



## Clinical trial results:

### 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus® in Insulin-Naïve Patients with Type 2 Diabetes Mellitus not Adequately Controlled with Non-Insulin Antihyperglycemic Drugs with a 6-month Safety Extension Period

#### Summary

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2012-000146-35                |
| Trial protocol           | DK SE FI EE CZ LV LT NL BG SK |
| Global end of trial date | 26 March 2014                 |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 01 April 2016 |
| First version publication date | 14 June 2015  |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | EFC12347 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | NCT01676220     |
| WHO universal trial number (UTN)   | U1111-1124-5261 |

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:

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**Results analysis stage**

|  |               |
|--|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 12 June 2014  |
| Is this the analysis of the primary completion data? | No            |
| <hr/>  |               |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 26 March 2014 |
| Was the trial ended prematurely?                     | No            |

Notes:

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**General information about the trial**

Main objective of the trial:

To compare the efficacy of a new formulation of insulin glargine and Lantus in terms of change of HbA1c from baseline to endpoint (scheduled at Month 6, Week 26) in subjects with type 2 diabetes mellitus.

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: -

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 31 August 2012 |
| Long term follow-up planned                               | No             |
| Independent data monitoring committee (IDMC) involvement? | No             |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Netherlands: 7     |
| Country: Number of subjects enrolled | Slovakia: 18       |
| Country: Number of subjects enrolled | Sweden: 5          |
| Country: Number of subjects enrolled | Bulgaria: 16       |
| Country: Number of subjects enrolled | Czech Republic: 7  |
| Country: Number of subjects enrolled | Denmark: 27        |
| Country: Number of subjects enrolled | Estonia: 4         |
| Country: Number of subjects enrolled | Finland: 18        |
| Country: Number of subjects enrolled | Hungary: 14        |
| Country: Number of subjects enrolled | Latvia: 7          |
| Country: Number of subjects enrolled | Lithuania: 20      |
| Country: Number of subjects enrolled | Canada: 51         |
| Country: Number of subjects enrolled | Romania: 47        |
| Country: Number of subjects enrolled | United States: 587 |
| Country: Number of subjects enrolled | Japan: 50          |

|                                    |     |
|------------------------------------|-----|
| Worldwide total number of subjects | 878 |
| EEA total number of subjects       | 190 |

Notes:

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### Subjects enrolled per age group

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|   |     |
|---|-----|
| 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)                      | 652 |
| From 65 to 84 years                       | 225 |
| 85 years and over                         | 1   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 1396 subjects were screened, of whom 518 subjects were screen failure and 878 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>             | HOE901-U300 |

Arm description:

HOE901-U300 for 12 months in combination with non-insulin antihyperglycemic drug(s).

|  |  |
|--|--|
| Arm type                               | Experimental                             |
| Investigational medicinal product name | Insulin glargine- new formulation        |
| Investigational medicinal product code | HOE901-U300                              |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled pen |
| Routes of administration               | Subcutaneous use                         |

Dosage and administration details:

HOE901-U300 (new insulin glargine 300 units per milliliter [U/mL]) once daily (evening). Dose titration seeking fasting plasma glucose 4.4-5.6 millimole per liter (mmol/L) (80 - 100 milligram per deciliter [mg/dL]).

|                  |        |
|------------------|--------|
| <b>Arm title</b> | Lantus |
|------------------|--------|

Arm description:

Lantus for 12 months in combination with non-insulin antihyperglycemic drug(s).

|  |  |
|--|--|
| Arm type                               | Active comparator                        |
| Investigational medicinal product name | Insulin glargine                         |
| Investigational medicinal product code | HOE901-U100                              |
| Other name                             | Lantus                                   |
| Pharmaceutical forms                   | Solution for injection in pre-filled pen |
| Routes of administration               | Subcutaneous use                         |

Dosage and administration details:

Lantus (HOE901-U100, insulin glargine 100 U/mL) once daily (evening). Dose titration seeking fasting plasma glucose 4.4-5.6 mmol/L (80 - 100 mg/dL).

| <b>Number of subjects in period 1</b>  | HOE901-U300 | Lantus |
|--|-------------|--------|
| Started                                | 439         | 439    |
| Treated                                | 435         | 438    |
| Modified Intent-To-Treat Population    | 432         | 430    |
| Completed                              | 337         | 314    |
| Not completed                          | 102         | 125    |
| Received Rescue Therapy                | 14          | 22     |
| Adverse Event                          | 10          | 8      |
| Perceived Lack of Efficacy             | 3           | 1      |
| Selection Criterion/Protocol Violation | 9           | 9      |
| No More Need of Insulin                | 1           | -      |
| Non Serious Hypoglycemia               | 2           | -      |
| Randomized But Not Treated             | 4           | 1      |
| Protocol Violation                     | 11          | 12     |
| Personal Reason                        | 34          | 45     |
| Lost to follow-up                      | 11          | 18     |
| Site Closure/Site Withdrawal           | 1           | 4      |
| Lack of efficacy                       | 2           | 5      |

## Baseline characteristics

### Reporting groups

|  |             |
|--|-------------|
| Reporting group title  | HOE901-U300 |
| Reporting group description:<br>HOE901-U300 for 12 months in combination with non-insulin antihyperglycemic drug(s). |             |
| Reporting group title  | Lantus      |
| Reporting group description:<br>Lantus for 12 months in combination with non-insulin antihyperglycemic drug(s).      |             |

| Reporting group values             | HOE901-U300 | Lantus | Total |
|------------------------------------|-------------|--------|-------|
| Number of subjects                 | 439         | 439    | 878   |
| Age categorical<br>Units: Subjects |             |        |       |

|  |                  |                  |     |
|--|------------------|------------------|-----|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation  | 58.2<br>± 9.9    | 57.2<br>± 10.3   | -   |
| Gender categorical<br>Units: Subjects  |                  |                  |     |
| Female   | 186              | 185              | 371 |
| Male   | 253              | 254              | 507 |
| Glycated Hemoglobin A1c (HbA1c)<br>Units: Subjects   |                  |                  |     |
| Less Than (<) 8%   | 141              | 142              | 283 |
| Greater Than or Equal to (>=) 8%   | 298              | 297              | 595 |
| Body Mass Index (BMI)<br>Units: kilogram per square meter<br>arithmetic mean<br>standard deviation                       | 32.8<br>± 6.9    | 33.2<br>± 6.6    | -   |
| Duration of Diabetes   |                  |                  |     |
| Number of subjects analyzed for this baseline characteristics = 435 and 436 in HOE901-U300 and Lantus arm, respectively. |                  |                  |     |
| Units: years<br>arithmetic mean<br>standard deviation  | 10.11<br>± 6.49  | 9.57<br>± 6.22   | -   |
| Basal Insulin Daily Dose   |                  |                  |     |
| Number of subjects analyzed for this baseline characteristics = 432 and 436 in HOE901-U300 and Lantus arm, respectively. |                  |                  |     |
| Units: units per kilogram (U/kg)<br>arithmetic mean<br>standard deviation  | 0.193<br>± 0.027 | 0.193<br>± 0.034 | -   |

## End points

### End points reporting groups

|  |             |
|--|-------------|
| Reporting group title  | HOE901-U300 |
| Reporting group description:<br>HOE901-U300 for 12 months in combination with non-insulin antihyperglycemic drug(s). |             |
| Reporting group title  | Lantus      |
| Reporting group description:<br>Lantus for 12 months in combination with non-insulin antihyperglycemic drug(s).      |             |

### Primary: Change in HbA1c From Baseline to Month 6 Endpoint

|   |   |
|---|---|
| End point title   | Change in HbA1c From Baseline to Month 6 Endpoint |
| End point description:<br>Only HbA1c measurements performed before initiation of rescue therapy were considered in the analysis. Month 6 Endpoint is either the observed value at Month 6 visit or value retrieved according to time windows. Modified Intent-to-Treat (mITT) population: randomized subjects who received at least 1 dose, had baseline and at least 1 post-baseline data of any efficacy variable, irrespective of compliance. Number of subjects analyzed=subjects included in mITT population with baseline and at least 1 post-baseline HbA1c data (Week 12 and/or Month 6). |   |
| End point type  | Primary   |
| End point timeframe:<br>Baseline, Month 6   |   |

| End point values                    | HOE901-U300          | Lantus               |  |  |
|-------------------------------------|----------------------|----------------------|--|--|
| Subject group type                  | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed         | 402                  | 394                  |  |  |
| Units: percentage of hemoglobin     |                      |                      |  |  |
| least squares mean (standard error) | -1.42 ( $\pm$ 0.047) | -1.46 ( $\pm$ 0.048) |  |  |

### Statistical analyses

|   |                        |
|---|------------------------|
| Statistical analysis title  | HOE901-U300 vs. Lantus |
| Statistical analysis description:<br>Analysis was performed using mixed model for repeated measurements (MMRM) with treatment groups, strata of screening HbA1c (<8.0, $\geq$ 8.0%), geographical region (Non-Japan; Japan), visit and visit-by-treatment groups interaction as fixed categorical effects; baseline HbA1c and baseline HbA1c-by-visit interaction as continuous fixed covariates. |                        |
| Comparison groups   | HOE901-U300 v Lantus   |

|   |                                    |
|---|------------------------------------|
| Number of subjects included in analysis | 796                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | non-inferiority <sup>[1]</sup>     |
| Parameter estimate                      | Least Squares (LS) Mean Difference |
| Point estimate                          | 0.04                               |
| Confidence interval                     |                                    |
| level                                   | 95 %                               |
| sides                                   | 2-sided                            |
| lower limit                             | -0.09                              |
| upper limit                             | 0.174                              |
| Variability estimate                    | Standard error of the mean         |
| Dispersion value                        | 0.067                              |

Notes:

- [1] - Stepwise closed testing approach was used to assess non-inferiority and superiority sequentially:
1. Non-inferiority of HOE901-U300 vs Lantus: Upper bound of two-sided 95% confidence interval (CI) of difference between HOE901-U300 and Lantus on mITT population is <0.4%.
  2. Superiority (only if non-inferiority has been demonstrated): Upper bound of two-sided 95% CI for difference in mean change in HbA1c from baseline to endpoint between HOE901-U300 and Lantus on mITT population is <0.

### Secondary: Percentage of Subjects With At Least One Severe and/or Confirmed Nocturnal Hypoglycemia From Start of Week 9 to Month 6

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects With At Least One Severe and/or Confirmed Nocturnal Hypoglycemia From Start of Week 9 to Month 6 |
|-----------------|---|

End point description:

Nocturnal hypoglycemia was hypoglycemia that occurred between 00:00 and 05:59 hours (clock time), regardless the subject was awake or woke up because of the event. Severe hypoglycemia was an event that required assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Confirmed hypoglycemia was an event associated with plasma glucose less than or equal to ( $\leq$ ) 3.9 millimoles per liter (mmol/L) (70 milligram per deciliter [mg/dL]). Only nocturnal hypoglycemia occurring before initiation of rescue therapy were considered in the analysis. Week 9 and Month 6 value correspond to the observed value at Week 9 and Month 6 visit respectively. Modified intent-to-treat population.

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

End point timeframe:

Week 9 Up to Month 6

| End point values              | HOE901-U300     | Lantus          |  |  |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type            | Reporting group | Reporting group |  |  |
| Number of subjects analysed   | 432             | 430             |  |  |
| Units: percentage of subjects |                 |                 |  |  |
| number (not applicable)       | 15.5            | 17.4            |  |  |

### Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | HOE901-U300 vs. Lantus |
|----------------------------|------------------------|

Statistical analysis description:

A one-sided test (at  $\alpha=0.025$ ) for superiority of HOE901-U300 over Lantus was to be performed in case the non-inferiority of HOE901-U300 vs Lantus for the primary endpoint was demonstrated. Analysis was performed using Cochran-Mantel-Haenszel (CMH) method stratified by randomization strata of



screening HbA1c (<8.0, >=8.0%), randomization strata of geographical region (Non-Japan; Japan).

|   |                         |
|---|-------------------------|
| Comparison groups                       | HOE901-U300 v Lantus    |
| Number of subjects included in analysis | 862                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.4536                |
| Method                                  | Cochran-Mantel-Haenszel |
| Parameter estimate                      | Risk ratio (RR)         |
| Point estimate                          | 0.89                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.66                    |
| upper limit                             | 1.2                     |

### Secondary: Change in Preinjection Self-Monitored Plasma Glucose (SMPG) From Baseline to Month 6 Endpoint

|  |   |
|--|---|
| End point title  | Change in Preinjection Self-Monitored Plasma Glucose (SMPG) From Baseline to Month 6 Endpoint |
| End point description:<br>Pre-injection SMPG was measured within 30 minutes prior to the injection of the study drug. Except for baseline value average of preinjection SMPG was assessed by the mean of at least 3 SMPG calculated over the 7 days preceding the assessment visit. Only preinjection SMPG measurements performed before initiation of rescue therapy were considered in the analysis. Month 6 Endpoint is either the observed value at Month 6 visit or value retrieved according to time windows. mITT population. Number of subjects analyzed = subjects included in the mITT population with baseline and at least one pre-injection SMPG assessment (Week 2, Week 4, Week 8, Week 12, Month 4 and/or Month 6) |   |
| End point type   | Secondary   |
| End point timeframe:<br>Baseline, Month 6  |   |

| End point values                    | HOE901-U300     | Lantus          |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 207             | 222             |  |  |
| Units: mmol/L                       |                 |                 |  |  |
| least squares mean (standard error) | -2.16 (± 0.162) | -2.33 (± 0.156) |  |  |

### Statistical analyses

|   |                        |
|---|------------------------|
| Statistical analysis title  | HOE901-U300 vs. Lantus |
| Statistical analysis description:<br>Change in pre-injection SMPG was analyzed using MMRM model with treatment groups, strata of screening HbA1c (<8.0, >=8.0%), geographical region (Non-Japan; Japan), visit and visit-by-treatment groups interaction as fixed categorical effects; baseline preinjection SMPG value and baseline preinjection SMPG value-by-visit interaction as continuous fixed covariates. |                        |
| Comparison groups   | HOE901-U300 v Lantus   |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 429                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| Parameter estimate                      | LS Mean Difference         |
| Point estimate                          | 0.17                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -0.275                     |
| upper limit                             | 0.605                      |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.224                      |

### Secondary: Variability of Preinjection SMPG at Month 6 Endpoint

|   |  |
|---|--|
| End point title   | Variability of Preinjection SMPG at Month 6 Endpoint |
| End point description:  |  |
| Pre-injection SMPG was measured within 30 minutes prior to the injection of the study drug. Variability was assessed by the mean of coefficient of variation calculated as 100 multiplied by (standard deviation/mean) over at least 3 SMPG measured during the 7 days preceding the assessment visit. Only preinjection SMPG measurements performed before initiation of rescue therapy were considered in the analysis. Month 6 Endpoint is either the observed value at Month 6 visit or value retrieved according to time windows. mITT population. Number of subjects analyzed = subjects included in the mITT Population with at least one pre-injection SMPG variability assessment (Week 2, Week 4, Week 8, Week 12, Month 4 and/or Month 6). |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Month 6   |  |

| End point values                    | HOE901-U300     | Lantus          |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 422             | 418             |  |  |
| Units: percentage of mean           |                 |                 |  |  |
| least squares mean (standard error) | 18.7 (± 0.502)  | 18.33 (± 0.521) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With HbA1c <7% at Month 6

|   |  |
|---|--|
| End point title   | Percentage of Subjects With HbA1c <7% at Month 6 |
| End point description:  |  |
| Only HbA1c measurements performed before initiation of rescue therapy were considered in the analysis. Month 6 value corresponds to the observed value at Month 6 visit. mITT Population. Subjects without any available Month 6 HbA1C assessment were considered as failures (non-responders). |  |
| End point type  | Secondary  |

End point timeframe:

Month 6

|                               |                 |                 |  |  |
|-------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>       | HOE901-U300     | Lantus          |  |  |
| Subject group type            | Reporting group | Reporting group |  |  |
| Number of subjects analysed   | 432             | 430             |  |  |
| Units: percentage of subjects |                 |                 |  |  |
| number (not applicable)       | 43.1            | 42.1            |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in Fasting Plasma Glucose (FPG) From Baseline to Month 6 Endpoint

|                 |  |
|-----------------|--|
| End point title | Change in Fasting Plasma Glucose (FPG) From Baseline to Month 6 Endpoint |
|-----------------|--|

End point description:

Only FPG measurements performed before initiation of rescue therapy were considered in the analysis. Month 6 Endpoint is either the observed value at Month 6 visit or value retrieved according to time windows. mITT Population. Number of subjects analyzed = subjects included in the mITT population with baseline and at least one post-baseline FPG assessment (Week 12 and/or Month 6).

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

End point timeframe:

Baseline, Month 6

|                                     |                      |                     |  |  |
|-------------------------------------|----------------------|---------------------|--|--|
| <b>End point values</b>             | HOE901-U300          | Lantus              |  |  |
| Subject group type                  | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed         | 398                  | 387                 |  |  |
| Units: mmol/L                       |                      |                     |  |  |
| least squares mean (standard error) | -3.41 ( $\pm$ 0.103) | -3.8 ( $\pm$ 0.105) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With FPG <5.6 mmol/L (100 mg/dL) at Month 6

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects With FPG <5.6 mmol/L (100 mg/dL) at Month 6 |
|-----------------|--|

End point description:

Only FPG measurements performed before initiation of rescue therapy were considered in the analysis. Month 6 value corresponds to the observed value at Month 6 visit. mITT Population. Subjects without

any available FPG assessment at Month 6 were considered as failures (non-responders).

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Month 6              |           |

| End point values              | HOE901-U300     | Lantus          |  |  |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type            | Reporting group | Reporting group |  |  |
| Number of subjects analysed   | 432             | 430             |  |  |
| Units: percentage of subjects |                 |                 |  |  |
| number (not applicable)       | 26.2            | 29.5            |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in 8-Point SMPG Profiles Per Time Point From Baseline to Month 6

|                 |   |
|-----------------|---|
| End point title | Change in 8-Point SMPG Profiles Per Time Point From Baseline to Month 6 |
|-----------------|---|

End point description:

Change in each time-point of 8-point SMPG profile: 03:00 hours (clock time) at night; before and 2 hours after breakfast; before and 2 hours after lunch; before and 2 hours after dinner; and at bedtime. Only 8-point SMPG profiles measurements performed before initiation of rescue therapy were considered in the analysis. Month 6 value corresponds to the observed value at Month 6 visit. mITT Population. Only subjects from the mITT population with a value at baseline and at specified timepoint were analyzed (represented by n=X, X in the category titles).

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Month 6    |           |

| End point values                                   | HOE901-U300     | Lantus          |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                                 | Reporting group | Reporting group |  |  |
| Number of subjects analysed                        | 432             | 430             |  |  |
| Units: mmol/L                                      |                 |                 |  |  |
| arithmetic mean (standard deviation)               |                 |                 |  |  |
| 03:00 at Night Plasma Glucose (n=281,277)          | -2.63 (± 3.24)  | -3.01 (± 3.75)  |  |  |
| Pre-Breakfast Plasma Glucose (n=292,286)           | -3.28 (± 2.72)  | -3.72 (± 2.96)  |  |  |
| 2 Hours After Breakfast Plasma Glucose (n=278,278) | -3.69 (± 3.65)  | -4.08 (± 4.03)  |  |  |
| Pre-Lunch Plasma Glucose (n=289,281)               | -2.58 (± 3.39)  | -3.39 (± 3.76)  |  |  |
| 2 Hours After Lunch Plasma Glucose (n=280,269)     | -2.19 (± 3.88)  | -3.13 (± 3.77)  |  |  |
| Pre-Dinner Plasma Glucose (n=291,285)              | -2.57 (± 3.49)  | -2.43 (± 3.79)  |  |  |

|   |                |                |  |  |
|---|----------------|----------------|--|--|
| 2 Hours After Dinner Plasma Glucose (n=282,269) | -2.36 (± 3.89) | -2.33 (± 4.03) |  |  |
| Bedtime Plasma Glucose (n=249,249)              | -2.19 (± 3.75) | -2.26 (± 3.66) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in 24-hour Average 8-point SMPG Profile From Baseline to Month 6 Endpoint

|                 |  |
|-----------------|--|
| End point title | Change in 24-hour Average 8-point SMPG Profile From Baseline to Month 6 Endpoint |
|-----------------|--|

End point description:

Change in 24-hour average of 8-point SMPG profile. 8-point SMPG was assessed at: 03:00 hours (clock time) at night; before and 2 hours after breakfast; before and 2 hours after lunch; before and 2 hours after dinner; and at bedtime. Only 24-hour average 8-point SMPG measurements performed before initiation of rescue therapy were considered in the analysis. Month 6 Endpoint is either the observed value at Month 6 visit or value retrieved according to time windows. mITT Population. Number of subjects analyzed = subjects included in the mITT population with baseline and at least one post-baseline 24-hour average 8-point SMPG assessment (Week 2, Week 4, Week 8, Week 12, Month 4 and/or Month 6).

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

End point timeframe:

Baseline, Month 6

| End point values                    | HOE901-U300     | Lantus          |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 381             | 393             |  |  |
| Units: mmol/L                       |                 |                 |  |  |
| least squares mean (standard error) | -2.72 (± 0.088) | -2.9 (± 0.089)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in Variability of 24 Hour Average 8-point SMPG Profiles From Baseline to Month 6 Endpoint

|                 |  |
|-----------------|--|
| End point title | Change in Variability of 24 Hour Average 8-point SMPG Profiles From Baseline to Month 6 Endpoint |
|-----------------|--|

End point description:

Variability is assessed by the mean of coefficient of variation calculated as 100 multiplied by (standard deviation/mean) over at least 5 measurements of the 8-point profiles. Only variability of 24-hour 8-point SMPG measurements performed before initiation of rescue therapy were considered in the analysis. Month 6 Endpoint is either the observed value at Month 6 visit or value retrieved according to time windows. mITT Population. Number of subjects analyzed = subjects included in the mITT population with baseline and at least one post-baseline variability of 24-hour average 8-point SMPG assessment (Week 2, Week 4, Week 8, Week 12, Month 4 and/or Month 6).

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Month 6    |           |

|                                     |                     |                     |  |  |
|-------------------------------------|---------------------|---------------------|--|--|
| <b>End point values</b>             | HOE901-U300         | Lantus              |  |  |
| Subject group type                  | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed         | 381                 | 393                 |  |  |
| Units: percentage of mean           |                     |                     |  |  |
| least squares mean (standard error) | 1.53 ( $\pm$ 0.643) | 1.41 ( $\pm$ 0.647) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in Daily Basal Insulin Dose From Baseline to Month 6

|  |   |
|--|---|
| End point title  | Change in Daily Basal Insulin Dose From Baseline to Month 6 |
| End point description:   |   |
| Only insulin dose measurements performed before initiation of rescue therapy were considered in the analysis. Month 6 value corresponds to the observed value at Month 6 visit. mITT Population. Number of subjects analyzed = subjects included in the mITT population with Baseline and Month 6 basal insulin dose assessment. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Baseline, Month 6  |   |

|                                      |                    |                    |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| <b>End point values</b>              | HOE901-U300        | Lantus             |  |  |
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 362                | 340                |  |  |
| Units: U/kg                          |                    |                    |  |  |
| arithmetic mean (standard deviation) | 0.43 ( $\pm$ 0.29) | 0.34 ( $\pm$ 0.24) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in Total Treatment Satisfaction Score Using The Diabetes Treatment Satisfaction Questionnaire (DTSQs) From Baseline to Month 6 Endpoint

|   |  |
|---|--|
| End point title   | Change in Total Treatment Satisfaction Score Using The Diabetes Treatment Satisfaction Questionnaire (DTSQs) From Baseline to Month 6 Endpoint |
| End point description:  |  |
| DTSQ is a validated measure to assess how satisfied subjects with diabetes are with their treatment and |  |

how they perceive hyper- and hypoglycemia. It consists of 8 questions which are answered on a Likert scale from 0 to 6. DTSQ treatment satisfaction score is the sum of question 1 and 4-8 scores and ranges between 0 and 36, where higher scores indicate more treatment satisfaction. Only DTSQ total score measurements performed before initiation of rescue therapy were considered in the analysis. Month 6 Endpoint is either the observed value at Month 6 visit or value retrieved according to time windows. mITT Population. Number of subjects analyzed = subjects included in the mITT population with Baseline and at least one post-baseline DTSQ assessment (Week 12 and/or Month 6).

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Month 6    |           |

| End point values                    | HOE901-U300         | Lantus              |  |  |
|-------------------------------------|---------------------|---------------------|--|--|
| Subject group type                  | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed         | 371                 | 367                 |  |  |
| Units: units on a scale             |                     |                     |  |  |
| least squares mean (standard error) | 4.89 ( $\pm$ 0.246) | 5.12 ( $\pm$ 0.251) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With Hypoglycemia (All and Nocturnal) Events From Baseline up to Month 12

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects With Hypoglycemia (All and Nocturnal) Events From Baseline up to Month 12 |
|-----------------|--|

End point description:

Hypoglycaemia included: Severe (required assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions); Documented symptomatic (typical symptoms of hypoglycaemia were accompanied by plasma glucose  $\leq$  3.9 mmol/L); Asymptomatic (not accompanied by typical symptoms of hypoglycaemia but with plasma glucose  $\leq$  3.9 mmol/L); Probable symptomatic (symptoms of hypoglycaemia were not accompanied by a plasma glucose determination, but was presumably caused by plasma glucose  $\leq$  3.9 mmol/L); and Relative (subject reported any of the typical symptoms of hypoglycaemia, and interpreted the symptoms as indicative of hypoglycaemia, but with plasma glucose  $>$  3.9 mmol/L). Safety population: all subjects randomized and treated, regardless of amount of treatment administered. In event of subjects having received treatments different from those assigned according to the randomization schedule, safety analyses were conducted according to treatment received.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Up to 12 months      |           |

| End point values                         | HOE901-U300     | Lantus          |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                       | Reporting group | Reporting group |  |  |
| Number of subjects analysed              | 435             | 438             |  |  |
| Units: percentage of subjects            |                 |                 |  |  |
| number (not applicable)                  |                 |                 |  |  |
| Any Hypoglycemia Event: All Hypoglycemia | 58.9            | 63.2            |  |  |

|   |      |      |  |  |
|---|------|------|--|--|
| Severe Hypoglycemia: All Hypoglycemia           | 1.4  | 2.1  |  |  |
| Documented Symptomatic: All Hypoglycemia        | 39.1 | 44.1 |  |  |
| Asymptomatic: All Hypoglycemia                  | 41.6 | 46.8 |  |  |
| Probable Symptomatic: All Hypoglycemia          | 3.2  | 3    |  |  |
| Relative: All Hypoglycemia                      | 10.6 | 11.6 |  |  |
| Severe and/or Confirmed: All Hypoglycemia       | 56.3 | 61.2 |  |  |
| Any Hypoglycemia Event: Nocturnal Hypoglycemia  | 27.6 | 30.1 |  |  |
| Severe Hypoglycemia: Nocturnal Hypoglycemia     | 0    | 0.7  |  |  |
| Documented Symptomatic: Nocturnal Hypoglycemia  | 18.6 | 20.8 |  |  |
| Asymptomatic: Nocturnal Hypoglycemia            | 13.3 | 16   |  |  |
| Probable Symptomatic: Nocturnal Hypoglycemia    | 0.7  | 0    |  |  |
| Relative: Nocturnal Hypoglycemia                | 4.4  | 3.2  |  |  |
| Severe and/or Confirmed: Nocturnal Hypoglycemia | 25.3 | 29.5 |  |  |

### 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 informed consent form up to study completion regardless of seriousness or relationship to study drug.

Adverse event reporting additional description:

Reported adverse events and deaths are treatment-emergent that is AEs that developed/worsened and death that occurred during on-treatment period (time from first injection of study drug up to 2 day after the last injection of study drug). Analysis was done on safety population.

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

### Dictionary used

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

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

### Reporting groups

|                       |        |
|-----------------------|--------|
| Reporting group title | Lantus |
|-----------------------|--------|

Reporting group description:

Lantus SC injection once daily for 12 months in combination with non-insulin antihyperglycemic drug(s).

|                       |             |
|-----------------------|-------------|
| Reporting group title | HOE901-U300 |
|-----------------------|-------------|

Reporting group description:

HOE901-U300 SC injection once daily for 12 months in combination with non-insulin antihyperglycemic drug(s).

| Serious adverse events  | Lantus           | HOE901-U300      |  |
|---|------------------|------------------|--|
| Total subjects affected by serious adverse events                   |                  |                  |  |
| subjects affected / exposed   | 39 / 438 (8.90%) | 35 / 435 (8.05%) |  |
| number of deaths (all causes)                                       | 0                | 1                |  |
| number of deaths resulting from adverse events                      |                  |                  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                  |  |
| Basal Cell Carcinoma  |                  |                  |  |
| subjects affected / exposed   | 1 / 438 (0.23%)  | 0 / 435 (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 / 438 (0.23%)  | 0 / 435 (0.00%)  |  |
| occurrences causally related to treatment / all                     | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0            |  |
| Prostate Cancer   |                  |                  |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 438 (0.23%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Vascular disorders                                   |                 |                 |  |
| Peripheral Arterial Occlusive Disease                |                 |                 |  |
| subjects affected / exposed                          | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Varicose Vein  |                 |                 |  |
| subjects affected / exposed                          | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Surgical and medical procedures                      |                 |                 |  |
| Medical Device Removal                               |                 |                 |  |
| subjects affected / exposed                          | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Non-Cardiac Chest Pain                               |                 |                 |  |
| subjects affected / exposed                          | 0 / 438 (0.00%) | 2 / 435 (0.46%) |  |
| 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                          | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Menorrhagia  |                 |                 |  |
| subjects affected / exposed                          | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders      |                 |                 |  |
| Acute Pulmonary Oedema                               |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute Respiratory Failure                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Asthma  |                 |                 |  |
| subjects affected / exposed                     | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic Obstructive Pulmonary Disease           |                 |                 |  |
| subjects affected / exposed                     | 2 / 438 (0.46%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea  |                 |                 |  |
| subjects affected / exposed                     | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Interstitial Lung Disease                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sleep Apnoea Syndrome                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Alanine Aminotransferase Increased              |                 |                 |  |
| subjects affected / exposed                     | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood Bilirubin Increased                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                           | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| <b>Injury, poisoning and procedural complications</b> |                 |                 |  |
| Fall  |                 |                 |  |
| subjects affected / exposed                           | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Limb Injury   |                 |                 |  |
| subjects affected / exposed                           | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Multiple Injuries                                     |                 |                 |  |
| subjects affected / exposed                           | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Rib Fracture  |                 |                 |  |
| subjects affected / exposed                           | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Road Traffic Accident                                 |                 |                 |  |
| subjects affected / exposed                           | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Upper Limb Fracture                                   |                 |                 |  |
| subjects affected / exposed                           | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| <b>Cardiac disorders</b>                              |                 |                 |  |
| Acute Myocardial Infarction                           |                 |                 |  |
| subjects affected / exposed                           | 2 / 438 (0.46%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all       | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Angina Pectoris                                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 438 (0.46%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina Unstable                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arteriosclerosis Coronary Artery                |                 |                 |  |
| subjects affected / exposed                     | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Atrial Fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 2 / 435 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac Failure Congestive                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary Artery Disease                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 438 (0.00%) | 2 / 435 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial Infarction                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ventricular Tachycardia                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Carotid Artery Aneurysm                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral Artery Embolism                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral Infarction                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebrovascular Accident                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Convulsion                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 0 / 435 (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                     | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ischaemic Stroke                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope   |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye disorders                                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Cataract  |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Retinal Detachment                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Abdominal Hernia                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal Pain                                  |                 |                 |  |
| subjects affected / exposed                     | 3 / 438 (0.68%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colitis Ischaemic                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulum Intestinal                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal Ulcer                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric Ulcer Haemorrhage                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal Haemorrhage                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 438 (0.46%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhoids                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peptic Ulcer                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Small Intestinal Obstruction                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Umbilical Hernia                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Cholecystitis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Haematuria                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nephrolithiasis                                 |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 438 (0.00%) | 2 / 435 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endocrine disorders                             |                 |                 |  |
| Goitre  |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Arthritis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chondrocalcinosis Pyrophosphate                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Flank Pain                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal Chest Pain                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteoarthritis                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 438 (0.46%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pain In Extremity                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Spinal Osteoarthritis                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Cystitis  |                 |                 |  |
| subjects affected / exposed                     | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetic Foot Infection                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulitis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 438 (0.00%) | 2 / 435 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Liver Abscess                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lobar Pneumonia                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung Infection                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postoperative Wound Infection                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary Mycosis                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 438 (0.00%) | 1 / 435 (0.23%) |  |
| 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                     | 1 / 438 (0.23%) | 0 / 435 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Lantus             | HOE901-U300        |  |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                    |                    |  |
| subjects affected / exposed                           | 107 / 438 (24.43%) | 115 / 435 (26.44%) |  |
| Nervous system disorders                              |                    |                    |  |
| Headache  |                    |                    |  |
| subjects affected / exposed                           | 22 / 438 (5.02%)   | 36 / 435 (8.28%)   |  |
| occurrences (all)                                     | 28                 | 48                 |  |
| Infections and infestations                           |                    |                    |  |
| Nasopharyngitis                                       |                    |                    |  |
| subjects affected / exposed                           | 47 / 438 (10.73%)  | 41 / 435 (9.43%)   |  |
| occurrences (all)                                     | 59                 | 48                 |  |
| Sinusitis   |                    |                    |  |
| subjects affected / exposed                           | 23 / 438 (5.25%)   | 11 / 435 (2.53%)   |  |
| occurrences (all)                                     | 30                 | 13                 |  |
| Upper Respiratory Tract Infection                     |                    |                    |  |
| subjects affected / exposed                           | 34 / 438 (7.76%)   | 45 / 435 (10.34%)  |  |
| occurrences (all)                                     | 44                 | 60                 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment   |
|----------------|---|
| 13 August 2013 | <ul style="list-style-type: none"><li>- Review of severe hypoglycemia classification by an external Review Board.</li><li>- Procedures when the titration extends beyond the originally planned 8 to 12 weeks post-randomization.</li><li>- Clarification of definition of an injection area and an injection site within that area.</li><li>- Clarification of timing of investigational medicinal product (IMP) injection.</li><li>- Clarification of the screening period.</li><li>- Clarification of serious adverse event (SAE) and adverse event of special interest (AESI) reporting.</li><li>- Clarification of uses and documentation of SMPG.</li><li>- Change to the scope of data recorded into the electronic case report form (e-CRF) upon phone call visits.</li></ul> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported