



Clinical trial results:

A Randomized, 30-Week, Active-controlled, Open-Label, 2-Treatment Arm, Parallel-group, Multicenter Study Comparing the Efficacy and Safety of the Insulin Glargine/Lixisenatide Fixed Ratio Combination to Insulin Glargine With or Without Metformin in Patients with Type 2 Diabetes Mellitus (T2DM)

Summary

| | |
|--------------------------|----------------------------|
| EudraCT number | 2013-003132-79 |
| Trial protocol | EE SE LT CZ NL ES HU SK DK |
| Global end of trial date | 09 July 2015 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 24 July 2016 |
| First version publication date | 24 July 2016 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | EFC12405 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-----------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02058160 |
| WHO universal trial number (UTN) | U1111-1148-4351 |
| Other trial identifiers | Study Name: LixiLan-L |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Sanofi aventis recherche & développement |
| Sponsor organisation address | 1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380 |
| Public contact | Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com |
| Scientific contact | Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 10 August 2015 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 09 July 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of the insulin glargine/lixisenatide fixed ratio combination (FRC) to insulin glargine in glycated hemoglobin (HbA1c) change from baseline to Week 30.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency.

Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy:

If previously taken at a stable dose of at least 1500 mg/day or maximal tolerated dose for at least 3 months prior to screening, metformin as a background treatment was to be continued at a stable dose throughout the study unless prevented by a specific issue related to this treatment. Other oral antidiabetic treatment (OAD) if previously taken, were to be discontinued at start of run-in (6 weeks prior randomization).

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 27 January 2014 |
| 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 | Australia: 6 |
| Country: Number of subjects enrolled | Canada: 22 |
| Country: Number of subjects enrolled | Chile: 29 |
| Country: Number of subjects enrolled | Mexico: 58 |
| Country: Number of subjects enrolled | Romania: 42 |
| Country: Number of subjects enrolled | Russian Federation: 101 |
| Country: Number of subjects enrolled | Ukraine: 62 |
| Country: Number of subjects enrolled | United States: 175 |
| Country: Number of subjects enrolled | Netherlands: 3 |
| Country: Number of subjects enrolled | Poland: 37 |
| Country: Number of subjects enrolled | Slovakia: 40 |
| Country: Number of subjects enrolled | Spain: 26 |
| Country: Number of subjects enrolled | Sweden: 16 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Czech Republic: 41 |
| Country: Number of subjects enrolled | Denmark: 9 |
| Country: Number of subjects enrolled | Estonia: 8 |
| Country: Number of subjects enrolled | Hungary: 42 |
| Country: Number of subjects enrolled | Lithuania: 19 |
| Worldwide total number of subjects | 736 |
| EEA total number of subjects | 283 |

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) | 506 |
| From 65 to 84 years | 228 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 187 centers in 18 countries. A total of 1930 subjects were screened between January 27, 2014 and October 15, 2014. 912 subjects were not eligible for run-in phase mainly due to HbA1c value being out of the protocol-defined range.

Pre-assignment

Screening details:

After screening phase, 1018 subjects entered 6 week run-in phase, during which subjects were switched (if necessary) to insulin glargine; and dose was titrated/stabilized. Any OAD other than metformin were stopped. 282 subjects were run-in failures and 736 were randomized in 1:1 to FRC & insulin glargine arms in open-label treatment period.

Period 1

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

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Insulin Glargine/Lixisenatide Fixed Ratio Combination |

Arm description:

Fixed Ratio Combination (FRC) of insulin glargine/lixisenatide once daily (QD) dose individually adjusted up to 30 weeks.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Insulin glargine (100 U/mL)/Lixisenatide |
| Investigational medicinal product code | HOE901/AVE0010 |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

FRC was self-administered QD in the morning within 1 hour before breakfast using one of the 2 available prefilled disposable SoloStar® pen-injectors: pen A or B, depending upon dose.

Pen A contained 100 U/mL insulin glargine (Lantus, 100 U/mL) and 50 mcg/mL lixisenatide in a ratio of 2 U:1 mcg and was used for administration doses from 10 U/5 mcg up to 40 U/20 mcg. Pen B contained 100 U/mL insulin glargine (Lantus, 100 U/mL) and 33 mcg/mL lixisenatide in a ratio of 3 U:1 mcg and was used for administration doses from 30 U/10 mcg up to the maximal daily dose of 60 U/20 mcg. In order not to exceed the highest recommended initiation dose of 10 mcg for lixisenatide, the FRC was initiated at a dose of either 20 U/10mcg with Pen A or 30 U/10 mcg with Pen B, depending on subject's dose on the day before randomization.

The dose was kept stable for 2 weeks and then adjusted to reach and maintain fasting self-monitored plasma glucose (SMPG) of 80 mg/dL to 100 mg/dL (4.4 mmol/L to 5 mmol/L).

| | |
|------------------|------------------|
| Arm title | Insulin Glargine |
|------------------|------------------|

Arm description:

Insulin glargine QD dose individually adjusted up to 30 weeks.

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Insulin glargine |
| Investigational medicinal product code | HOE901 |
| Other name | Lantus |
| Pharmaceutical forms | Solution for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Insulin glargine 100 U/mL was self-administered QD at approximately the same time every day. The

time of the injection was decided at the discretion of the subject and Investigator, at run-in start, and was to remain roughly the same throughout the study.

The first dose after randomization was the same as the one administered on the day before randomization, and then dose was adjusted to reach and maintain fasting SMPG of 80 mg/dL to 100 mg/dL (4.4 mmol/L to 5.6 mmol/L).

| Number of subjects in period 1 | Insulin Glargine/Lixisenatide Fixed Ratio Combination | Insulin Glargine |
|--------------------------------|---|------------------|
| | | |
| Started | 367 | 369 |
| Treated | 365 | 365 |
| Completed | 336 | 355 |
| Not completed | 31 | 14 |
| Other than specified above | 12 | 6 |
| Adverse events | 12 | 3 |
| Randomized but not treated | 2 | 4 |
| Poor compliance to protocol | 4 | 1 |
| Lost to follow-up | 1 | - |

Baseline characteristics

Reporting groups

| | |
|---|---|
| Reporting group title | Insulin Glargine/Lixisenatide Fixed Ratio Combination |
| Reporting group description: Fixed Ratio Combination (FRC) of insulin glargine/lixisenatide once daily (QD) dose individually adjusted up to 30 weeks. | |
| Reporting group title | Insulin Glargine |
| Reporting group description: Insulin glargine QD dose individually adjusted up to 30 weeks. | |

| Reporting group values | Insulin Glargine/Lixisenatide Fixed Ratio Combination | Insulin Glargine | Total |
|------------------------------------|---|------------------|-------|
| Number of subjects | 367 | 369 | 736 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|---------------|---------------|-----|
| Age continuous Units: years arithmetic mean standard deviation | 59.6 ± 9.4 | 60.3 ± 8.7 | - |
| Gender categorical Units: Subjects | | | |
| Female | 202 | 190 | 392 |
| Male | 165 | 179 | 344 |
| Race Units: Subjects | | | |
| Caucasian | 337 | 338 | 675 |
| Black | 17 | 21 | 38 |
| Asian/Oriental | 12 | 8 | 20 |
| Other | 1 | 2 | 3 |
| Ethnicity Units: Subjects | | | |
| Hispanic | 66 | 66 | 132 |
| Not Hispanic | 301 | 303 | 604 |
| Oral Antidiabetic Drug (OAD) Use Units: Subjects | | | |
| Yes | 349 | 350 | 699 |
| No | 18 | 19 | 37 |
| OAD Use at Screening By Class Units: Subjects | | | |
| Metformin | 170 | 190 | 360 |
| Sulfonylurea | 16 | 14 | 30 |
| Sodiumglucose cotransporter-2 (SGLT-2) inhibitor | 0 | 1 | 1 |
| Dipeptidyl peptidase-4 (DPP-4) inhibitor | 2 | 4 | 6 |
| Glinide | 1 | 1 | 2 |
| Metformin + Sulfonylurea | 137 | 118 | 255 |

| | | | |
|--------------------------------|---------|---------|----|
| Metformin + DPP-4 inhibitor | 20 | 18 | 38 |
| Metformin + Glinide | 2 | 3 | 5 |
| Sulfonylurea + DPP-4 inhibitor | 1 | 1 | 2 |
| None | 18 | 19 | 37 |
| Body Mass Index (BMI) | | | |
| Units: kg/m ² | | | |
| arithmetic mean | 31.33 | 30.96 | |
| standard deviation | ± 4.25 | ± 4.15 | - |
| Duration of Diabetes | | | |
| (N = 367, 368) | | | |
| Units: years | | | |
| arithmetic mean | 12.02 | 12.13 | |
| standard deviation | ± 6.64 | ± 6.85 | - |
| Daily Dose of Metformin | | | |
| (N = 329, 329) | | | |
| Units: mg | | | |
| arithmetic mean | 2082.8 | 2042 | |
| standard deviation | ± 499.2 | ± 455.9 | - |
| HbA1c | | | |
| Units: Percentage of HbA1c | | | |
| arithmetic mean | 8.07 | 8.08 | |
| standard deviation | ± 0.68 | ± 0.73 | - |
| Fasting Plasma Glucose (FPG) | | | |
| Units: mmol/L | | | |
| arithmetic mean | 7.34 | 7.36 | |
| standard deviation | ± 1.95 | ± 2.12 | - |

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | Insulin Glargine/Lixisenatide Fixed Ratio Combination |
| Reporting group description: Fixed Ratio Combination (FRC) of insulin glargine/lixisenatide once daily (QD) dose individually adjusted up to 30 weeks. | |
| Reporting group title | Insulin Glargine |
| Reporting group description: Insulin glargine QD dose individually adjusted up to 30 weeks. | |

Primary: Change in HbA1c From Baseline to Week 30

| | |
|--|--|
| End point title | Change in HbA1c From Baseline to Week 30 |
| End point description: Change in HbA1c was calculated by subtracting baseline value from Week 30 value. Modified intent-to-treat (mITT) population: all randomized subjects who had both baseline and at least one post-baseline efficacy assessment. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline HbA1c assessment during study period. | |
| End point type | Primary |
| End point timeframe: Baseline, Week 30 | |

| End point values | Insulin Glargine/Lixisenatide Fixed Ratio Combination | Insulin Glargine | | |
|-------------------------------------|---|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 364 | 364 | | |
| Units: Percentage of hemoglobin | | | | |
| least squares mean (standard error) | -1.13 (± 0.057) | -0.62 (± 0.055) | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Insulin Glargine/Lixisenatide vs Insulin Glargine |
| Statistical analysis description: Analysis was performed using Mixed-effect model with repeated measures (MMRM) with treatment groups, randomization strata of Week -1 HbA1c (<8.0, ≥8.0%), randomization strata of metformin use at screening, visits, treatment-by-visit interaction and country as fixed effects and baseline HbA1c value-by-visit interaction as covariates. A hierarchical testing procedure was used to control type I error and handle multiple endpoint analyses. | |
| Comparison groups | Insulin Glargine/Lixisenatide Fixed Ratio Combination v Insulin Glargine |

| | |
|---|-----------------------------------|
| Number of subjects included in analysis | 728 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | < 0.0001 ^[2] |
| Method | Mixed models analysis |
| Parameter estimate | Least Square (LS) Mean Difference |
| Point estimate | -0.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.633 |
| upper limit | -0.397 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.06 |

Notes:

[1] - Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.05 level.

[2] - Threshold for significance at 0.05 level.

Secondary: Percentage of Subjects with HbA1c <7.0% or ≤6.5% at Week 30

| | |
|------------------------|--|
| End point title | Percentage of Subjects with HbA1c <7.0% or ≤6.5% at Week 30 |
| End point description: | mITT population. Subjects with no value for HbA1c at Week 30 were counted as non-responders. |
| End point type | Secondary |
| End point timeframe: | Week 30 |

| End point values | Insulin Glargine/Lixise natide Fixed Ratio Combination | Insulin Glargine | | |
|-------------------------------|--|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 366 | 365 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| HbA1c <7.0% | 54.9 | 29.6 | | |
| HbA1c ≤ 6.5% | 33.9 | 14.2 | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | HbA1c <7.0%: FRC vs Insulin Glargine |
| Statistical analysis description: | Analysis was performed using Cochran-Mantel-Haenszel method stratified on randomization strata of Week -1 HbA1c (<8.0%, ≥8.0%) and randomization strata of metformin use at screening. This analysis was out of testing order. |
| Comparison groups | Insulin Glargine/Lixisenatide Fixed Ratio Combination v Insulin Glargine |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 731 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[3] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Percentage Difference |
| Point estimate | 25.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 18.94 |
| upper limit | 32.1 |

Notes:

[3] - Threshold for significance at 0.05 level.

| | |
|-----------------------------------|--------------------------------------|
| Statistical analysis title | HbA1c ≤6.5%: FRC vs Insulin Glargine |
|-----------------------------------|--------------------------------------|

Statistical analysis description:

Analysis was performed using Cochran-Mantel-Haenszel method stratified on randomization strata of Week -1 HbA1c (<8.0%, ≥8.0%) and randomization strata of metformin use at screening. This analysis was out of testing order.

| | |
|---|--|
| Comparison groups | Insulin Glargine/Lixisenatide Fixed Ratio Combination v Insulin Glargine |
| Number of subjects included in analysis | 731 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[4] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Percentage Difference |
| Point estimate | 19.76 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 13.9 |
| upper limit | 25.62 |

Notes:

[4] - Threshold for significance at 0.05 level.

Secondary: Change in 2-hour Plasma Blood Glucose Excursion from Baseline to Week 30

| | |
|-----------------|--|
| End point title | Change in 2-hour Plasma Blood Glucose Excursion from Baseline to Week 30 |
|-----------------|--|

End point description:

Plasma glucose excursion = 2-hour postprandial glucose (PPG) minus plasma glucose value obtained 30 minutes prior to the start of the meal and before investigational medicinal product (IMP) administration, if IMP was injected before breakfast. Change in plasma glucose excursions were calculated by subtracting baseline value from Week 30 value. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline plasma glucose excursion assessment during study period. Missing data was imputed using last observation carried forward (LOCF).

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

End point timeframe:

Baseline, Week 30

| End point values | Insulin Glargine/Lixisenatide Fixed Ratio Combination | Insulin Glargine | | |
|-------------------------------------|---|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 329 | 336 | | |
| Units: mmol/L | | | | |
| least squares mean (standard error) | -3.9 (\pm 0.285) | -0.47 (\pm 0.274) | | |

Statistical analyses

| Statistical analysis title | FRC vs Insulin Glargine |
|----------------------------|-------------------------|
|----------------------------|-------------------------|

Statistical analysis description:

Testing according to the hierarchical testing procedure (continued only if previous endpoints were statistically significant). Analysis was performed using analysis of covariance (ANCOVA) model with treatment groups, randomization strata of Week -1 HbA1c [<8.0 , $\geq 8.0\%$], randomization strata of metformin use at screening and country as fixed effects and baseline 2-hour plasma glucose excursion value as a covariate.

| | |
|---|--|
| Comparison groups | Insulin Glargine/Lixisenatide Fixed Ratio Combination v Insulin Glargine |
| Number of subjects included in analysis | 665 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[5] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -3.43 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.925 |
| upper limit | -2.939 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.251 |

Notes:

[5] - Threshold for significance at 0.05 level.

Secondary: Change in Body Weight From Baseline to Week 30

| | |
|-----------------|--|
| End point title | Change in Body Weight From Baseline to Week 30 |
|-----------------|--|

End point description:

Change in body weight was calculated by subtracting baseline value from Week 30 value. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline body weight assessment during study period.

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

End point timeframe:

Baseline, Week 30

| End point values | Insulin Glargine/Lixise natide Fixed Ratio Combination | Insulin Glargine | | |
|-------------------------------------|--|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 365 | 365 | | |
| Units: kg | | | | |
| least squares mean (standard error) | -0.67 (\pm 0.181) | 0.7 (\pm 0.178) | | |

Statistical analyses

| Statistical analysis title | FRC vs Insulin Glargine |
|----------------------------|-------------------------|
|----------------------------|-------------------------|

Statistical analysis description:

Testing according to the hierarchical testing procedure (continued only if previous endpoints were statistically significant). Analysis was performed using MMRM model with treatment groups, randomization strata of Week -1 HbA1c (<8.0, \geq 8.0%), randomization strata of metformin use at screening, scheduled visits, treatment-by-visit interaction and country as fixed effects and baseline body weight value-by-visit interaction as covariates.

| | |
|---|--|
| Comparison groups | Insulin Glargine/Lixisenatide Fixed Ratio Combination v Insulin Glargine |
| Number of subjects included in analysis | 730 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[6] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.37 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.808 |
| upper limit | -0.93 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.224 |

Notes:

[6] - Threshold for significance at 0.05 level.

Secondary: Mean Change in 7-point SMPG Profile From Baseline to Week 30

| | |
|-----------------|--|
| End point title | Mean Change in 7-point SMPG Profile From Baseline to Week 30 |
|-----------------|--|

End point description:

Subjects recorded a 7-point plasma glucose profile measured before and 2-hours after each meal and at bedtime, two times in a week before baseline, before visit Week 12 and before visit Week 30 and the average value across the profiles performed in the week before a visit for the 7 time points was calculated. Change in average 7 point SMPG was calculated by subtracting baseline value from Week 30 value. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post baseline 7-point SMPG assessment during study period.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 30 | |

| End point values | Insulin Glargine/Lixise natide Fixed Ratio Combination | Insulin Glargine | | |
|-------------------------------------|--|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 323 | 320 | | |
| Units: mmol/L | | | | |
| least squares mean (standard error) | -1.5 (± 0.137) | -0.6 (± 0.13) | | |

Statistical analyses

| Statistical analysis title | FRC vs Insulin Glargine |
|--|--|
| Statistical analysis description: | |
| Testing according to the hierarchical testing procedure (continued only if previous endpoints were statistically significant). Analysis was performed using MMRM model with treatment groups, randomization strata of Week -1 HbA1c (<8.0, ≥8.0%), randomization strata of metformin use at screening, scheduled visits, treatment-by-visit interaction and country as fixed effects and baseline average SMPG value-by-visit interaction as covariates. | |
| Comparison groups | Insulin Glargine/Lixisenatide Fixed Ratio Combination v Insulin Glargine |
| Number of subjects included in analysis | 643 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[7] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.154 |
| upper limit | -0.64 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.131 |

Notes:

[7] - Threshold for significance at 0.05 level.

Secondary: Percentage of Subjects Reaching HbA1c <7.0% With No Body Weight Gain at Week 30

| | |
|-----------------|---|
| End point title | Percentage of Subjects Reaching HbA1c <7.0% With No Body Weight Gain at Week 30 |
|-----------------|---|

End point description:

mITT population. Subjects without HbA1c and/or body weight value at Week 30 were counted as non-responders.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 30 | |

| End point values | Insulin Glargine/Lixisenatide Fixed Ratio Combination | Insulin Glargine | | |
|-------------------------------|---|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 366 | 365 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 34.2 | 13.4 | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | FRC vs Insulin Glargine |
| Statistical analysis description: | |
| Testing according to the hierarchical testing procedure (continued only if previous endpoints were statistically significant). Analysis was performed using Cochran-Mantel-Haenszel method stratified on randomization strata of Week-1 HbA1c (<8.0%, ≥8.0%) and randomization strata of metformin use at screening. | |
| Comparison groups | Insulin Glargine/Lixisenatide Fixed Ratio Combination v Insulin Glargine |
| Number of subjects included in analysis | 731 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[8] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Percentage Difference |
| Point estimate | 20.82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 14.98 |
| upper limit | 26.66 |

Notes:

[8] - Threshold for significance at 0.05 level.

Secondary: Change in Daily Insulin Glargine Dose From Baseline to Week 30

| | |
|---|--|
| End point title | Change in Daily Insulin Glargine Dose From Baseline to Week 30 |
| End point description: | |
| mITT population. The analysis included scheduled measurements obtained up to the date of last injection of IMP. Here, number of subjects analyzed=subjects with insulin glargine dose assessment during study period. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 30 | |

| End point values | Insulin Glargine/Lixise natide Fixed Ratio Combination | Insulin Glargine | | |
|-------------------------------------|--|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 364 | 365 | | |
| Units: Units (U) | | | | |
| least squares mean (standard error) | 10.64 (± 0.601) | 10.89 (± 0.587) | | |

Statistical analyses

| Statistical analysis title | FRC vs Insulin Glargine |
|----------------------------|-------------------------|
|----------------------------|-------------------------|

Statistical analysis description:

Testing according to the hierarchical testing procedure (continued only if previous endpoints were statistically significant). Analysis was performed using MMRM model with treatment groups, randomization strata of Week -1 HbA1c (<8.0, ≥8.0%), randomization strata of metformin use at screening, scheduled visits, treatment-by-visit interaction, and country as fixed effects, and baseline daily insulin glargine dose-by-visit interaction as a covariate.

| | |
|---|--|
| Comparison groups | Insulin Glargine/Lixisenatide Fixed Ratio Combination v Insulin Glargine |
| Number of subjects included in analysis | 729 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7362 ^[9] |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.762 |
| upper limit | 1.246 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.766 |

Notes:

[9] - Threshold for significance at 0.05 level.

Secondary: Percentage of Subjects Reaching HbA1c <7.0% with No Body Weight Gain at Week 30 and No Documented (Plasma Glucose [PG] ≤ 70 mg/dL [3.9 mmol/L]) Symptomatic Hypoglycemia During 30-Week Treatment Period

| | |
|-----------------|--|
| End point title | Percentage of Subjects Reaching HbA1c <7.0% with No Body Weight Gain at Week 30 and No Documented (Plasma Glucose [PG] ≤ 70 mg/dL [3.9 mmol/L]) Symptomatic Hypoglycemia During 30-Week Treatment Period |
|-----------------|--|

End point description:

Documented symptomatic hypoglycemia was an event during which typical symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of ≤70 mg/dL (3.9 mmol/L). mITT population. Subjects without HbA1c and/or body weight value at Week 30 were counted as non-

responders.

| | |
|------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to Week 30 | |

| End point values | Insulin Glargine/Lixise natide Fixed Ratio Combination | Insulin Glargine | | |
|-------------------------------|--|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 366 | 365 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 19.9 | 9 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Fasting Plasma Glucose (FPG) From Baseline to Week 30

| | |
|-----------------|---|
| End point title | Change in Fasting Plasma Glucose (FPG) From Baseline to Week 30 |
|-----------------|---|

End point description:

Change in FPG was calculated by subtracting baseline value from Week 30 value. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline FPG assessment during study period.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 30 | |

| End point values | Insulin Glargine/Lixise natide Fixed Ratio Combination | Insulin Glargine | | |
|-------------------------------------|--|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 364 | 364 | | |
| Units: mmol/L | | | | |
| least squares mean (standard error) | -0.35 (± 0.142) | -0.46 (± 0.138) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in 2-Hour PPG From Baseline to Week 30

| | |
|-----------------|---|
| End point title | Change in 2-Hour PPG From Baseline to Week 30 |
|-----------------|---|

End point description:

Change in PPG was calculated by subtracting baseline value from Week 30 value. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline PPG assessment during study period. Missing data was imputed using LOCF.

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

End point timeframe:

Baseline, Week 30

| End point values | Insulin Glargine/Lixise natide Fixed Ratio Combination | Insulin Glargine | | |
|-------------------------------------|---|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 332 | 340 | | |
| Units: mmol/L | | | | |
| least squares mean (standard error) | -4.72 (± 0.322) | -1.39 (± 0.31) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reaching HbA1c <7.0% with No Documented Symptomatic Hypoglycemia (PG ≤ 70 mg/dL [3.9 mmol/L]) During 30-Week Treatment Period

| | |
|-----------------|--|
| End point title | Percentage of Subjects Reaching HbA1c <7.0% with No Documented Symptomatic Hypoglycemia (PG ≤ 70 mg/dL [3.9 mmol/L]) During 30-Week Treatment Period |
|-----------------|--|

End point description:

Documented symptomatic hypoglycemia was an event during which typical symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of ≤70 mg/dL (3.9 mmol/L). mITT population. Subjects with no value for HbA1c at Week 30 were counted as non-responders.

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

End point timeframe:

Baseline up to Week 30

| End point values | Insulin Glargine/Lixise natide Fixed Ratio Combination | Insulin Glargine | | |
|-------------------------------|---|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 366 | 365 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 31.7 | 18.6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Requiring Rescue Therapy During 30-Week Treatment Period

| | |
|-----------------|---|
| End point title | Percentage of Subjects Requiring Rescue Therapy During 30-Week Treatment Period |
|-----------------|---|

End point description:

Routine fasting SMPG and central laboratory FPG (and HbA1c after Week 12) values were used to determine the requirement of rescue medication. If fasting SMPG value exceeded the specified limit for 3 consecutive days, the central laboratory FPG (and HbA1c after week 12) were performed. mITT population.

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

End point timeframe:

Baseline up to Week 30

| End point values | Insulin Glargine/Lixise natide Fixed Ratio Combination | Insulin Glargine | | |
|-------------------------------|--|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 366 | 365 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 2.7 | 6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Documented Symptomatic Hypoglycemia Events Per Subject-Year

| | |
|-----------------|---|
| End point title | Number of Documented Symptomatic Hypoglycemia Events Per Subject-Year |
|-----------------|---|

End point description:

Documented symptomatic hypoglycemia was an event during which symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of ≤ 70 mg/dL (3.9 mmol/L). Analysis was performed on safety population defined as all randomized subjects who received at least one dose of IMP regardless of the amount of treatment administered.

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

End point timeframe:

First dose of study drug up to 1 day after the last dose administration (median treatment exposure 211 days [FRC], 210 days [Insulin glargine])

| End point values | Insulin Glargine/Lixise natide Fixed Ratio Combination | Insulin Glargine | | |
|--------------------------------|---|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 365 | 365 | | |
| Units: Events per subject-year | | | | |
| number (not applicable) | 3.03 | 4.22 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Documented Symptomatic Hypoglycemia

| | |
|-----------------|---|
| End point title | Percentage of Subjects with Documented Symptomatic Hypoglycemia |
|-----------------|---|

End point description:

Documented symptomatic hypoglycemia was an event during which symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of ≤ 70 mg/dL (3.9 mmol/L). Analysis was performed on safety population.

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

End point timeframe:

First dose of study drug up to 1 day after the last dose administration (median treatment exposure 211 days [FRC], 210 days [Insulin glargine])

| End point values | Insulin Glargine/Lixise natide Fixed Ratio Combination | Insulin Glargine | | |
|-------------------------------|---|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 365 | 365 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 40 | 42.5 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Severe Symptomatic Hypoglycemia

| | |
|-----------------|---|
| End point title | Percentage of Subjects with Severe Symptomatic Hypoglycemia |
|-----------------|---|

End point description:

Severe symptomatic hypoglycemia was an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Plasma glucose measurements might not have been available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal was considered sufficient evidence that the event had been induced by a low plasma glucose concentration. Severe symptomatic hypoglycemia included all episodes in which neurological impairment was severe enough to prevent self-treatment, and which were thus thought to place subjects at risk for injury to themselves or others. Analysis was performed on safety population.

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

End point timeframe:

First dose of study drug up to 1 day after the last dose administration (median treatment exposure 211 days [FRC], 210 days [Insulin glargine])

| End point values | Insulin Glargine/Lixise natide Fixed Ratio Combination | Insulin Glargine | | |
|-------------------------------|---|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 365 | 365 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 1.1 | 0.3 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Week 30) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs and deaths are treatment-emergent that is AEs that developed/worsened and deaths that occurred during on-emergent period' (time from first injection of open-label IMP up to 3 days after the last injection of IMP. Analysis was performed on safety population.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Insulin Glargine/Lixisenatide Fixed Ratio Combination |
|-----------------------|---|

Reporting group description:

Fixed Ratio Combination (FRC) of Insulin glargine /lixisenatide QD dose individually adjusted up to 30 weeks (median exposure: 211 days).

| | |
|-----------------------|------------------|
| Reporting group title | Insulin Glargine |
|-----------------------|------------------|

Reporting group description:

Insulin glargine QD dose individually adjusted up to 30 weeks (median exposure: 210 days).

| Serious adverse events | Insulin Glargine/Lixisenatide Fixed Ratio Combination | Insulin Glargine | |
|---|---|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 20 / 365 (5.48%) | 18 / 365 (4.93%) | |
| number of deaths (all causes) | 1 | 2 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Benign Breast Neoplasm | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 365 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Benign Gastric Neoplasm | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 365 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast Cancer | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 365 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gallbladder Cancer | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 365 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Kaposi's Sarcoma | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 365 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous Cell Carcinoma Of The Tongue | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 365 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 365 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Chest Discomfort | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 365 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-Cardiac Chest Pain | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 2 / 365 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Benign Prostatic Hyperplasia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 365 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Meniscus Injury | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 365 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Scar | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 365 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural Haematoma | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 365 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute Myocardial Infarction | | | |
| subjects affected / exposed | 2 / 365 (0.55%) | 0 / 365 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina Unstable | | | |
| subjects affected / exposed | 2 / 365 (0.55%) | 0 / 365 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriosclerosis Coronary Artery | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 365 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac Failure Congestive | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 365 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Cardiopulmonary Failure | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 365 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Myocardial Infarction | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 365 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular Tachycardia | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 365 (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 | | | |
| Hypoglycaemic Seizure | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 365 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemic Unconsciousness | | | |
| subjects affected / exposed | 2 / 365 (0.55%) | 0 / 365 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Glaucoma | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 365 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis Acute | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 365 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis Chronic | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 365 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal Impairment | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 365 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Intervertebral Disc Protrusion | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 365 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 365 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendonitis | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 0 / 365 (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 | | | |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 365 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 365 (0.27%) | 1 / 365 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Wound Infection | | | |
| subjects affected / exposed | 0 / 365 (0.00%) | 1 / 365 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Metabolism and nutrition disorders | | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 2 / 365 (0.55%) | 1 / 365 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Insulin Glargine/Lixisenatid e Fixed Ratio Combination | Insulin Glargine | |
|---|---|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 81 / 365 (22.19%) | 42 / 365 (11.51%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 21 / 365 (5.75%) | 10 / 365 (2.74%) | |
| occurrences (all) | 32 | 11 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 38 / 365 (10.41%) | 2 / 365 (0.55%) | |
| occurrences (all) | 44 | 3 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 32 / 365 (8.77%) | 32 / 365 (8.77%) | |
| occurrences (all) | 35 | 36 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|--------------|---|
| 03 July 2014 | - Exclusion criterion was modified to limit exclusion to subjects who used insulin products other than basal insulin within 1 year prior to screening and to clarify the duration of short-term treatment. - Monitoring and evaluating of device/pen-related events was added. - Changes to collection of pharmacokinetic (PK) and antibody sampling were made. - The calculated creatinine clearance categories at screening used for the description of demographic and baseline characteristics were changed. - Contraceptive methods allowed for women of childbearing potential were clarified. - The statistical method used for the efficacy analyses was changed. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported