludec in Participants with Type 1 Diabetes Treated with Multiple Daily Injection Therapy

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 12 August 2022 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Poland: 132 |
| Country: Number of subjects enrolled | Slovakia: 32 |
| Country: Number of subjects enrolled | Argentina: 197 |
| Country: Number of subjects enrolled | Japan: 101 |
| Country: Number of subjects enrolled | Taiwan: 32 |
| Country: Number of subjects enrolled | United States: 198 |
| Worldwide total number of subjects | 692 |
| EEA total number of subjects | 164 |

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) | 631 |
| From 65 to 84 years | 61 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Not Applicable

### Period 1

| | |
|---|---|
| Period 1 title | Treatment Period |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | 500 U/mL Insulin Efsitora Alfa |

Arm description:

Participants who were treated with prestudy basal insulin and prandial insulin therapy (100 units per milliliter (U/mL) Insulin Lispro) received 500 U/mL of insulin efsitora alfa administered once weekly (QW) for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Insulin Efsitora Alfa |
| Investigational medicinal product code | LY3209590 |
| Other name | Basal Insulin-FC |
| Pharmaceutical forms | Solution for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Participants who were treated with prestudy basal insulin and prandial insulin therapy (100 U/mL Insulin Lispro) received 500 U/mL of insulin efsitora alfa administered QW for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.

| | |
|---|---|
| **Arm title** | 100 U/mL Insulin Degludec |

Arm description:

Participants who were treated with prestudy basal insulin and prandial insulin therapy (100 U/mL Insulin Lispro) received 100 U/mL of Insulin Degludec administered once daily (QD) for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Insulin Degludec |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Participants who were treated with prestudy basal insulin and prandial insulin therapy (100 U/mL Insulin Lispro) received 100 U/mL of Insulin Degludec administered QD for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.

| Number of subjects in period 1 | 500 U/mL Insulin Efsitora Alfa | 100 U/mL Insulin Degludec |
|---|---|---|
| Started | 343 | 349 |
| Received at Least one Dose of Study Drug | 343 | 349 |
| Completed | 316 | 319 |
| Not completed | 27 | 30 |
| Non-compliance with Study Drug | 1 | - |
| Consent withdrawn by subject | 19 | 16 |
| Physician decision | - | 1 |
| Adverse event, non-fatal | 4 | 4 |
| Death | - | 1 |
| Pregnancy | - | 3 |
| Inadvertent enrollment | 2 | 1 |
| Lost to follow-up | 1 | 3 |
| Subject Terminated by Sponsor | - | 1 |

## Period 2

| | |
|---|---|
| Period 2 title | Follow-up Period |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | No |
| **Arm title** | 500 U/mL Insulin Efsitora Alfa |

Arm description:

Participants who were treated with prestudy basal insulin and prandial insulin therapy (100U/mL Insulin Lispro) received 500 U/mL of insulin efsitora alfa administered QW for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Insulin Efsitora Alfa |
| Investigational medicinal product code | LY3209590 |
| Other name | Basal Insulin-FC |
| Pharmaceutical forms | Solution for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Participants who were treated with prestudy basal insulin and prandial insulin therapy (100 U/mL Insulin Lispro) received 500 U/mL of insulin efsitora alfa administered QW for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.

| | |
|---|---|
| **Arm title** | 100 U/mL Insulin Degludec |

Arm description:

Participants who were treated with prestudy basal insulin and prandial insulin therapy (100 U/mL Insulin Lispro) received 100 U/mL of Insulin Degludec administered QD for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | Insulin Degludec |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Participants who were treated with prestudy basal insulin and prandial insulin therapy (100 U/mL Insulin Lispro) received 100 U/mL of Insulin Degludec administered QD for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.

| **Number of subjects in period 2** | 500 U/mL Insulin Efsitora Alfa | 100 U/mL Insulin Degludec |
|---|---|---|
| Started | 332 | 326 |
| Completed | 328 | 324 |
| Not completed | 4 | 2 |
| Consent withdrawn by subject | 3 | 1 |
| Lost to follow-up | 1 | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | 500 U/mL Insulin Efsitora Alfa |
| Reporting group description: | |
| Participants who were treated with prestudy basal insulin and prandial insulin therapy (100 units per milliliter (U/mL) Insulin Lispro) received 500 U/mL of insulin efsitora alfa administered once weekly (QW) for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up. | |
| Reporting group title | 100 U/mL Insulin Degludec |
| Reporting group description: | |
| Participants who were treated with prestudy basal insulin and prandial insulin therapy (100 U/mL Insulin Lispro) received 100 U/mL of Insulin Degludec administered once daily (QD) for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up. | |

| Reporting group values | 500 U/mL Insulin Efsitora Alfa | 100 U/mL Insulin Degludec | Total |
|---|---|---|---|
| Number of subjects | 343 | 349 | 692 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous | | | |
| Analysis Population Description (APD): All randomized participants who received at least one dose of the study drug. | | | |
| Units: years | | | |
| arithmetic mean | 44.40 | 43.60 | |
| standard deviation | ± 14.22 | ± 14.01 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 150 | 158 | 308 |
| Male | 193 | 191 | 384 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 121 | 116 | 237 |
| Not Hispanic or Latino | 221 | 230 | 451 |
| Unknown or Not Reported | 1 | 3 | 4 |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 0 | 1 |
| Asian | 69 | 73 | 142 |
| Native Hawaiian or Other Pacific Islander | 1 | 0 | 1 |
| Black or African American | 11 | 13 | 24 |
| White | 259 | 262 | 521 |
| More than one race | 2 | 1 | 3 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Region of Enrollment<br>Units: Subjects | | | |
| Argentina | 98 | 99 | 197 |
| Japan | 48 | 53 | 101 |
| Poland | 66 | 66 | 132 |
| Slovakia | 15 | 17 | 32 |

| | | | |
|---|---|---|---|
| Taiwan | 15 | 17 | 32 |
| United States | 101 | 97 | 198 |

| HemoglobinA1c (HbA1c) | | | |
|---|---|---|---|
| HbA1c is the glycosylated fraction of hemoglobin A. It is measured primarily to identify the average plasma glucose concentration over prolonged periods of time. | | | |
| Units: Percentage of HbA1c | | | |
| arithmetic mean | 7.88 | 7.94 | |
| standard deviation | ± 0.75 | ± 0.72 | - |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | 500 U/mL Insulin Efsitora Alfa |
| Reporting group description: | |
| Participants who were treated with prestudy basal insulin and prandial insulin therapy (100 units per milliliter (U/mL) Insulin Lispro) received 500 U/mL of insulin efsitora alfa administered once weekly (QW) for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up. | |
| Reporting group title | 100 U/mL Insulin Degludec |
| Reporting group description: | |
| Participants who were treated with prestudy basal insulin and prandial insulin therapy (100 U/mL Insulin Lispro) received 100 U/mL of Insulin Degludec administered once daily (QD) for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up. | |
| Reporting group title | 500 U/mL Insulin Efsitora Alfa |
| Reporting group description: | |
| Participants who were treated with prestudy basal insulin and prandial insulin therapy (100U/mL Insulin Lispro) received 500 U/mL of insulin efsitora alfa administered QW for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up. | |
| Reporting group title | 100 U/mL Insulin Degludec |
| Reporting group description: | |
| Participants who were treated with prestudy basal insulin and prandial insulin therapy (100 U/mL Insulin Lispro) received 100 U/mL of Insulin Degludec administered QD for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up. | |

### Primary: Change from Baseline in Hemoglobin A1c (HbA1c) at Week 26 [Noninferiority Analysis]

| | |
|---|---|
| End point title | Change from Baseline in Hemoglobin A1c (HbA1c) at Week 26 [Noninferiority Analysis] |
| End point description: | |
| HbA1c is the glycosylated fraction of hemoglobin A. It is measured primarily to identify the average plasma glucose concentration over prolonged periods of time.<br>Least Squares (LS) mean was determined using Analysis of Covariance (ANCOVA) model treatment + country + CGM use prior to study entry [yes/no]+ carbohydrate counting for prandial insulin[yes/no] + baseline value of the dependent variable (Type III sum of squares) as variables. Missing data at Week 26 were imputed by return-to-baseline multiple imputations approach.<br>APD: All randomized participants who received at least one dose of the study drug and had HbA1c measurement at baseline or Week 26. Participants who discontinued the study drug due to inadvertent enrollment were excluded. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline, Week 26 | |

| End point values | 500 U/mL Insulin Efsitora Alfa | 100 U/mL Insulin Degludec | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 341 | 348 | | |
| Units: millimoles per mole (mmol/mol) | | | | |
| least squares mean (standard error) | -5.53 (± 0.512) | -6.10 (± 0.506) | | |

### Statistical analyses

| Statistical analysis title | Statistical Analysis |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |
| Number of subjects included in analysis | 689 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[1] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.57 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.85 |
| upper limit | 1.98 |

Notes:

[1] - 0.4% noninferiority margin (NIM)

### Secondary: Change from Baseline in Hemoglobin A1c (HbA1c) at Week 26 [Superiority Analysis]

| End point title | Change from Baseline in Hemoglobin A1c (HbA1c) at Week 26 [Superiority Analysis] |
|---|---|

End point description:

HbA1c is the glycosylated fraction of hemoglobin A. It is measured primarily to identify the average plasma glucose concentration over prolonged periods of time.
LS mean was determined using ANCOVA model with treatment + country + CGM use prior to study entry [yes/no] + carbohydrate counting for prandial insulin[yes/no] + baseline value of the dependent variable (Type III sum of squares) as variables. Missing data at Week 26 were imputed by return-to-baseline multiple imputations approach.
APD: All randomized participants who received at least one dose of the study drug and had HbA1c measurement at baseline or Week 26. Participants who discontinued the study drug due to inadvertent enrollment were excluded.

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

End point timeframe:

Baseline, Week 26

| End point values | 500 U/mL Insulin Efsitora Alfa | 100 U/mL Insulin Degludec | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 341 | 348 | | |
| Units: mmol/mol | | | | |
| least squares mean (standard error) | -5.53 (± 0.512) | -6.10 (± 0.506) | | |

### Statistical analyses

| Statistical analysis title | Statistical Analysis |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |
| Number of subjects included in analysis | 689 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.432 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.57 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.85 |
| upper limit | 1.98 |

## Secondary: Percentage of Time-in-Glucose Range Between 70 and 180 mg/dL [3.9 and 10.0 mmol/L]

| End point title | Percentage of Time-in-Glucose Range Between 70 and 180 mg/dL [3.9 and 10.0 mmol/L] |
|---|---|

End point description:

Time in glucose range between 70 and 180 milligram per deciliter (mg/dL) [3.9 and 10.0 millimole per liter (mmol/L)], measured by continued glucose monitoring (CGM) from week 23-26 inclusive over a 24-Hour Period. The time component of the time-in-range statistic was calculated using the display time recorded by the CGM device.
LS mean was determined using ANCOVA model with treatment+country+CGM use prior to study entry [yes/no]+carbohydrate counting for prandial insulin dosing [yes/no]+Hemoglobin A1c Stratum at Baseline and baseline value of the dependent variable (Type III sum of squares) as variables.Missing data at Week 23-26 were imputed by return-to-baseline multiple imputations approach.
APD:All randomized participants who took at least one dose of study drug and had evaluable data for this outcome at baseline or Week 23-26 were included. Participants who discontinued study drug due to inadvertent enrollment were excluded

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

End point timeframe:

Week 23 to Week 26

| End point values | 500 U/mL Insulin Efsitora Alfa | 100 U/mL Insulin Degludec | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 339 | 347 | | |
| Units: Percentage of time | | | | |
| least squares mean (standard error) | 52.54 (± 0.691) | 52.85 (± 0.684) | | |

**Statistical analyses**

| Statistical analysis title | Statistical Analysis |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |
| Number of subjects included in analysis | 686 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.751 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.22 |
| upper limit | 1.6 |

**Secondary: Nocturnal Hypoglycemia Event Rate**

| End point title | Nocturnal Hypoglycemia Event Rate |
|---|---|

End point description:

The event rate of participant-reported clinically significant nocturnal hypoglycemia (defined as blood glucose level <54 mg/dL (3.0 mmol/L) or severe hypoglycemia and occurs at night and presumably during sleep between midnight and 6:00 AM), measured during treatment phase up to week 52.
Group mean was reported and determined by Negative binomial model using Number of episodes = Baseline hypoglycemia rate + HbA1c at Baseline (%) + Treatment, with log (exposure in days/365.25) as an offset variable.
APD: All randomized participants who received at least one dose of the study drug and had evaluable data for this outcome.

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

End point timeframe:

Baseline up to Week 52

| End point values | 500 U/mL Insulin Efsitora Alfa | 100 U/mL Insulin Degludec | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 343 | 349 | | |
| Units: events per year | | | | |
| arithmetic mean (standard error) | 1.99 (± 0.180) | 1.96 (± 0.177) | | |

**Statistical analyses**

| Statistical analysis title | Statistical Analysis |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |
| Number of subjects included in analysis | 692 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9 |
| Method | Negative binomial model |
| Parameter estimate | Relative Rate |
| Point estimate | 1.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 1.31 |

**Secondary: Change from Baseline in HbA1c at Week 52 [Noninferiority Analysis]**

| End point title | Change from Baseline in HbA1c at Week 52 [Noninferiority Analysis] |
|---|---|

End point description:

HbA1c is the glycosylated fraction of hemoglobin A. It is measured primarily to identify the average plasma glucose concentration over prolonged periods of time.
LS mean was determined using ANCOVA model with treatment + country + CGM use prior to study entry [yes/no]+ carbohydrate counting for prandial insulin[yes/no] + baseline value of the dependent variable (Type III sum of squares) as variables. Missing data at Week 52 were imputed by return-to-baseline multiple imputations approach.
APD: All randomized participants who received at least one dose of the study drug and had HbA1c measurement at baseline or Week 52. Participants who discontinued the study drug due to inadvertent enrollment were excluded.

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

End point timeframe:

Baseline, Week 52

| End point values | 500 U/mL Insulin Efsitora Alfa | 100 U/mL Insulin Degludec | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 341 | 348 | | |
| Units: mmol/mol | | | | |
| least squares mean (standard error) | -4.10 (± 0.529) | -4.36 (± 0.524) | | |

**Statistical analyses**

| Statistical analysis title | Statistical Analysis |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |
| Number of subjects included in analysis | 689 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[2] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.2 |
| upper limit | 1.72 |

Notes:

[2] - 0.4% noninferiority margin (NIM)

**Secondary: Change from Baseline in Fasting Blood Glucose**

| End point title | Change from Baseline in Fasting Blood Glucose |
|---|---|

End point description:

Change from baseline in fasting glucose measured by self-monitoring blood glucose (SMBG).
LS mean was determined using ANCOVA model with treatment, country, CGM use prior to study entry [yes/no], carbohydrate counting for prandial insulin dosing [yes/no]) and baseline value of the dependent variable as variables. Missing data at Baseline were imputed with multiple imputation with assumption of missing at random. Missing data were imputed by return-to-baseline multiple imputations approach.
APD: All randomized participants who received at least one dose of the study drug and had evaluable data for this outcome at Baseline, Week 26, or Week 52 were included in the analysis. For the Week 26 analysis, data from Baseline or Week 26 were considered, while for the Week 52 analysis, data from Baseline or Week 52 were included. Participants who discontinued the study drug due to inadvertent enrollment were excluded.

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

End point timeframe:

Baseline, Week 26, and Week 52

| End point values | 500 U/mL Insulin Efsitora Alfa | 100 U/mL Insulin Degludec | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 341 | 348 | | |
| Units: millimoles per liter | | | | |
| least squares mean (standard error) | | | | |
| Week 26 | -1.48 (± 0.125) | -1.41 (± 0.123) | | |
| Week 52 | -1.38 (± 0.138) | -1.11 (± 0.136) | | |

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1: Week 26 |
|---|---|
| Comparison groups | 100 U/mL Insulin Degludec v 500 U/mL Insulin Efsitora Alfa |
| Number of subjects included in analysis | 689 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.697 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.41 |
| upper limit | 0.27 |

| Statistical analysis title | Statistical Analysis 2: Week 52 |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |
| Number of subjects included in analysis | 689 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.163 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.65 |
| upper limit | 0.11 |

## Secondary: Glucose Variability

| End point title | Glucose Variability |
|---|---|

End point description:

Glucose variability measured as coefficient of variation (CV) for blood glucose during the CGM session over a 24-hour period, between Week 23 to Week 26 and Week 49 to Week 52 was reported.
LS mean was determined using mixed model repeated measures (MMRM) model with BASELINE + Country + Prior CGM use + Carbohydrate counting for Prandial Dose + Hemoglobin A1c Stratum at Baseline + Treatment + Time + Treatment*Time (Type III sum of squares) as variables. Unstructured variance-covariance structure was used.
APD: All randomized participants who took at least one dose of the study drug and had a baseline and at least one post- baseline value for this outcome. Participants who discontinued the study drug due to inadvertent enrollment were excluded.

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

End point timeframe:

Week 23 to Week 26 and Week 49 to Week 52

| **End point values** | 500 U/mL Insulin Efsitora Alfa | 100 U/mL Insulin Degludec | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 331 | 332 | | |
| Units: percentage of CV | | | | |
| least squares mean (standard error) | | | | |
| Week 23 to Week 26 | 33.72 (± 0.230) | 33.69 (± 0.229) | | |
| Week 49 to Week 52 | 33.69 (± 0.233) | 33.18 (± 0.233) | | |

**Statistical analyses**

| **Statistical analysis title** | Statistical Analysis 1: Week 23 to Week 26 |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |
| Number of subjects included in analysis | 663 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.939 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.61 |
| upper limit | 0.66 |

| **Statistical analysis title** | Statistical Analysis 2: Week 49 to Week 52 |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |

| | |
|---|---|
| Number of subjects included in analysis | 663 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.116 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.13 |
| upper limit | 1.17 |

## Secondary: Percentage of Time in the Blood Glucose Range Between 70 and 180 mg/dL [3.9 and 10.0 mmol/L]

| | |
|---|---|
| End point title | Percentage of Time in the Blood Glucose Range Between 70 and 180 mg/dL [3.9 and 10.0 mmol/L] |

End point description:

Percentage of time spent within the blood glucose range of 70 to 180 mg/dL [3.9 to 10.0 mmol/L], as measured during the CGM session over a 24-hour period, from Week 49 to Week 52.
LS mean was determined using ANCOVA model with treatment, country, CGM use prior to study entry [yes/no], carbohydrate counting for prandial insulin dosing [yes/no]) and Hemoglobin A1c Stratum at baseline and baseline value of the dependent variable as variables. Missing data at Baseline were imputed with multiple imputation with assumption of missing at random. Missing data were imputed by return-to-baseline multiple imputations approach.
APD: All randomized participants who received at least one dose of the study drug and had evaluable data for this outcome at baseline or Week 49-52 were included in the analysis. Participants who discontinued the study drug due to inadvertent enrollment were excluded.

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

End point timeframe:

Week 49 to Week 52

| **End point values** | 500 U/mL Insulin Efsitora Alfa | 100 U/mL Insulin Degludec | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 338 | 347 | | |
| Units: percentage of time | | | | |
| least squares mean (standard error) | 50.28 (± 0.755) | 49.74 (± 0.744) | | |

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |

| | |
|---|---|
| Number of subjects included in analysis | 685 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.61 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.54 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.54 |
| upper limit | 2.62 |

## Secondary: Basal Insulin Dose

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

End point description:

The insulin dose was recorded daily or weekly in an electronic diary. The average weekly basal insulin dose at Week 26 and Week 52 was reported.
LS mean was determined using MMRM model with BASELINE + Hemoglobin A1c Stratum at Baseline + Country + Prior CGM use + Carbohydrate counting for Prandial Dose + Treatment + Time + Treatment*Time (Type III sum of squares) as variables. Variance-covariance structure was set as compound symmetry.
APD: All randomized participants who received at least one dose of the study drug and had a baseline and at least one post-baseline value for this outcome. Participants who discontinued the study drug due to inadvertent enrollment were excluded.

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

End point timeframe:

Week 26 and Week 52

| **End point values** | 500 U/mL Insulin Efsitora Alfa | 100 U/mL Insulin Degludec | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 341 | 347 | | |
| Units: Units per week (U/week) | | | | |
| least squares mean (standard error) | | | | |
| Week 26 | 199.51 (± 4.47) | 208.47 (± 4.43) | | |
| Week 52 | 204.37 (± 4.50) | 211.25 (± 4.46) | | |

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1: Week 26 |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |

| | |
|---|---|
| Number of subjects included in analysis | 688 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.155 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -8.96 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -21.3 |
| upper limit | 3.38 |

| **Statistical analysis title** | Statistical Analysis 2: Week 52 |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |
| Number of subjects included in analysis | 688 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.278 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -6.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -19.31 |
| upper limit | 5.55 |

## Secondary: Bolus Insulin Dose

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

End point description:

The insulin dose was recorded daily or weekly in an electronic diary. The average daily bolus insulin dose at Week 26 and Week 52 was reported.
LS mean was determined using MMRM model with BASELINE + Hemoglobin A1c Stratum at Baseline + Country + Prior CGM use + Carbohydrate counting for Prandial Dose + Treatment + Time + Treatment*Time (Type III sum of squares) as variables. Variance-covariance structure was set as compound symmetry.
APD: All randomized participants who received at least one dose of the study drug and had a baseline and at least one post-baseline value for this outcome. Participants who discontinued the study drug due to inadvertent enrollment were excluded.

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

End point timeframe:

Week 26 and Week 52

| End point values | 500 U/mL Insulin Efsitora Alfa | 100 U/mL Insulin Degludec | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 307 | 327 | | |
| Units: Units per day (U/day) | | | | |
| least squares mean (standard error) | | | | |
| Week 26 | 21.48 (± 0.64) | 25.25 (± 0.62) | | |
| Week 52 | 22.62 (± 0.65) | 26.10 (± 0.63) | | |

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1: Week 26 |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |
| Number of subjects included in analysis | 634 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -3.77 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.52 |
| upper limit | -2.03 |

| Statistical analysis title | Statistical Analysis 2: Week 52 |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |
| Number of subjects included in analysis | 634 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -3.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.26 |
| upper limit | -1.71 |

## Secondary: Total Insulin Dose

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

End point description:

The average weekly total insulin dose is the sum of the average weekly basal and bolus doses. LS mean was determined using MMRM model with BASELINE + Hemoglobin A1c Stratum at Baseline + Country + Prior CGM use + Carbohydrate counting for Prandial Dose + Treatment + Time + Treatment*Time (Type III sum of squares) as variables. Variance-covariance structure was set as compound symmetry.
APD: All randomized participants who received at least one dose of the study drug and had a baseline and at least one post-baseline value for this outcome. Participants who discontinued the study drug due to inadvertent enrollment were excluded.

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

End point timeframe:

Week 26 and Week 52

| **End point values** | 500 U/mL Insulin Efsitora Alfa | 100 U/mL Insulin Degludec | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 305 | 327 | | |
| Units: Units per week (U/week) | | | | |
| least squares mean (standard error) | | | | |
| Week 26 | 343.91 (± 6.72) | 383.19 (± 6.47) | | |
| Week 52 | 355.66 (± 6.81) | 391.60 (± 6.53) | | |

**Statistical analyses**

| **Statistical analysis title** | Statistical Analysis 1: Week 26 |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |
| Number of subjects included in analysis | 632 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -39.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -57.59 |
| upper limit | -20.98 |

| **Statistical analysis title** | Statistical Analysis 2: Week 52 |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |

| | |
|---|---|
| Number of subjects included in analysis | 632 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -35.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -54.44 |
| upper limit | -17.43 |

## Secondary: Basal Insulin Dose to Total Insulin Dose Ratio

| | |
|---|---|
| End point title | Basal Insulin Dose to Total Insulin Dose Ratio |

End point description:

The basal/total insulin dose ratio is the average weekly basal dose divided by the average weekly total dose.
LS mean was determined using MMRM model with BASELINE + Hemoglobin A1c Stratum at Baseline + Country + Prior CGM use + Carbohydrate counting for Prandial Dose + Treatment + Time + Treatment*Time (Type III sum of squares) as variables. Variance-covariance structure was set as compound symmetry.
APD: All randomized participants who received at least one dose of the study drug and had a baseline and at least one post-baseline value for this outcome. Participants who discontinued the study drug due to inadvertent enrollment were excluded.

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

End point timeframe:

Week 26 and Week 52

| **End point values** | 500 U/mL Insulin Efsitora Alfa | 100 U/mL Insulin Degludec | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 305 | 327 | | |
| Units: Ratio | | | | |
| least squares mean (standard error) | | | | |
| Week 26 | 56.4 (± 0.69) | 53.2 (± 0.66) | | |
| Week 52 | 55.4 (± 0.70) | 52.6 (± 0.67) | | |

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1: Week 26 |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |

| | |
|---|---|
| Number of subjects included in analysis | 632 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | 3.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.32 |
| upper limit | 5.06 |

| **Statistical analysis title** | Statistical Analysis 2: Week 52 |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |
| Number of subjects included in analysis | 632 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.004 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | 2.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.91 |
| upper limit | 4.7 |

## Secondary: Hypoglycemia Event Rate

| End point title | Hypoglycemia Event Rate |
|---|---|

End point description:

Rate of Composite Level 2 and 3 Hypoglycemia Events were reported. Hypoglycemia with glucose <54 mg/dL (Level 2) or Severe Hypoglycemia confirmed by the investigator to be an event that required assistance for treatment (Level 3) was reported. A severe hypoglycemic event is characterized by altered mental or physical status requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions for the treatment of hypoglycemia.
Group mean was reported and determined by Negative binomial model using Number of episodes = Baseline hypoglycemia rate + HbA1c at Baseline (%) + Treatment, with log (exposure in days/365.25) as an offset variable.
APD: All randomized participants who received at least one dose of the study drug.

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

End point timeframe:

Baseline up to Week 52

| End point values | 500 U/mL Insulin Efsitora Alfa | 100 U/mL Insulin Degludec | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 343 | 349 | | |
| Units: Events per year | | | | |
| arithmetic mean (standard error) | 14.03 (± 0.816) | 11.59 (± 0.681) | | |

**Statistical analyses**

| Statistical analysis title | Statistical Analysis |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |
| Number of subjects included in analysis | 692 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.016 |
| Method | Negative binomial model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 1.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.04 |
| upper limit | 1.41 |

**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 was reported. LS Mean was determined by MMRM model using Baseline + Treatment + Time + Treatment*Time (Type III sum of squares) as variables. Variance-covariance structure was set as compound symmetry.
APD: All randomized participants who received at least one dose of the study drug and had baseline, at least one post-baseline evaluable data for this outcome.

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

End point timeframe:

Baseline, Week 26, and Week 52

| End point values | 500 U/mL Insulin Efsitora Alfa | 100 U/mL Insulin Degludec | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 342 | 348 | | |
| Units: kilograms (kg) | | | | |
| least squares mean (standard error) | | | | |
| Baseline, Week 26 | 1.71 (± 0.159) | 1.62 (± 0.158) | | |

| | | | | |
|---|---|---|---|---|
| Baseline, Week 52 | 1.96 (± 0.160) | 1.85 (± 0.159) | | |

**Statistical analyses**

| **Statistical analysis title** | Statistical Analysis 1: Week 26 |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |
| Number of subjects included in analysis | 690 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.702 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.086 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.35 |
| upper limit | 0.53 |

| **Statistical analysis title** | Statistical Analysis 2: Week 52 |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |
| Number of subjects included in analysis | 690 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.609 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.33 |
| upper limit | 0.56 |

**Secondary: Percentage of Time in Hypoglycemia Range With Blood Glucose <54 mg/dL (3.0 mmol/L)**

| End point title | Percentage of Time in Hypoglycemia Range With Blood Glucose <54 mg/dL (3.0 mmol/L) |
|---|---|

End point description:

Percentage of time spent in the hypoglycemia range with blood glucose < 54 mg/dL (3.0 mmol/L), as measured during the CGM session over a 24-hour period from week 23 to week 26 and week 49 to week 52 was reported. LS Mean was determined by ANCOVA model using treatment + country + CGM use prior to study entry [yes/no] + carbohydrate counting for prandial insulin dosing [yes/no] + Hemoglobin A1c Stratum at Baseline and baseline value of the dependent variable (Type III sum of squares). as

variables. Missing data at Baseline were imputed with multiple imputation with assumption of missing at random. Missing data at week 23-week 26 and week 49-week 52 were imputed by return-to-baseline multiple imputations approach.
APD: For the Week 23-26 analysis, data from Baseline or Week 23-26 were considered, while for the Week 49-52 analysis, data from Baseline or Week 49-52 were included. Participants who discontinued the study drug due to inadvertent enrollment were excluded.

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

End point timeframe:

Week 23 to Week 26 and Week 49 to Week 52
APD: All randomized participants who received at least one dose of the study drug and had evaluable data for this outcome at Baseline, Week 23-26, or Week 49-52 were included in the analysis.

| **End point values** | 500 U/mL Insulin Efsitora Alfa | 100 U/mL Insulin Degludec | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 339 | 347 | | |
| Units: percentage of time | | | | |
| least squares mean (standard error) | | | | |
| Week 23 to Week 26 | 0.75 (± 0.058) | 0.72 (± 0.057) | | |
| Week 49 to Week 52 | 0.74 (± 0.053) | 0.64 (± 0.052) | | |

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1: Week 23 to Week 26 |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |
| Number of subjects included in analysis | 686 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.681 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.13 |
| upper limit | 0.19 |

| **Statistical analysis title** | Statistical Analysis 2: Week 49 to Week 52 |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |

| | |
|---|---|
| Number of subjects included in analysis | 686 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.182 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.05 |
| upper limit | 0.24 |

## Secondary: Percentage of Time in Hyperglycemia Range With Blood Glucose >180 mg/dL (10.0 mmol/L) from Week 23 to Week 26

| | |
|---|---|
| End point title | Percentage of Time in Hyperglycemia Range With Blood Glucose >180 mg/dL (10.0 mmol/L) from Week 23 to Week 26 |

End point description:

Percentage of time spent in the hyperglycemia range with blood glucose greater than (>) 180 mg/dL (10.0 mmol/L), as measured during the CGM session over a 24-hour period from Week 23 to Week 26 was reported.
LS Mean was determined by ANCOVA model using treatment + country + CGM use prior to study entry [yes/no] + carbohydrate counting for prandial insulin dosing [yes/no] + Hemoglobin A1c Stratum at Baseline and baseline value of the dependent variable (Type III sum of squares) as variables. Missing data at Baseline were imputed with multiple imputation with assumption of missing at random. Missing data at week 23-week 26 were imputed by return-to-baseline multiple imputations approach.
APD: All randomized participants who received at least one dose of the study drug and had evaluable data for this outcome at baseline or Week 23-26 were included in the analysis. Participants who discontinued the study drug due to inadvertent enrollment were excluded

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

End point timeframe:

Week 23 to Week 26

| **End point values** | 500 U/mL Insulin Efsitora Alfa | 100 U/mL Insulin Degludec | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 339 | 347 | | |
| Units: percentage of time | | | | |
| least squares mean (standard error) | 44.29 (± 0.743) | 44.29 (± 0.735) | | |

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |

| | |
|---|---|
| Number of subjects included in analysis | 686 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.999 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.06 |
| upper limit | 2.05 |

## Secondary: Diabetes Treatment Satisfaction as Measured by the Diabetes Treatment Satisfaction Questionnaire, Change Version (DTSQc) at Week 26

| | |
|---|---|
| End point title | Diabetes Treatment Satisfaction as Measured by the Diabetes Treatment Satisfaction Questionnaire, Change Version (DTSQc) at Week 26 |

End point description:

The DTSQc score is used to assess relative change in participant satisfaction from baseline. The questionnaire consists of 8 items, 6 of which measure Treatment Satisfaction, dealing with: 1. satisfaction with current treatment; 2. convenience of the treatment; 3. flexibility; 4. satisfaction with own understanding of participant's diabetes; 5. how likely to recommend their present treatment; and 6. how satisfied to continue with their present treatment. Each item is rated on a 7-point Likert scale (which ranges from -3 (much less satisfied) to +3 (much more satisfied). The scores from the 6 treatment satisfaction items are summed to a Total Treatment Satisfaction Score, which ranges from -18 (much less satisfied) to +18 (much more satisfied). Higher the score the greater the improvement in satisfaction with treatment. The lower the score the greater the deterioration in satisfaction with treatment.

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

End point timeframe:

Week 26
APD: All randomized participants who received at least one dose of the study drug and had evaluable data for this outcome. Participants who discontinued the study drug due to inadvertent enrollment were excluded.

| **End point values** | 500 U/mL Insulin Efsitora Alfa | 100 U/mL Insulin Degludec | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 306 | 314 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | 14.4 (± 4.53) | 13.2 (± 5.20) | | |

## Statistical analyses

| Statistical analysis title | Statistical Analysis: Week 26 |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |
| Number of subjects included in analysis | 620 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.008 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Diabetes Treatment Satisfaction as Measured by the Diabetes Treatment Satisfaction Questionnaire, Change Version (DTSQc) at Week 52

| End point title | Diabetes Treatment Satisfaction as Measured by the Diabetes Treatment Satisfaction Questionnaire, Change Version (DTSQc) at Week 52 |
|---|---|

End point description:

The DTSQc score is used to assess relative change in participant satisfaction from baseline. The questionnaire consists of 8 items, 6 of which measure Treatment Satisfaction, dealing with: 1. satisfaction with current treatment; 2. convenience of the treatment; 3. flexibility; 4. satisfaction with own understanding of participant's diabetes; 5. how likely to recommend their present treatment; and 6. how satisfied to continue with their present treatment. Each item is rated on a 7-point Likert scale (which ranges from -3 (much less satisfied) to +3 (much more satisfied). The scores from the 6 treatment satisfaction items are summed to a Total Treatment Satisfaction Score, which ranges from -18 (much less satisfied) to +18 (much more satisfied). Higher the score the greater the improvement in satisfaction with treatment. The lower the score the greater the deterioration in satisfaction with treatment.

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

End point timeframe:

Week 52
APD: All randomized participants who received at least one dose of the study drug and had evaluable data for this outcome. Participants who discontinued the study drug due to inadvertent enrollment were excluded.

| End point values | 500 U/mL Insulin Efsitora Alfa | 100 U/mL Insulin Degludec | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 310 | 312 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | 14.4 (± 5.31) | 12.8 (± 5.67) | | |

### Statistical analyses

| Statistical analysis title | Statistical Analysis: Week 52 |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |

| | |
|---|---|
| Number of subjects included in analysis | 622 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Change From Baseline in Short Form-36 Version 2 (SF-36 v2) Acute Form (Physical-Component and Mental-Component) Scores

| | |
|---|---|
| End point title | Change From Baseline in Short Form-36 Version 2 (SF-36 v2) Acute Form (Physical-Component and Mental-Component) Scores |

End point description:

The SF-36v2 is a participant-reported measure designed to assess health status using 36 items across 8 domains: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health. The 8 health domains are aggregated into two summary scores known as the physical component summary (PCS) score and the mental component summary (MCS) score. Scoring of each domain and both summary scores are norm based and presented in the form of T-scores, with a mean of 50 and a standard deviation of 10. Higher scores indicate better levels of function and/or better health. Range cannot be specified in norm-based scores.
LS Mean was determined by MMRM model with Baseline + Country + Carbohydrate counting for Prandial Dose + Prior CGM use + Hemoglobin A1c Stratum at Baseline + Treatment + Time + Treatment*Time (Type III sum of squares). as variables. Unstructured variance-covariance structure was used.

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

End point timeframe:

Baseline, Week 26, and Week 52
APD:All randomized participants who received at least one dose of study drug,had baseline and atleast one post-baseline value for this outcome.Participants discontinued study drug due to inadvertent enrollment were excluded

| **End point values** | 500 U/mL Insulin Efsitora Alfa | 100 U/mL Insulin Degludec | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 327 | 330 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | | | | |
| Physical Component Score: Baseline, Week 26 | 0.19 (± 0.275) | -0.24 (± 0.272) | | |
| Physical Component Score: Baseline, Week 52 | 0.48 (± 0.262) | -0.25 (± 0.260) | | |
| Mental Component Score: Baseline, Week 26 | 0.58 (± 0.419) | 0.36 (± 0.415) | | |
| Mental Component Score: Baseline, Week 52 | 0.61 (± 0.419) | 0.16 (± 0.417) | | |

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1: PCS: Baseline, Week 26 |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |

| | |
|---|---|
| Number of subjects included in analysis | 657 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.27 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.43 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.33 |
| upper limit | 1.19 |

| **Statistical analysis title** | Statistical Analysis 2: PCS: Baseline, Week 52 |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |
| Number of subjects included in analysis | 657 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.73 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 1.45 |

| **Statistical analysis title** | Statistical Analysis 3: MCS: Baseline, Week 26 |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |
| Number of subjects included in analysis | 657 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.71 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.94 |
| upper limit | 1.38 |

| **Statistical analysis title** | Statistical Analysis 4: MCS: Baseline, Week 52 |
|---|---|

| | |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |
| Number of subjects included in analysis | 657 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.447 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.71 |
| upper limit | 1.61 |

## Secondary: Percentage of Time in Hyperglycemia Range With Blood Glucose >180 mg/dL (10.0 mmol/L) From Week 49 to Week 52

| | |
|---|---|
| End point title | Percentage of Time in Hyperglycemia Range With Blood Glucose >180 mg/dL (10.0 mmol/L) From Week 49 to Week 52 |

End point description:

Percentage of time spent in the hyperglycemia range with blood glucose greater than (>) 180 mg/dL (10.0 mmol/L), as measured during the CGM session over a 24-hour period from Week 49 to Week 52 was reported.
LS Mean was determined by ANCOVA model using treatment + country + CGM use prior to study entry [yes/no] + carbohydrate counting for prandial insulin dosing [yes/no] + Hemoglobin A1c Stratum at Baseline and baseline value of the dependent variable (Type III sum of squares) as variables. Missing data at Baseline were imputed with multiple imputation with assumption of missing at random. Missing data at week 49-week 52 were imputed by return-to-baseline multiple imputations approach.
APD: All randomized participants who received at least one dose of the study drug and had evaluable data for this outcome at baseline or Week 49-52 were included in the analysis. Participants who discontinued the study drug due to inadvertent enrollment were excluded.

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

End point timeframe:

Week 49 to Week 52

| **End point values** | 500 U/mL Insulin Efsitora Alfa | 100 U/mL Insulin Degludec | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 338 | 347 | | |
| Units: percentage of time | | | | |
| least squares mean (standard error) | 46.73 (± 0.811) | 47.56 (± 0.797) | | |

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis |
|---|---|
| Comparison groups | 500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec |

| | |
|---|---|
| Number of subjects included in analysis | 685 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.468 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.83 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.06 |
| upper limit | 1.41 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline to end of safety follow-up (up to 57 weeks)

Adverse event reporting additional description:

All randomized participants who received at least one dose of study drug. Gender specific events occurring only in male or female participants have had the number of participants at risk adjusted accordingly.
Participants were analyzed based on the actual treatment they received.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 27.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | 100 U/mL Insulin Degludec |

Reporting group description:

Participants who were treated with prestudy basal insulin and prandial insulin therapy (100 U/mL Insulin Lispro) received 100 U/mL of Insulin Degludec administered once QW for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.

| | |
|---|---|
| Reporting group title | 500 U/mL Insulin Efsitora Alfa |

Reporting group description:

Participants who were treated with prestudy basal insulin and prandial insulin therapy (100 U/mL) Insulin Lispro) received 500 U/mL of insulin efsitora alfa administered QD for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.

| Serious adverse events | 100 U/mL Insulin Degludec | 500 U/mL Insulin Efsitora Alfa | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 24 / 349 (6.88%) | 45 / 343 (13.12%) | |
| number of deaths (all causes) | 1 | 0 | |
| number of deaths resulting from adverse events | | | |
| Vascular disorders | | | |
| aortic stenosis | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 0 / 349 (0.00%) | 1 / 343 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| abortion spontaneous | | | |
| alternative dictionary used: MedDRA 27.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed[1] | 0 / 158 (0.00%) | 2 / 150 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| dyspnoea | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 1 / 349 (0.29%) | 0 / 343 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| completed suicide | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 1 / 349 (0.29%) | 0 / 343 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| ankle fracture | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 1 / 349 (0.29%) | 0 / 343 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| limb injury | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 1 / 349 (0.29%) | 0 / 343 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| meniscus injury | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 1 / 349 (0.29%) | 0 / 343 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| road traffic accident | | | |
| alternative dictionary used: MedDRA 27.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 349 (0.00%) | 1 / 343 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| chronic granulomatous disease | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 1 / 349 (0.29%) | 0 / 343 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| limb reduction defect | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 0 / 349 (0.00%) | 1 / 343 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| angina pectoris | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 2 / 349 (0.57%) | 0 / 343 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| angina unstable | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 1 / 349 (0.29%) | 0 / 343 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| coronary artery disease | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 2 / 349 (0.57%) | 0 / 343 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| acute myocardial infarction | | | |
| alternative dictionary used: MedDRA 27.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 349 (0.29%) | 0 / 343 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| aphasia | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 0 / 349 (0.00%) | 1 / 343 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| dizziness | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 0 / 349 (0.00%) | 1 / 343 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| seizure | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 0 / 349 (0.00%) | 1 / 343 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| epilepsy | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 0 / 349 (0.00%) | 1 / 343 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| generalised tonic-clonic seizure | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 0 / 349 (0.00%) | 1 / 343 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypoglycaemic seizure | | | |
| alternative dictionary used: MedDRA 27.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 349 (0.29%) | 1 / 343 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypoglycaemic unconsciousness | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 4 / 349 (1.15%) | 10 / 343 (2.92%) | |
| occurrences causally related to treatment / all | 3 / 5 | 4 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| vertigo | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 0 / 349 (0.00%) | 1 / 343 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| gastritis | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 0 / 349 (0.00%) | 1 / 343 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| arthralgia | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 0 / 349 (0.00%) | 1 / 343 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| costochondritis | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 1 / 349 (0.29%) | 0 / 343 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| abscess limb | | | |
| alternative dictionary used: MedDRA 27.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 349 (0.00%) | 1 / 343 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| appendicitis | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 1 / 349 (0.29%) | 0 / 343 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| bronchitis | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 1 / 349 (0.29%) | 0 / 343 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| sepsis | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 2 / 349 (0.57%) | 0 / 343 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| osteomyelitis | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 2 / 349 (0.57%) | 0 / 343 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pneumonia | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 1 / 349 (0.29%) | 0 / 343 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| tooth infection | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 0 / 349 (0.00%) | 1 / 343 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| sinusitis | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 0 / 349 (0.00%) | 1 / 343 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| diabetic ketoacidosis | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 2 / 349 (0.57%) | 0 / 343 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypoglycaemia | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 7 / 349 (2.01%) | 27 / 343 (7.87%) | |
| occurrences causally related to treatment / all | 3 / 7 | 16 / 33 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Gender specific events occurring only in male or female participants have had the number of participants at risk adjusted accordingly.

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

| **Non-serious adverse events** | 100 U/mL Insulin Degludec | 500 U/mL Insulin Efsitora Alfa | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 119 / 349 (34.10%) | 117 / 343 (34.11%) | |
| Skin and subcutaneous tissue disorders | | | |
| dermatitis contact | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 16 / 349 (4.58%) | 19 / 343 (5.54%) | |
| occurrences (all) | 16 | 20 | |
| Infections and infestations | | | |
| covid-19 | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 23 / 349 (6.59%) | 16 / 343 (4.66%) | |
| occurrences (all) | 24 | 16 | |
| urinary tract infection | | | |
| alternative dictionary used: | | | |

| | | | |
|---|---|---|---|
| MedDRA 27.0 | | | |
| subjects affected / exposed | 11 / 349 (3.15%) | 21 / 343 (6.12%) | |
| occurrences (all) | 16 | 24 | |
| nasopharyngitis | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 42 / 349 (12.03%) | 40 / 343 (11.66%) | |
| occurrences (all) | 54 | 45 | |
| upper respiratory tract infection | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 30 / 349 (8.60%) | 24 / 343 (7.00%) | |
| occurrences (all) | 35 | 29 | |
| influenza | | | |
| alternative dictionary used: MedDRA 27.0 | | | |
| subjects affected / exposed | 18 / 349 (5.16%) | 27 / 343 (7.87%) | |
| occurrences (all) | 22 | 30 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 10 May 2022 | - Objectives, Endpoints, and Estimands were modified.<br>- Inclusion and Exclusion Criteria were modified.<br>- Updated the analysis populations/sets.<br>- Statistical Considerations: Made updates to endpoint word order throughout section and subsections for clarity<br>- Primary Endpoint(s)/Estimand(s) Analysis: Replaced the stratification factor "prestudy basal insulin glargine U-300 or other basal insulin" with a new stratification factor "CGM use prior to study entry [yes/no]" in ANCOVA and MMRM models.<br>- Safety Analyses: Removed inadvertently hidden text format applied to hypoglycemia time period definitions. |
| 21 June 2022 | - Schedule of Activities (SoA) have been updated.<br>- Deleted text "Potential intrinsic and extrinsic factors" from tertiary endpoints for PK/PD of LY3209590.<br>- Edited text to describe use of the unblinded Continuous glucose monitoring (CGM) system receive |
| 12 October 2022 | - SoA updated for clarity<br>- Inclusion and Exclusion Criteria were modified<br>- Added "if the participants can safely do this" for participants advised to check SMBG readings for suspected hypoglycemia for clarification.<br>- Added a note for participants to not manually calibrate the study CGM with fingerstick blood glucose readings for clarification. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported