



## Clinical trial results:

### A Randomized, Open-Label, Active-Controlled, 3-Arm Parallel-Group, 26-Week Study Comparing the Efficacy and Safety of Lixisenatide to That of Insulin Glulisine Once Daily and Insulin Glulisine Three Times Daily in Patients With Type 2 Diabetes Insufficiently Controlled With Insulin Glargine With or Without Metformin

#### Summary

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2012-004096-38                |
| Trial protocol           | CZ GB HU ES IT DE PL EE LV LT |
| Global end of trial date | 03 December 2014              |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 28 July 2016 |
| First version publication date | 28 July 2016 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | EFC12626 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |                           |
|------------------------------------|---------------------------|
| ISRCTN number                      | -                         |
| ClinicalTrials.gov id (NCT number) | NCT01768559               |
| WHO universal trial number (UTN)   | U1111-1131-4936           |
| Other trial identifiers            | Study Name: GETGOAL DUO-2 |

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                       | 16 January 2015  |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 03 December 2014 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate in subjects with type 2 diabetes mellitus (T2DM) not adequately controlled on insulin glargine with or without metformin: The non-inferiority of lixisenatide versus insulin glulisine once daily (QD) (Basal Plus regimen) on glycated hemoglobin A1c (HbA1c) reduction at Week 26; The non-inferiority of lixisenatide versus insulin glulisine thrice daily (TID)(Basal Bolus regimen) on HbA1c reduction or superiority on body weight change at Week 26.

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:

Subjects received insulin glargine throughout the study. During the run-in phase, the dose of insulin glargine was titrated every 3 days to maintain a fasting self-monitored plasma glucose (SMPG) between 80 and 100 mg/dL (4.4 and 5.6 mmol/L, respectively). After randomization, except during the 4 weeks following randomization where a stable dose should be maintained, the dose was adjusted weekly as necessary to maintain a fasting SMPG in the same range. Subjects who were receiving metformin prior to entering the study, continued to receive metformin at a dose of  $\geq 1.5$  g/day or at the maximal tolerated dose throughout the study, at a stable dose unless there was a specific safety issue related to this treatment.

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 08 January 2013 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Poland: 27         |
| Country: Number of subjects enrolled | Spain: 35          |
| Country: Number of subjects enrolled | United Kingdom: 23 |
| Country: Number of subjects enrolled | Czech Republic: 27 |
| Country: Number of subjects enrolled | Estonia: 14        |
| Country: Number of subjects enrolled | France: 28         |
| Country: Number of subjects enrolled | Germany: 30        |
| Country: Number of subjects enrolled | Hungary: 54        |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Italy: 16              |
| Country: Number of subjects enrolled | Latvia: 14             |
| Country: Number of subjects enrolled | Lithuania: 15          |
| Country: Number of subjects enrolled | Canada: 65             |
| Country: Number of subjects enrolled | Chile: 50              |
| Country: Number of subjects enrolled | Mexico: 100            |
| Country: Number of subjects enrolled | Romania: 118           |
| Country: Number of subjects enrolled | Russian Federation: 86 |
| Country: Number of subjects enrolled | Ukraine: 54            |
| Country: Number of subjects enrolled | United States: 138     |
| Worldwide total number of subjects   | 894                    |
| EEA total number of subjects         | 401                    |

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)                      | 616 |
| From 65 to 84 years                       | 277 |
| 85 years and over                         | 1   |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 199 centers in 18 countries between January 08, 2013 and December 03, 2014.

### Pre-assignment

Screening details:

A total of 2159 subjects were screened. Subjects underwent a 12 week run-in period with switch from other basal insulins to insulin glargine. 1265 subjects were screen failures/run-in failures; the most frequent reason for run-in failure was that HbA1C criteria were not met at the end of run-in phase. A total of 894 subjects were randomized.

### 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          |
| <b>Arm title</b>             | Lixisenatide |

Arm description:

Lixisenatide 10 mcg QD subcutaneously for 2 weeks post-randomization, then at a maintenance dose of 20 mcg QD up to Week 26 on top of insulin glargine with or without metformin.

|  |  |
|--|--|
| Arm type                               | Experimental                             |
| Investigational medicinal product name | Lixisenatide                             |
| Investigational medicinal product code | AVE0010                                  |
| Other name                             | Lyxumia®                                 |
| Pharmaceutical forms                   | Solution for injection in pre-filled pen |
| Routes of administration               | Subcutaneous use                         |

Dosage and administration details:

Lixisenatide was self-administered QD by subcutaneous injection 30 to 60 minutes before breakfast or dinner using disposable pre-filled pen.

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | Insulin Glulisine QD |
|------------------|----------------------|

Arm description:

Insulin glulisine QD subcutaneously from randomization up to Week 26 on top of insulin glargine with or without metformin.

|  |  |
|--|--|
| Arm type                               | Experimental                             |
| Investigational medicinal product name | Insulin glulisine                        |
| Investigational medicinal product code |  |
| Other name                             | Apidra®                                  |
| Pharmaceutical forms                   | Solution for injection in pre-filled pen |
| Routes of administration               | Subcutaneous use                         |

Dosage and administration details:

Insulin glulisine was administered QD within 15 minutes before breakfast or dinner. The initial dose was 3-5 units and then individually titrated to obtain the SMPG value  $>5.6$  mmol/L (100 mg/dL) and  $\leq 7.8$  mmol/L (140 mg/dL) before lunch (if administered at breakfast) or at bedtime (if administered at dinner).

|                  |                       |
|------------------|-----------------------|
| <b>Arm title</b> | Insulin Glulisine TID |
|------------------|-----------------------|

Arm description:

Insulin Glulisine TID subcutaneously from randomization up to Week 26 on top of insulin glargine with or without metformin.

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

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

Dosage and administration details:

Insulin glulisine was administered TID within 15 minutes before each meal. The initial dose was 3-5 units for each meal and then individually titrated to obtain the SMPG value >5.6 mmol/L (100 mg/dL) and ≤7.8 mmol/L (140 mg/dL) before the next meal (for injections at breakfast or at lunch) or at bedtime (for injection at dinner).

| <b>Number of subjects in period 1</b> | Lixisenatide | Insulin Glulisine QD | Insulin Glulisine TID |
|---------------------------------------|--------------|----------------------|-----------------------|
| Started                               | 298          | 298                  | 298                   |
| Treated                               | 298          | 298                  | 297                   |
| Completed                             | 268          | 281                  | 285                   |
| Not completed                         | 30           | 17                   | 13                    |
| Randomized but not treated            | -            | -                    | 1                     |
| Adverse event                         | 15           | 2                    | 5                     |
| Other than specified                  | 9            | 8                    | 5                     |
| Poor compliance to protocol           | -            | 3                    | 2                     |
| Lack of efficacy                      | 6            | 4                    | -                     |

## Baseline characteristics

### Reporting groups

|   |                       |
|---|-----------------------|
| Reporting group title   | Lixisenatide          |
| Reporting group description:<br>Lixisenatide 10 mcg QD subcutaneously for 2 weeks post-randomization, then at a maintenance dose of 20 mcg QD up to Week 26 on top of insulin glargine with or without metformin. |                       |
| Reporting group title   | Insulin Glulisine QD  |
| Reporting group description:<br>Insulin glulisine QD subcutaneously from randomization up to Week 26 on top of insulin glargine with or without metformin.  |                       |
| Reporting group title   | Insulin Glulisine TID |
| Reporting group description:<br>Insulin Glulisine TID subcutaneously from randomization up to Week 26 on top of insulin glargine with or without metformin.   |                       |

| Reporting group values   | Lixisenatide  | Insulin Glulisine QD | Insulin Glulisine TID |
|--|---------------|----------------------|-----------------------|
| Number of subjects   | 298           | 298                  | 298                   |
| Age categorical<br>Units: Subjects   |               |                      |                       |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation      | 59.8<br>± 8.6 | 60.2<br>± 8.6        | 59.4<br>± 9.5         |
| Gender categorical<br>Units: Subjects  |               |                      |                       |
| Female   | 160           | 163                  | 166                   |
| Male   | 138           | 135                  | 132                   |
| Race<br>Units: Subjects  |               |                      |                       |
| Caucasian/White  | 276           | 280                  | 272                   |
| Black  | 13            | 11                   | 12                    |
| Asian/Oriental   | 9             | 7                    | 13                    |
| Other  | 0             | 0                    | 1                     |
| Ethnicity<br>Units: Subjects   |               |                      |                       |
| Hispanic   | 63            | 58                   | 68                    |
| Non-Hispanic   | 235           | 240                  | 230                   |
| Metformin use at screening<br>Units: Subjects                                |               |                      |                       |
| Yes  | 262           | 260                  | 259                   |
| No   | 36            | 38                   | 39                    |
| Number of Subjects with Categorical Body Mass Index (BMI)<br>Units: Subjects |               |                      |                       |
| <30 kg/m <sup>2</sup>  | 97            | 118                  | 97                    |
| ≥30 kg/m <sup>2</sup>  | 201           | 180                  | 200                   |
| Subjects not analyzed for BMI  | 0             | 0                    | 1                     |

|  |         |         |         |
|--|---------|---------|---------|
| BMI  |         |         |         |
| 893 subjects (298 in lixisenatide arm; 298 in Insulin Glulisine QD and 297 in Insulin Glulisine TID) were included for baseline BMI analysis.          |         |         |         |
| Units: kg/m <sup>2</sup>   |         |         |         |
| arithmetic mean  | 32.27   | 31.86   | 32.5    |
| standard deviation   | ± 4.57  | ± 4.39  | ± 4.6   |
| Weight   |         |         |         |
| 893 subjects (298 in lixisenatide arm; 298 in Insulin Glulisine QD and 297 in Insulin Glulisine TID) were included for baseline weight analysis.       |         |         |         |
| Units: kg  |         |         |         |
| arithmetic mean  | 90.06   | 88.45   | 90.08   |
| standard deviation   | ± 17.31 | ± 15.84 | ± 17.18 |
| HbA1c  |         |         |         |
| 893 subjects (298 in lixisenatide arm; 298 in Insulin Glulisine QD and 297 in Insulin Glulisine TID) were included for HbA1c analysis.                 |         |         |         |
| Units: Percentage of hemoglobin  |         |         |         |
| arithmetic mean  | 7.77    | 7.73    | 7.79    |
| standard deviation   | ± 0.55  | ± 0.59  | ± 0.6   |
| Fasting Plasma Glucose (FPG)   |         |         |         |
| 893 subjects (298 in lixisenatide arm; 298 in Insulin Glulisine QD and 297 in Insulin Glulisine TID) were included for FPG analysis.                   |         |         |         |
| Units: mmol/L  |         |         |         |
| arithmetic mean  | 6.58    | 6.84    | 6.65    |
| standard deviation   | ± 1.82  | ± 1.98  | ± 1.89  |
| 2-Hour Postprandial Plasma Glucose (PPG)   |         |         |         |
| 258 subjects (79 in lixisenatide arm; 77 in Insulin Glulisine QD and 102 in Insulin Glulisine TID) were included for PPG analysis.                     |         |         |         |
| Units: mmol/L  |         |         |         |
| arithmetic mean  | 14.26   | 14.02   | 14.25   |
| standard deviation   | ± 3.55  | ± 3.59  | ± 3.35  |
| 2-Hour Glucose Excursion   |         |         |         |
| 243 subjects (73 in lixisenatide arm; 74 in Insulin Glulisine QD and 96 in Insulin Glulisine TID) were included for 2-hour glucose excursion analysis. |         |         |         |
| Units: mmol/L  |         |         |         |
| arithmetic mean  | 7.31    | 7.31    | 7.35    |
| standard deviation   | ± 3.19  | ± 3.63  | ± 3.34  |
| Average 7-Point SMPG   |         |         |         |
| 877 subjects (292 in lixisenatide arm; 291 in Insulin Glulisine QD and 294 in Insulin Glulisine TID) were included for average 7-point SMPG analysis.  |         |         |         |
| Units: mmol/L  |         |         |         |
| arithmetic mean  | 9.02    | 9.07    | 8.99    |
| standard deviation   | ± 1.75  | ± 1.74  | ± 1.57  |
| Insulin Glargine Dose  |         |         |         |
| 893 subjects (298 in lixisenatide arm; 298 in Insulin Glulisine QD and 297 in Insulin Glulisine TID) were included for insulin glargine dose analysis. |         |         |         |
| Units: Units (U)   |         |         |         |
| arithmetic mean  | 67.25   | 64.72   | 64.97   |
| standard deviation   | ± 31.95 | ± 32.07 | ± 26.9  |
| Duration of Diabetes   |         |         |         |
| Units: years   |         |         |         |
| arithmetic mean  | 11.89   | 12.33   | 12.41   |

|                    |        |        |       |
|--------------------|--------|--------|-------|
| standard deviation | ± 6.43 | ± 6.75 | ± 6.8 |
|--------------------|--------|--------|-------|

| Reporting group values | Total |  |  |
|------------------------|-------|--|--|
| Number of subjects     | 894   |  |  |
| Age categorical        |       |  |  |
| Units: Subjects        |       |  |  |

|  |     |  |  |
|--|-----|--|--|
| Age continuous   |     |  |  |
| Units: years   |     |  |  |
| arithmetic mean  |     |  |  |
| standard deviation   | -   |  |  |
| Gender categorical   |     |  |  |
| Units: Subjects  |     |  |  |
| Female   | 489 |  |  |
| Male   | 405 |  |  |
| Race   |     |  |  |
| Units: Subjects  |     |  |  |
| Caucasian/White  | 828 |  |  |
| Black  | 36  |  |  |
| Asian/Oriental   | 29  |  |  |
| Other  | 1   |  |  |
| Ethnicity  |     |  |  |
| Units: Subjects  |     |  |  |
| Hispanic   | 189 |  |  |
| Non-Hispanic   | 705 |  |  |
| Metformin use at screening   |     |  |  |
| Units: Subjects  |     |  |  |
| Yes  | 781 |  |  |
| No   | 113 |  |  |
| Number of Subjects with Categorical Body Mass Index (BMI)  |     |  |  |
| Units: Subjects  |     |  |  |
| <30 kg/m <sup>2</sup>  | 312 |  |  |
| ≥30 kg/m <sup>2</sup>  | 581 |  |  |
| Subjects not analyzed for BMI  | 1   |  |  |
| BMI  |     |  |  |
| 893 subjects (298 in lixisenatide arm; 298 in Insulin Glulisine QD and 297 in Insulin Glulisine TID) were included for baseline BMI analysis.    |     |  |  |
| Units: kg/m <sup>2</sup>   |     |  |  |
| arithmetic mean  |     |  |  |
| standard deviation   | -   |  |  |
| Weight   |     |  |  |
| 893 subjects (298 in lixisenatide arm; 298 in Insulin Glulisine QD and 297 in Insulin Glulisine TID) were included for baseline weight analysis. |     |  |  |
| Units: kg  |     |  |  |
| arithmetic mean  |     |  |  |
| standard deviation   | -   |  |  |
| HbA1c  |     |  |  |
| 893 subjects (298 in lixisenatide arm; 298 in Insulin Glulisine QD and 297 in Insulin Glulisine TID) were included for HbA1c analysis.           |     |  |  |



|  |   |  |  |
|--|---|--|--|
| Units: Percentage of hemoglobin<br>arithmetic mean<br>standard deviation   | - |  |  |
| Fasting Plasma Glucose (FPG)   |   |  |  |
| 893 subjects (298 in lixisenatide arm; 298 in Insulin Glulisine QD and 297 in Insulin Glulisine TID) were included for FPG analysis.                   |   |  |  |
| Units: mmol/L<br>arithmetic mean<br>standard deviation   | - |  |  |
| 2-Hour Postprandial Plasma Glucose (PPG)   |   |  |  |
| 258 subjects (79 in lixisenatide arm; 77 in Insulin Glulisine QD and 102 in Insulin Glulisine TID) were included for PPG analysis.                     |   |  |  |
| Units: mmol/L<br>arithmetic mean<br>standard deviation   | - |  |  |
| 2-Hour Glucose Excursion   |   |  |  |
| 243 subjects (73 in lixisenatide arm; 74 in Insulin Glulisine QD and 96 in Insulin Glulisine TID) were included for 2-hour glucose excursion analysis. |   |  |  |
| Units: mmol/L<br>arithmetic mean<br>standard deviation   | - |  |  |
| Average 7-Point SMPG   |   |  |  |
| 877 subjects (292 in lixisenatide arm; 291 in Insulin Glulisine QD and 294 in Insulin Glulisine TID) were included for average 7-point SMPG analysis.  |   |  |  |
| Units: mmol/L<br>arithmetic mean<br>standard deviation   | - |  |  |
| Insulin Glargine Dose  |   |  |  |
| 893 subjects (298 in lixisenatide arm; 298 in Insulin Glulisine QD and 297 in Insulin Glulisine TID) were included for insulin glargine dose analysis. |   |  |  |
| Units: Units (U)<br>arithmetic mean<br>standard deviation  | - |  |  |
| Duration of Diabetes<br>Units: years<br>arithmetic mean<br>standard deviation  | - |  |  |

## End points

### End points reporting groups

|   |                       |
|---|-----------------------|
| Reporting group title   | Lixisenatide          |
| Reporting group description:<br>Lixisenatide 10 mcg QD subcutaneously for 2 weeks post-randomization, then at a maintenance dose of 20 mcg QD up to Week 26 on top of insulin glargine with or without metformin.   |                       |
| Reporting group title   | Insulin Glulisine QD  |
| Reporting group description:<br>Insulin glulisine QD subcutaneously from randomization up to Week 26 on top of insulin glargine with or without metformin.  |                       |
| Reporting group title   | Insulin Glulisine TID |
| Reporting group description:<br>Insulin Glulisine TID subcutaneously from randomization up to Week 26 on top of insulin glargine with or without metformin.   |                       |
| Subject analysis set title  | Insulin Glulisine QD  |
| Subject analysis set type   | Safety analysis       |
| Subject analysis set description:<br>Insulin glulisine QD subcutaneously from randomization up to Week 26 on top of insulin glargine with or without metformin. 4 subjects were randomized to Insulin glulisine TID group, but received insulin glulisine QD for more than 50% of treatment period. These subjects were included in QD arm for safety analysis. |                       |
| Subject analysis set title  | Insulin Glulisine TID |
| Subject analysis set type   | Safety analysis       |
| Subject analysis set description:<br>Insulin Glulisine TID subcutaneously from randomization up to Week 26 on top of insulin glargine with or without metformin. 1 subject was randomized to Insulin glulisine QD group, but received insulin glulisine TID for more than 50% of treatment period. This subject was included in TID arm for safety analysis.    |                       |

### Primary: Change in HbA1c From Baseline to Week 26

|  |  |
|--|--|
| End point title  | Change in HbA1c From Baseline to Week 26 |
| End point description:<br>Change in HbA1C was calculated by subtracting baseline value from Week 26 value. Missing data was imputed using last on-treatment observation carried forward (LOCF). On-treatment period for this efficacy variable was defined as the time from the first dose of study drug up to 14 days after the last dose of study drug. mITT population: all randomized subjects who received at least one dose of study drug; and had both baseline and at least one post-baseline efficacy assessment, irrespective of compliance with study protocol/procedures. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline HbA1c assessment during on-treatment period. |  |
| End point type   | Primary                                  |
| End point timeframe:<br>Baseline, Week 26  |  |

| End point values                    | Lixisenatide         | Insulin Glulisine QD | Insulin Glulisine TID |  |
|-------------------------------------|----------------------|----------------------|-----------------------|--|
| Subject group type                  | Reporting group      | Reporting group      | Reporting group       |  |
| Number of subjects analysed         | 292                  | 292                  | 295                   |  |
| Units: Percentage of hemoglobin     |                      |                      |                       |  |
| least squares mean (standard error) | -0.63 ( $\pm$ 0.054) | -0.58 ( $\pm$ 0.054) | -0.84 ( $\pm$ 0.053)  |  |

## Statistical analyses

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>   | Lixisenatide vs Insulin Glulisine QD |
| Statistical analysis description:   |                                      |
| Analysis was performed using analysis of covariance (ANCOVA) model with treatment groups, strata of Week -1 HbA1c (<8.0, ≥8.0%), randomization strata of metformin use, and country as fixed effects and baseline HbA1c value as a covariate. The non-inferiority was assessed using upper bound of 2-sided 95% CI. |                                      |
| Comparison groups   | Lixisenatide v Insulin Glulisine QD  |
| Number of subjects included in analysis   | 584                                  |
| Analysis specification  | Pre-specified                        |
| Analysis type   | non-inferiority <sup>[1]</sup>       |
| Method  | ANCOVA                               |
| Parameter estimate  | Least Square (LS) Mean Difference    |
| Point estimate  | -0.05                                |
| Confidence interval   |                                      |
| level   | 95 %                                 |
| sides   | 2-sided                              |
| lower limit   | -0.17                                |
| upper limit   | 0.064                                |
| Variability estimate  | Standard error of the mean           |
| Dispersion value  | 0.059                                |

Notes:

[1] - Pre-specified non-inferiority margin of 0.4%

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>   | Lixisenatide vs Insulin Glulisine TID |
| Statistical analysis description:   |                                       |
| Analysis was performed using ANCOVA model as described above. Hochberg procedure was used to control type 1 error at significance level = 0.025 (1-sided) for comparison between lixisenatide vs insulin glulisine TID in HbA1c and body weight. If both comparisons were met, then both would be declared significant. Otherwise, if only one was met, then the one met should be tested at $\alpha=0.0125$ (1-sided). |                                       |
| Comparison groups   | Lixisenatide v Insulin Glulisine TID  |
| Number of subjects included in analysis   | 587                                   |
| Analysis specification  | Pre-specified                         |
| Analysis type   | non-inferiority <sup>[2]</sup>        |
| Method  | ANCOVA                                |
| Parameter estimate  | LS Mean Difference                    |
| Point estimate  | 0.21                                  |
| Confidence interval   |                                       |
| level   | 95 %                                  |
| sides   | 2-sided                               |
| lower limit   | 0.095                                 |
| upper limit   | 0.328                                 |
| Variability estimate  | Standard error of the mean            |
| Dispersion value  | 0.059                                 |

Notes:

[2] - Pre-specified non-inferiority margin of 0.4%

### Primary: Change in Body Weight From Baseline to Week 26

|  |  |
|--|--|
| End point title  | Change in Body Weight From Baseline to Week 26 |
| End point description:<br>Change in body weight was calculated by subtracting baseline value from Week 26 value. Missing data was imputed using LOCF. On-treatment period for this efficacy variable was defined as the time from the first dose of study drug up to 3 days after the last dose of study drug. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline body weight assessment during on-treatment period. |  |
| End point type   | Primary  |
| End point timeframe:<br>Baseline, Week 26  |  |

| End point values                    | Lixisenatide         | Insulin Glulisine QD | Insulin Glulisine TID |  |
|-------------------------------------|----------------------|----------------------|-----------------------|--|
| Subject group type                  | Reporting group      | Reporting group      | Reporting group       |  |
| Number of subjects analysed         | 295                  | 295                  | 295                   |  |
| Units: kg                           |                      |                      |                       |  |
| least squares mean (standard error) | -0.63 ( $\pm$ 0.276) | 1.03 ( $\pm$ 0.276)  | 1.37 ( $\pm$ 0.271)   |  |

### Statistical analyses

|   |                                       |
|---|---------------------------------------|
| Statistical analysis title  | Lixisenatide vs Insulin Glulisine TID |
| Statistical analysis description:<br>Analysis was performed using ANCOVA model as described above. Hochberg procedure was used to control type 1 error at $\alpha = 0.025$ (1-sided) for comparison between lixisenatide vs insulin glulisine TID in HbA1c and body weight . If both comparisons were met, then both would be declared significant. Otherwise, if only one was met, then the one met should be tested at $\alpha=0.0125$ (1-sided). |                                       |
| Comparison groups   | Lixisenatide v Insulin Glulisine TID  |
| Number of subjects included in analysis   | 590                                   |
| Analysis specification  | Pre-specified                         |
| Analysis type   | superiority <sup>[3]</sup>            |
| P-value   | < 0.0001 <sup>[4]</sup>               |
| Method  | ANCOVA                                |
| Parameter estimate  | LS Mean Difference                    |
| Point estimate  | -1.99                                 |
| Confidence interval   |                                       |
| level   | 95 %                                  |
| sides   | 2-sided                               |
| lower limit   | -2.593                                |
| upper limit   | -1.396                                |
| Variability estimate  | Standard error of the mean            |
| Dispersion value  | 0.305                                 |

Notes:

[3] - The superiority was assessed by comparing the P-value at significance level = 0.025 or 0.0125.

[4] - Threshold for significance at 0.025 level.

---

**Secondary: Percentage of Subjects with HbA1c level <7% and ≤6.5% at Week 26**

---

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects with HbA1c level <7% and ≤6.5% at Week 26 |
|-----------------|--|

End point description:

The on-treatment period for this efficacy variable was defined as the time from the first dose of study drug up to 14 days after the last dose of study drug. Missing data was imputed using LOCF. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline HbA1c assessment during on-treatment period.

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

End point timeframe:

Week 26

---

| End point values              | Lixisenatide    | Insulin Glulisine QD | Insulin Glulisine TID |  |
|-------------------------------|-----------------|----------------------|-----------------------|--|
| Subject group type            | Reporting group | Reporting group      | Reporting group       |  |
| Number of subjects analysed   | 292             | 292                  | 295                   |  |
| Units: Percentage of subjects |                 |                      |                       |  |
| number (not applicable)       |                 |                      |                       |  |
| HbA1c ≤6.5%                   | 20.5            | 17.8                 | 30.8                  |  |
| HbA1c <7.0%                   | 42.1            | 38.4                 | 49.2                  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Change in Body Weight from Baseline to Week 26- Lixisenatide arm versus Insulin Glulisine QD arm**

---

|                 |  |
|-----------------|--|
| End point title | Change in Body Weight from Baseline to Week 26- Lixisenatide arm versus Insulin Glulisine QD arm |
|-----------------|--|

End point description:

Change in body weight was calculated by subtracting baseline value from Week 26 value. Missing data was imputed using LOCF. On-treatment period for this efficacy variable was defined as the time from the first dose of study drug up to 3 days after the last dose of study drug. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline body weight assessment during on-treatment period.

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

End point timeframe:

Baseline, Week 26

---

| End point values                    | Lixisenatide         | Insulin Glulisine QD | Insulin Glulisine TID |  |
|-------------------------------------|----------------------|----------------------|-----------------------|--|
| Subject group type                  | Reporting group      | Reporting group      | Reporting group       |  |
| Number of subjects analysed         | 295                  | 295                  | 295                   |  |
| Units: kg                           |                      |                      |                       |  |
| least squares mean (standard error) | -0.63 ( $\pm$ 0.276) | 1.03 ( $\pm$ 0.276)  | 1.37 ( $\pm$ 0.271)   |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects with no Weight Gain at Week 26

|   |   |
|---|---|
| End point title   | Percentage of Subjects with no Weight Gain at Week 26 |
| End point description:  |   |
| The on-treatment period for this efficacy variable was the time from the first dose of study drug up to 3 days after the last dose of study drug. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline body weight assessment during on-treatment period. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Week 26   |   |

| End point values              | Lixisenatide    | Insulin Glulisine QD | Insulin Glulisine TID |  |
|-------------------------------|-----------------|----------------------|-----------------------|--|
| Subject group type            | Reporting group | Reporting group      | Reporting group       |  |
| Number of subjects analysed   | 295             | 295                  | 295                   |  |
| Units: Percentage of subjects |                 |                      |                       |  |
| number (not applicable)       | 64.7            | 36.6                 | 30.5                  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in Average 7-point SMPG Profiles from Baseline to Week 26

|   |  |
|---|--|
| End point title   | Change in Average 7-point SMPG Profiles from Baseline to Week 26 |
| End point description:  |  |
| Subjects recorded a 7-point plasma glucose profile measured before and 2 hours after each meal and at bedtime three times in a week before baseline, before visit Week 12 and before visit Week 26 and the average value across the profiles performed in the week a visit for the 7-time points was calculated. Change in average 7-point SMPG was calculated by subtracting baseline value from Week 26 value. Missing data was imputed using LOCF. The on-treatment period for this efficacy variable was defined as the time from the first dose of study drug up to the day of last dose of study drug. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline 7-point SMPG assessment during on-treatment period. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Baseline, Week 26   |  |

| End point values                    | Lixisenatide           | Insulin Glulisine QD   | Insulin Glulisine TID  |  |
|-------------------------------------|------------------------|------------------------|------------------------|--|
| Subject group type                  | Reporting group        | Reporting group        | Reporting group        |  |
| Number of subjects analysed         | 270                    | 268                    | 278                    |  |
| Units: mmol/L                       |                        |                        |                        |  |
| least squares mean (standard error) | -0.784 ( $\pm$ 0.1141) | -0.782 ( $\pm$ 0.1133) | -1.053 ( $\pm$ 0.1105) |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in FPG from Baseline to Week 26

|   |  |
|---|--|
| End point title   | Change in FPG from Baseline to Week 26 |
| End point description:<br>Change in FPG was calculated by subtracting baseline value from Week 26 value. Missing data was imputed using LOCF. The on-treatment period for this efficacy variable was the time from the first dose of study drug up to 1 day after the last dose of study drug. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline FPG assessment during on-treatment period |  |
| End point type  | Secondary                              |
| End point timeframe:<br>Baseline, Week 26   |  |

| End point values                    | Lixisenatide         | Insulin Glulisine QD | Insulin Glulisine TID |  |
|-------------------------------------|----------------------|----------------------|-----------------------|--|
| Subject group type                  | Reporting group      | Reporting group      | Reporting group       |  |
| Number of subjects analysed         | 295                  | 295                  | 294                   |  |
| Units: mmol/L                       |                      |                      |                       |  |
| least squares mean (standard error) | -0.23 ( $\pm$ 0.143) | -0.21 ( $\pm$ 0.142) | -0.06 ( $\pm$ 0.14)   |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in PPG from Baseline to Week 26 (in Subjects who had an Injection of Investigational Medicinal Product [IMP] Before Breakfast)

|                 |   |
|-----------------|---|
| End point title | Change in PPG from Baseline to Week 26 (in Subjects who had an Injection of Investigational Medicinal Product [IMP] Before Breakfast) |
|-----------------|---|

End point description:

The 2-hour PPG test measured blood glucose 2 hours after eating a standardized meal. Change in PPG

was calculated by subtracting baseline value from Week 26 value. Missing data was imputed using LOCF. The on-treatment period for this efficacy variable was the time from the first dose of study drug up to the day of last dose of study drug. mITT population. Here, number of subjects analyzed=subjects with IMP injection before breakfast and baseline and at least one post-baseline 2-hour PPG assessment during on-treatment period.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Week 26    |           |

| End point values                     | Lixisenatide    | Insulin Glulisine QD | Insulin Glulisine TID |  |
|--------------------------------------|-----------------|----------------------|-----------------------|--|
| Subject group type                   | Reporting group | Reporting group      | Reporting group       |  |
| Number of subjects analysed          | 69              | 55                   | 68                    |  |
| Units: mmol/L                        |                 |                      |                       |  |
| arithmetic mean (standard deviation) | -3.93 (± 4.29)  | -1.62 (± 4.01)       | -1.87 (± 3.18)        |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in Glucose Excursions from Baseline to Week 26 (in Subjects who had an Injection of IMP Before Breakfast)

|                 |  |
|-----------------|--|
| End point title | Change in Glucose Excursions from Baseline to Week 26 (in Subjects who had an Injection of IMP Before Breakfast) |
|-----------------|--|

End point description:

Glucose excursion = 2-hour PPG minus plasma glucose 30 minutes prior to the standardized meal test, before study drug administration. Change in glucose excursions was calculated by subtracting baseline value from Week 26 value. Missing data was imputed using LOCF. The on-treatment period for this efficacy variable was the time from the first dose of study drug up to the day of last dose of study drug. mITT population. Here, number of subjects analyzed=subjects with IMP injection before breakfast and baseline and at least one post-baseline glucose excursion assessment during on-treatment period.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Week 26    |           |

| End point values                     | Lixisenatide    | Insulin Glulisine QD | Insulin Glulisine TID |  |
|--------------------------------------|-----------------|----------------------|-----------------------|--|
| Subject group type                   | Reporting group | Reporting group      | Reporting group       |  |
| Number of subjects analysed          | 64              | 53                   | 66                    |  |
| Units: mmol/L                        |                 |                      |                       |  |
| arithmetic mean (standard deviation) | -3.42 (± 4.13)  | -1.59 (± 3.42)       | -1.56 (± 2.52)        |  |

## Statistical analyses



No statistical analyses for this end point

### Secondary: Change in Insulin Glargine Dose From Baseline to Week 26

|   |  |
|---|--|
| End point title   | Change in Insulin Glargine Dose From Baseline to Week 26 |
| End point description:<br>Change in Insulin glargine dose was calculated by subtracting the baseline value from Week 26 value. Missing data was imputed using LOCF. The on-treatment period for this efficacy variable was the time from the first dose of study drug up to the day of last dose of study drug. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline insulin glargine dose assessment during on-treatment period. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Baseline, Week 26   |  |

| End point values                    | Lixisenatide       | Insulin Glulisine QD | Insulin Glulisine TID |  |
|-------------------------------------|--------------------|----------------------|-----------------------|--|
| Subject group type                  | Reporting group    | Reporting group      | Reporting group       |  |
| Number of subjects analysed         | 292                | 294                  | 294                   |  |
| Units: U                            |                    |                      |                       |  |
| least squares mean (standard error) | 0.7 ( $\pm$ 1.002) | -0.06 ( $\pm$ 0.999) | -3.13 ( $\pm$ 0.982)  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Insulin Glulisine Dose at Week 26

|   |  |
|---|--|
| End point title   | Insulin Glulisine Dose at Week 26 <sup>[5]</sup> |
| End point description:<br>The on-treatment period for this efficacy variable was the time from the first dose of study drug up to the day of last dose of study drug. Missing data was imputed using LOCF. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline insulin glulisine dose assessment during on-treatment period. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Week 26   |  |

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The end point is reporting results only for the arms in which Insulin Glulisine was administered.

| End point values                     | Insulin Glulisine QD | Insulin Glulisine TID |  |  |
|--------------------------------------|----------------------|-----------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group       |  |  |
| Number of subjects analysed          | 295                  | 293                   |  |  |
| Units: U                             |                      |                       |  |  |
| arithmetic mean (standard deviation) | 9.97 ( $\pm$ 7.8)    | 20.24 ( $\pm$ 13.04)  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Total Insulin Dose at Week 26

|                 |  |
|-----------------|--|
| End point title | Total Insulin Dose at Week 26 <sup>[6]</sup> |
|-----------------|--|

End point description:

The on-treatment period for this efficacy variable was the time from the first dose of study drug up to the day of last dose of study drug. Missing data was imputed using LOCF. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline total insulin dose assessment during on-treatment period.

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

End point timeframe:

Week 26

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The end point is reporting results only of the arms in which Insulin Glulisine was administered, and therefore Total Insulin was derived by adding the Insuline Glulisine amount and Insulin Glargine amount.

| End point values                     | Insulin Glulisine QD | Insulin Glulisine TID |  |  |
|--------------------------------------|----------------------|-----------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group       |  |  |
| Number of subjects analysed          | 295                  | 294                   |  |  |
| Units: U                             |                      |                       |  |  |
| arithmetic mean (standard deviation) | 73.61 (± 39.13)      | 81.05 (± 33.55)       |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects with Documented Symptomatic and Severe Symptomatic Hypoglycemia

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects with Documented Symptomatic and Severe Symptomatic Hypoglycemia <sup>[7]</sup> |
|-----------------|---|

End point description:

Documented symptomatic hypoglycemia was an event during which typical symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of <60 mg/dL (3.3 mmol/L). Severe symptomatic hypoglycemia was symptomatic hypoglycemia event in which the subject required the assistance of another person and was associated with either a plasma glucose level below 36 mg/dL (2.0 mmol/L) or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration, if no plasma glucose measurement was available. Safety population included all randomized subjects who were exposed to at least one dose of study drug, regardless of the amount of treatment administered.

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

End point timeframe:

First dose of study drug up to 3 days after the last dose administration (maximum of 185 days)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The end point is reporting statistics for safety set.

| End point values                    | Lixisenatide    | Insulin Glulisine QD | Insulin Glulisine TID |  |
|-------------------------------------|-----------------|----------------------|-----------------------|--|
| Subject group type                  | Reporting group | Subject analysis set | Subject analysis set  |  |
| Number of subjects analysed         | 298             | 301                  | 294                   |  |
| Units: Percentage of subjects       |                 |                      |                       |  |
| number (not applicable)             |                 |                      |                       |  |
| Documented Symptomatic hypoglycemia | 31.5            | 37.5                 | 44.6                  |  |
| Severe symptomatic hypoglycemia     | 0               | 0.7                  | 0                     |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects who Reached the Target of HbA1c <7% at Week 26 and did not Experienced Documented (Plasma Glucose <60 mg/dL) Symptomatic Hypoglycemia During 26-Week Treatment Period

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects who Reached the Target of HbA1c <7% at Week 26 and did not Experienced Documented (Plasma Glucose <60 mg/dL) Symptomatic Hypoglycemia During 26-Week Treatment Period |
|-----------------|--|

End point description:

The on-treatment period for HbA1c assessment was defined as the time from the first dose of study drug up to 14 days after the last dose of study drug. The on-treatment period for symptomatic hypoglycemia assessment was defined as the time from the first dose of study drug up to 1 day after the last dose of study drug. mITT population. Subjects without any post-baseline on-treatment value for HbA1c were counted as non-responders if they experienced at least one symptomatic hypoglycemia. Otherwise, they were counted as missing.

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

End point timeframe:

Week 26

| End point values              | Lixisenatide    | Insulin Glulisine QD | Insulin Glulisine TID |  |
|-------------------------------|-----------------|----------------------|-----------------------|--|
| Subject group type            | Reporting group | Reporting group      | Reporting group       |  |
| Number of subjects analysed   | 296             | 293                  | 295                   |  |
| Units: Percentage of subjects |                 |                      |                       |  |
| number (not applicable)       | 29.4            | 24.2                 | 26.1                  |  |

## Statistical analyses

**Secondary: Percentage of Subjects who Reached the Target of HbA1c <7% and had no Weight Gain at Week 26**

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects who Reached the Target of HbA1c <7% and had no Weight Gain at Week 26 |
|-----------------|--|

## End point description:

The on-treatment period for HbA1c assessment was defined as the time from the first dose of study drug up to 14 days after the last dose of study drug. The on-treatment period for body weight assessment was defined as the time from the first dose of study drug up to 3 days after the last dose of study drug. mITT population. Subjects without post-baseline on-treatment values (for HbA1c and body weight) that were no more than 30 days apart were counted as non-responders if at least one of the components (HbA1c and/or body weight) was available and showed non-response. Otherwise, they were counted as missing data.

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

End point timeframe:

Week 26

| End point values              | Lixisenatide    | Insulin Glulisine QD | Insulin Glulisine TID |  |
|-------------------------------|-----------------|----------------------|-----------------------|--|
| Subject group type            | Reporting group | Reporting group      | Reporting group       |  |
| Number of subjects analysed   | 295             | 293                  | 295                   |  |
| Units: Percentage of subjects |                 |                      |                       |  |
| number (not applicable)       | 31.2            | 16.7                 | 17.6                  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Percentage of Subjects who Reached the Target of HbA1c <7%, had no Weight Gain at Week 26, and did not Experience Documented (Plasma Glucose <60 mg/dL) Symptomatic Hypoglycemia During 26-Week Treatment Period**

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects who Reached the Target of HbA1c <7%, had no Weight Gain at Week 26, and did not Experience Documented (Plasma Glucose <60 mg/dL) Symptomatic Hypoglycemia During 26-Week Treatment Period |
|-----------------|--|

## End point description:

The on-treatment period for HbA1c assessment was defined as the time from the first dose of study drug up to 14 days after the last dose of study drug. The on-treatment period for body weight assessment was defined as the time from the first dose of study drug up to 3 days after the last dose of study drug. The on-treatment period for symptomatic hypoglycemia assessment was defined as the time from the first dose of study drug up to 1 day after the last dose of study drug. mITT population. Subjects without post-baseline on-treatment values (HbA1c and body weight) that were no more than 30 days apart were counted as non-responders if at least one of the components (HbA1c and/or body weight) was available and showed non-response, or if they experienced at least one documented symptomatic hypoglycemia during the on-treatment period. Otherwise, they were counted as missing data.

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

End point timeframe:

Week 26

| <b>End point values</b>       | Lixisenatide    | Insulin<br>Glulisine QD | Insulin<br>Glulisine TID |  |
|-------------------------------|-----------------|-------------------------|--------------------------|--|
| Subject group type            | Reporting group | Reporting group         | Reporting group          |  |
| Number of subjects analysed   | 297             | 294                     | 295                      |  |
| Units: Percentage of subjects |                 |                         |                          |  |
| number (not applicable)       | 22.2            | 9.2                     | 10.8                     |  |

### 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 (Day 185) regardless of seriousness or relationship to IMP.

Adverse event reporting additional description:

Reported adverse events and deaths are treatment-emergent adverse events that is AEs that developed/worsened and death that occurred during the 'on treatment period' (time from the first dose of study drug up to 3 days after the last dose of study drug). Analysis was done on safety population.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Lixisenatide |
|-----------------------|--------------|

Reporting group description:

Lixisenatide 10 mcg QD subcutaneously for 2 weeks post-randomization, then at a maintenance dose of 20 mcg QD up to Week 26 on top of insulin glargine with or without metformin (Median exposure of 182 days).

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Insulin Glulisine QD |
|-----------------------|----------------------|

Reporting group description:

Insulin glulisine QD subcutaneously on top of insulin glargine with or without metformin (Median exposure of 182 days). 4 subjects were randomized to Insulin glulisine TID group, but received insulin glulisine QD for more than 50% of treatment period. These subjects were included in QD arm for safety analysis.

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Insulin Glulisine TID |
|-----------------------|-----------------------|

Reporting group description:

Insulin glulisine TID subcutaneously on top of insulin glargine with or without metformin (Median exposure of 182 days). 1 subject was randomized to Insulin glulisine QD group, but received insulin glulisine TID for more than 50% of treatment period. This subject was included in TID arm for safety analysis.

| Serious adverse events  | Lixisenatide     | Insulin Glulisine QD | Insulin Glulisine TID |
|---|------------------|----------------------|-----------------------|
| Total subjects affected by serious adverse events                   |                  |                      |                       |
| subjects affected / exposed   | 11 / 298 (3.69%) | 11 / 301 (3.65%)     | 14 / 294 (4.76%)      |
| number of deaths (all causes)                                       | 1                | 0                    | 2                     |
| number of deaths resulting from adverse events                      |                  |                      |                       |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                      |                       |
| Basal Cell Carcinoma  |                  |                      |                       |
| subjects affected / exposed   | 0 / 298 (0.00%)  | 0 / 301 (0.00%)      | 1 / 294 (0.34%)       |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 0                | 0 / 1                 |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0                | 0 / 0                 |
| Invasive Ductal Breast Carcinoma                                    |                  |                      |                       |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 298 (0.34%) | 0 / 301 (0.00%) | 1 / 294 (0.34%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Neoplasm Malignant                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 298 (0.00%) | 0 / 301 (0.00%) | 1 / 294 (0.34%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pancreatic Carcinoma Metastatic                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 298 (0.34%) | 0 / 301 (0.00%) | 0 / 294 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Uterine Cancer                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 298 (0.34%) | 0 / 301 (0.00%) | 0 / 294 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Accidental Overdose                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 298 (0.00%) | 2 / 301 (0.66%) | 1 / 294 (0.34%) |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ankle Fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 298 (0.00%) | 1 / 301 (0.33%) | 0 / 294 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Incisional Hernia                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 298 (0.00%) | 1 / 301 (0.33%) | 0 / 294 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders                              |                 |                 |                 |
| Hypertension                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 298 (0.00%) | 0 / 301 (0.00%) | 1 / 294 (0.34%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Cardiac disorders                               |                 |                 |                 |
| Angina Pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 298 (0.34%) | 0 / 301 (0.00%) | 1 / 294 (0.34%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina Unstable                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 298 (0.00%) | 1 / 301 (0.33%) | 0 / 294 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial Fibrillation                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 298 (0.00%) | 1 / 301 (0.33%) | 0 / 294 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrioventricular Block Complete                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 298 (0.00%) | 0 / 301 (0.00%) | 1 / 294 (0.34%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac Failure Chronic                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 298 (0.00%) | 0 / 301 (0.00%) | 1 / 294 (0.34%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Cardiac Failure Congestive                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 298 (0.00%) | 0 / 301 (0.00%) | 1 / 294 (0.34%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial Infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 298 (0.00%) | 1 / 301 (0.33%) | 0 / 294 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial Ischaemia                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 298 (0.00%) | 0 / 301 (0.00%) | 1 / 294 (0.34%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Cerebrovascular Accident                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 298 (0.34%) | 0 / 301 (0.00%) | 2 / 294 (0.68%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypoglycaemic Unconsciousness                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 298 (0.00%) | 2 / 301 (0.66%) | 0 / 294 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Neuritis Cranial                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 298 (0.00%) | 1 / 301 (0.33%) | 0 / 294 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Abdominal Pain                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 298 (0.34%) | 0 / 301 (0.00%) | 0 / 294 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Epigastric Discomfort                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 298 (0.34%) | 0 / 301 (0.00%) | 0 / 294 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastric Ulcer Haemorrhage                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 298 (0.34%) | 0 / 301 (0.00%) | 0 / 294 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Hepatic Mass                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 298 (0.34%) | 0 / 301 (0.00%) | 0 / 294 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |                 |                 |
| Diabetic Bullosis                               |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 298 (0.34%) | 0 / 301 (0.00%) | 0 / 294 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin Ulcer Haemorrhage                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 298 (0.00%) | 0 / 301 (0.00%) | 1 / 294 (0.34%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Renal and urinary disorders                     |                 |                 |                 |
| Renal Failure                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 298 (0.34%) | 0 / 301 (0.00%) | 0 / 294 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal Failure Acute                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 298 (0.34%) | 0 / 301 (0.00%) | 0 / 294 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                 |                 |                 |
| Cellulitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 298 (0.00%) | 1 / 301 (0.33%) | 1 / 294 (0.34%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Erysipelas                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 298 (0.34%) | 0 / 301 (0.00%) | 0 / 294 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Penile Infection                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 298 (0.34%) | 0 / 301 (0.00%) | 0 / 294 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Septic Arthritis Staphylococcal                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 298 (0.34%) | 0 / 301 (0.00%) | 0 / 294 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Decreased Appetite                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 298 (0.34%) | 0 / 301 (0.00%) | 0 / 294 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dehydration                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 298 (0.34%) | 1 / 301 (0.33%) | 0 / 294 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypoglycaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 298 (0.00%) | 1 / 301 (0.33%) | 0 / 294 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

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

| <b>Non-serious adverse events</b>                     | Lixisenatide       | Insulin Glulisine QD | Insulin Glulisine TID |
|---|--------------------|----------------------|-----------------------|
| Total subjects affected by non-serious adverse events |                    |                      |                       |
| subjects affected / exposed                           | 183 / 298 (61.41%) | 186 / 301 (61.79%)   | 195 / 294 (66.33%)    |
| Investigations  |                    |                      |                       |
| Blood Glucose Decreased                               |                    |                      |                       |
| subjects affected / exposed                           | 60 / 298 (20.13%)  | 67 / 301 (22.26%)    | 82 / 294 (27.89%)     |
| occurrences (all)                                     | 153                | 254                  | 344                   |
| Injury, poisoning and procedural complications        |                    |                      |                       |
| Accidental Overdose                                   |                    |                      |                       |
| subjects affected / exposed                           | 0 / 298 (0.00%)    | 12 / 301 (3.99%)     | 20 / 294 (6.80%)      |
| occurrences (all)                                     | 0                  | 15                   | 21                    |
| Nervous system disorders                              |                    |                      |                       |
| Headache  |                    |                      |                       |
| subjects affected / exposed                           | 20 / 298 (6.71%)   | 8 / 301 (2.66%)      | 12 / 294 (4.08%)      |
| occurrences (all)                                     | 22                 | 15                   | 14                    |
| Gastrointestinal disorders                            |                    |                      |                       |
| Diarrhoea   |                    |                      |                       |
| subjects affected / exposed                           | 20 / 298 (6.71%)   | 10 / 301 (3.32%)     | 4 / 294 (1.36%)       |
| occurrences (all)                                     | 21                 | 12                   | 4                     |
| Nausea  |                    |                      |                       |

|                                    |                    |                    |                    |
|------------------------------------|--------------------|--------------------|--------------------|
| subjects affected / exposed        | 75 / 298 (25.17%)  | 5 / 301 (1.66%)    | 3 / 294 (1.02%)    |
| occurrences (all)                  | 97                 | 6                  | 3                  |
| Vomiting                           |                    |                    |                    |
| subjects affected / exposed        | 26 / 298 (8.72%)   | 5 / 301 (1.66%)    | 6 / 294 (2.04%)    |
| occurrences (all)                  | 40                 | 6                  | 6                  |
| Infections and infestations        |                    |                    |                    |
| Nasopharyngitis                    |                    |                    |                    |
| subjects affected / exposed        | 14 / 298 (4.70%)   | 21 / 301 (6.98%)   | 18 / 294 (6.12%)   |
| occurrences (all)                  | 16                 | 23                 | 18                 |
| Metabolism and nutrition disorders |                    |                    |                    |
| Hypoglycaemia                      |                    |                    |                    |
| subjects affected / exposed        | 107 / 298 (35.91%) | 140 / 301 (46.51%) | 154 / 294 (52.38%) |
| occurrences (all)                  | 455                | 630                | 844                |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 04 September 2013 | <p>It included following changes:</p> <ul style="list-style-type: none"><li>- Revised inclusion/exclusion criteria as follows: Glinides were added as allowed previous oral antidiabetic medication within 3 months before the study entry; Previous use of glucagon-like peptide 1 (GLP-1) receptor agonist (except lixisenatide) was changed from forbidden to allowed, provided that GLP-1 receptor agonist treatment was stopped for other reason than safety/tolerability issue or lack of efficacy</li><li>- A new safety committee was added, the pancreatic safety assessment committee (PSAC), to ensure the independent assessment of pancreatic event data by external experts. The PSAC reviewed pancreatic events reported on a specific adverse event form.</li><li>- Clarified that alanine aminotransferase (ALT) increase was to be reported as an adverse event of special interest (AESI) with immediate notification to be in line with the updated requirements for safety information collection.</li></ul> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27222510>