



## Clinical trial results:

### A Randomized, Double-Blind Trial Comparing the Effect of Dulaglutide 1.5 mg with Placebo on Glycemic Control in Patients with Type 2 Diabetes on Basal Insulin Glargine

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2012-004229-25  |
| Trial protocol           | IT HU CZ ES GB  |
| Global end of trial date | 15 October 2015 |

#### Results information

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

#### Trial information

##### Trial identification

|                       |       |
|-----------------------|-------|
| Sponsor protocol code | 13195 |
|-----------------------|-------|

##### Additional study identifiers

|                                    |  |
|------------------------------------|--|
| ISRCTN number                      | -  |
| ClinicalTrials.gov id (NCT number) | NCT02152371                                |
| WHO universal trial number (UTN)   | -  |
| Other trial identifiers            | Trial Alias: H9X-MC-GBDI, Trial ID : 13195 |

Notes:

#### Sponsors

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

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 15 October 2015 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 15 October 2015 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

The main purpose of this study is to evaluate the use of the study drug known as dulaglutide in participants with type II diabetes who are taking once-daily insulin glargine. The study will last about 31 weeks for each participant.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 28 May 2014 |
| 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 | Czech Republic: 52 |
| Country: Number of subjects enrolled | Puerto Rico: 28    |
| Country: Number of subjects enrolled | Hungary: 72        |
| Country: Number of subjects enrolled | United States: 61  |
| Country: Number of subjects enrolled | Italy: 28          |
| Country: Number of subjects enrolled | United Kingdom: 4  |
| Country: Number of subjects enrolled | Spain: 55          |
| Worldwide total number of subjects   | 300                |
| EEA total number of subjects         | 211                |

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)      | 187 |
| From 65 to 84 years       | 113 |
| 85 years and over         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Participants who met all inclusion criteria and none of the exclusion criteria entered a 2-week lead-in period. Only those participants who required further up-titration of the insulin glargine dose per treat-to-target (TTT) algorithm were randomized to one of two treatment groups.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Double blind                   |
| Roles blinded                | Investigator, Subject          |

### Arms

|                              |                                |
|------------------------------|--------------------------------|
| Are arms mutually exclusive? | Yes                            |
| <b>Arm title</b>             | Dulaglutide + Insulin Glargine |

Arm description:

1.5 milligrams (mg) dulaglutide administered subcutaneously (SQ) once weekly for 28 weeks. Titrated insulin glargine administered SQ once daily for 28 weeks. Participants who are taking metformin should remain on stable doses.

Dulaglutide: Administered SQ

Insulin Glargine: Administered SQ

Metformin: Administered orally

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Dulaglutide      |
| Investigational medicinal product code | LY2189265        |
| Other name                             |                  |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

Dosage and administration details:

1.5 milligrams (mg) Dulaglutide administered subcutaneously (SQ) once weekly for 28 weeks.

|  |           |
|--|-----------|
| Investigational medicinal product name | Metformin |
| Investigational medicinal product code |           |
| Other name                             |           |
| Pharmaceutical forms                   | Tablet    |
| Routes of administration               | Oral use  |

Dosage and administration details:

Metformin administered orally daily.

|  |                  |
|--|------------------|
| Investigational medicinal product name | Insulin Glargine |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

Dosage and administration details:

Titrated insulin glargine administered SQ once weekly for 28 weeks.

|                  |                            |
|------------------|----------------------------|
| <b>Arm title</b> | Placebo + Insulin Glargine |
|------------------|----------------------------|

Arm description:

Placebo administered SQ once weekly for 28 weeks. Titrated insulin glargine administered SQ once daily for 28 weeks. Participants who are taking metformin should remain on stable doses.

Placebo: Administered SQ

Insulin Glargine: Administered SQ

Metformin: Administered orally

|  |                  |
|--|------------------|
| Arm type                               | Placebo          |
| Investigational medicinal product name | Insulin Glargine |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

Dosage and administration details:

Insulin Glargine administered subcutaneous once daily for 28 weeks.

|  |                  |
|--|------------------|
| Investigational medicinal product name | Placebo          |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

Dosage and administration details:

Placebo administered SQ once weekly for 28 weeks.

|  |           |
|--|-----------|
| Investigational medicinal product name | Metformin |
| Investigational medicinal product code |           |
| Other name                             |           |
| Pharmaceutical forms                   | Tablet    |
| Routes of administration               | Oral use  |

Dosage and administration details:

Metformin administered orally daily.

| <b>Number of subjects in period 1</b>   | <b>Dulaglutide +<br/>Insulin Glargine</b> | <b>Placebo + Insulin<br/>Glargine</b> |
|---|---|---------------------------------------|
| Started                                 | 150                                       | 150                                   |
| Received at least 1 dose of study drug. | 150                                       | 150                                   |
| Completed                               | 138                                       | 134                                   |
| Not completed                           | 12  | 16                                    |
| Consent withdrawn by subject            | 3   | 7                                     |
| Physician decision                      | -   | 2                                     |
| Adverse event, non-fatal                | 6   | 2                                     |
| Reason Not Given                        | -   | 1                                     |
| Lost to follow-up                       | 1   | -                                     |
| Protocol deviation                      | 2   | 3                                     |
| Lack of efficacy                        | -   | 1                                     |



## Baseline characteristics

### Reporting groups

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Dulaglutide + Insulin Glargine |
|-----------------------|--------------------------------|

Reporting group description:

1.5 milligrams (mg) dulaglutide administered subcutaneously (SQ) once weekly for 28 weeks. Titrated insulin glargine administered SQ once daily for 28 weeks. Participants who are taking metformin should remain on stable doses.

Dulaglutide: Administered SQ

Insulin Glargine: Administered SQ

Metformin: Administered orally

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Placebo + Insulin Glargine |
|-----------------------|----------------------------|

Reporting group description:

Placebo administered SQ once weekly for 28 weeks. Titrated insulin glargine administered SQ once daily for 28 weeks. Participants who are taking metformin should remain on stable doses.

Placebo: Administered SQ

Insulin Glargine: Administered SQ

Metformin: Administered orally

| Reporting group values                             | Dulaglutide + Insulin Glargine | Placebo + Insulin Glargine | Total |
|--|--------------------------------|----------------------------|-------|
| Number of subjects                                 | 150                            | 150                        | 300   |
| Age categorical<br>Units: Subjects                 |                                |                            |       |
| In utero   | 0                              | 0                          | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0                              | 0                          | 0     |
| Newborns (0-27 days)                               | 0                              | 0                          | 0     |
| Infants and toddlers (28 days-23 months)           | 0                              | 0                          | 0     |
| Children (2-11 years)                              | 0                              | 0                          | 0     |
| Adolescents (12-17 years)                          | 0                              | 0                          | 0     |
| Adults (18-64 years)                               | 95                             | 92                         | 187   |
| From 65-84 years                                   | 55                             | 58                         | 113   |
| 85 years and over                                  | 0                              | 0                          | 0     |
| Age Continuous<br>Units: years                     |                                |                            |       |
| arithmetic mean                                    | 60.2                           | 60.6                       |       |
| standard deviation                                 | ± 9.47                         | ± 10.07                    | -     |
| Gender, Male/Female<br>Units: participants         |                                |                            |       |
| Female   | 65                             | 62                         | 127   |
| Male   | 85                             | 88                         | 173   |
| Ethnicity (NIH/OMB)<br>Units: Subjects             |                                |                            |       |
| Hispanic or Latino                                 | 26                             | 25                         | 51    |
| Not Hispanic or Latino                             | 104                            | 104                        | 208   |
| Unknown or Not Reported                            | 20                             | 21                         | 41    |

|   |         |         |     |
|---|---------|---------|-----|
| Race (NIH/OMB)  |         |         |     |
| Units: Subjects                                       |         |         |     |
| American Indian or Alaska Native                      | 0       | 0       | 0   |
| Asian   | 0       | 1       | 1   |
| Native Hawaiian or Other Pacific Islander             | 1       | 2       | 3   |
| Black or African American                             | 5       | 6       | 11  |
| White   | 143     | 138     | 281 |
| More than one race                                    | 1       | 3       | 4   |
| Unknown or Not Reported                               | 0       | 0       | 0   |
| Region of Enrollment                                  |         |         |     |
| Units: Subjects                                       |         |         |     |
| Czech Republic  | 25      | 27      | 52  |
| Puerto Rico   | 12      | 16      | 28  |
| Hungary   | 37      | 35      | 72  |
| United States   | 32      | 29      | 61  |
| Italy   | 13      | 15      | 28  |
| United Kingdom  | 2       | 2       | 4   |
| Spain   | 29      | 26      | 55  |
| Metformin Use   |         |         |     |
| Number of participants with Metformin use at baseline |         |         |     |
| Units: Subjects                                       |         |         |     |
| Metformin Use   | 134     | 131     | 265 |
| No Metformin Use                                      | 16      | 19      | 35  |
| Mean Insulin Glargine Dose                            |         |         |     |
| Units: Units  |         |         |     |
| arithmetic mean                                       | 40.71   | 36.59   |     |
| standard deviation                                    | ± 23.12 | ± 21.46 | -   |



## End points

### End points reporting groups

|   |                                |
|---|--------------------------------|
| Reporting group title   | Dulaglutide + Insulin Glargine |
| Reporting group description:<br>1.5 milligrams (mg) dulaglutide administered subcutaneously (SQ) once weekly for 28 weeks. Titrated insulin glargine administered SQ once daily for 28 weeks. Participants who are taking metformin should remain on stable doses.<br><br>Dulaglutide: Administered SQ<br><br>Insulin Glargine: Administered SQ<br><br>Metformin: Administered orally |                                |
| Reporting group title   | Placebo + Insulin Glargine     |
| Reporting group description:<br>Placebo administered SQ once weekly for 28 weeks. Titrated insulin glargine administered SQ once daily for 28 weeks. Participants who are taking metformin should remain on stable doses.<br><br>Placebo: Administered SQ<br><br>Insulin Glargine: Administered SQ<br><br>Metformin: Administered orally  |                                |

### Primary: Change from Baseline to 28 Weeks in Hemoglobin A1c (HbA1c)

|  |  |
|--|--|
| End point title  | Change from Baseline to 28 Weeks in Hemoglobin A1c (HbA1c) |
| End point description:<br>HbA1c is a form of hemoglobin that is measured primarily to identify the average plasma glucose concentration over prolonged periods of time. Least-squares (LS) mean and standard error (SE) changes from baseline in HbA1c at 28 weeks were measured using mixed model regression and restricted maximum likelihood (REML) with treatment, pooled country, visit, and treatment-by -visit interaction as fixed effects, baseline as covariate, and participant as a random effect. |  |
| End point type   | Primary  |
| End point timeframe:<br>Baseline, 28 Weeks   |  |

| End point values                    | Dulaglutide +<br>Insulin<br>Glargine | Placebo +<br>Insulin<br>Glargine |  |  |
|-------------------------------------|--------------------------------------|----------------------------------|--|--|
| Subject group type                  | Reporting group                      | Reporting group                  |  |  |
| Number of subjects analysed         | 150                                  | 150                              |  |  |
| Units: percentage of change         |                                      |                                  |  |  |
| least squares mean (standard error) | -1.44 (± 0.09)                       | -0.67 (± 0.09)                   |  |  |

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Change from Baseline to 28 Weeks HbA1c                      |
| Comparison groups                       | Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine |
| Number of subjects included in analysis | 300   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| P-value                                 | < 0.001   |
| Method                                  | Mixed-effect Model Repeated Measure                         |
| Parameter estimate                      | LS Means Diff   |
| Point estimate                          | -0.77   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -0.97   |
| upper limit                             | -0.56   |
| Variability estimate                    | Standard error of the mean                                  |
| Dispersion value                        | 0.1   |

### Secondary: Change from Baseline to 28 Weeks in Fasting Serum Glucose (FSG)

|   |   |
|---|---|
| End point title   | Change from Baseline to 28 Weeks in Fasting Serum Glucose (FSG) |
| End point description:  |   |
| FSG is a test to determine glucose levels after an overnight fast and prior to any meal. LS means of the FSG change from baseline to primary endpoint at wee 28 was adjusted by treatment, country, metformin use, week, treatment-by-week interaction, and baseline FSG as covariate, via a MMRM analysis. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Baseline, 28 Weeks  |   |

| End point values                       | Dulaglutide +<br>Insulin<br>Glargine | Placebo +<br>Insulin<br>Glargine |  |  |
|--|--------------------------------------|----------------------------------|--|--|
| Subject group type                     | Reporting group                      | Reporting group                  |  |  |
| Number of subjects analysed            | 150                                  | 150                              |  |  |
| Units: milligram per deciliter (mg/dL) |                                      |                                  |  |  |
| least squares mean (standard error)    | -44.63 (± 4.16)                      | -27.9 (± 4.08)                   |  |  |

### Statistical analyses

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Change from Baseline to 28 Weeks in FSG                     |
| Comparison groups                 | Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 300                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           |                            |
| P-value                                 | < 0.001                    |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | LS Mean Diff               |
| Point estimate                          | -16.73                     |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -26.02                     |
| upper limit                             | -7.44                      |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 4.72                       |

### Secondary: Change from Baseline to 28 Weeks in 7-Point Self Monitored Plasma Glucose (SMPG)

|  |  |
|--|--|
| End point title  | Change from Baseline to 28 Weeks in 7-Point Self Monitored Plasma Glucose (SMPG) |
| End point description:   |  |
| The LS means of the 7-point SMPG change from baseline (BL) to primary endpoint at week 28 was measured using a MMRM analysis adjusted by treatment, country, metformin use, week, treatment-by-week interaction, and baseline SMPG as covariate. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Baseline, 28 Weeks   |  |

| End point values                             | Dulaglutide +<br>Insulin<br>Glargine | Placebo +<br>Insulin<br>Glargine |  |  |
|--|--------------------------------------|----------------------------------|--|--|
| Subject group type                           | Reporting group                      | Reporting group                  |  |  |
| Number of subjects analysed                  | 150                                  | 150                              |  |  |
| Units: mg/dL                                 |                                      |                                  |  |  |
| least squares mean (standard error)          |                                      |                                  |  |  |
| Pre-Morning Meal (n=133,129)                 | -44.03 (± 2.71)                      | -35.97 (± 2.64)                  |  |  |
| Morning Meal 2-Hour Postprandial (n=123,119) | -64.16 (± 4.31)                      | -46.97 (± 4.27)                  |  |  |
| Pre-Midday Meal (n=133,127)                  | -40.89 (± 3.72)                      | -25.34 (± 3.62)                  |  |  |
| Midday Meal 2-Hour Post Prandial (n=123,117) | -51.13 (± 4.4)                       | -32.98 (± 4.33)                  |  |  |
| Pre-Evening Meal (n=133,129)                 | -43.68 (± 4.21)                      | -28.71 (± 4.07)                  |  |  |
| Evening Meal 2-Hour Postprandial (n=126,122) | -48.63 (± 5.22)                      | -27.35 (± 5.16)                  |  |  |
| 3:00 AM (n=124,117)                          | -39.77 (± 4.27)                      | -20.3 (± 4.23)                   |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Change from BL to 28 Weeks SMPG Pre-Morning Meal            |
| Comparison groups                       | Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine |
| Number of subjects included in analysis | 300   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| P-value                                 | = 0.007   |
| Method                                  | Mixed models analysis                                       |
| Parameter estimate                      | LS Mean Diff  |
| Point estimate                          | -8.06   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -13.87  |
| upper limit                             | -2.25   |
| Variability estimate                    | Standard error of the mean                                  |
| Dispersion value                        | 2.95  |

|  |   |
|--|---|
| <b>Statistical analysis title</b>                                      | BL to 28 Wks SMPG Morning Meal 2hr Postprandial             |
| Statistical analysis description:                                      |   |
| Change from Baseline to 28 Weeks SMPG Morning Meal 2-Hour Postprandial |   |
| Comparison groups  | Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine |
| Number of subjects included in analysis                                | 300   |
| Analysis specification   | Pre-specified   |
| Analysis type  |   |
| P-value  | < 0.001   |
| Method   | Mixed models analysis                                       |
| Parameter estimate   | LS Mean Diff  |
| Point estimate   | -17.18  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | -25.96  |
| upper limit  | -8.4  |
| Variability estimate   | Standard error of the mean                                  |
| Dispersion value   | 4.45  |

|                                   |                                     |
|-----------------------------------|-------------------------------------|
| <b>Statistical analysis title</b> | BL to 28 Weeks SMPG Pre-Midday Meal |
|-----------------------------------|-------------------------------------|

Statistical analysis description:

Change from Baseline to 28 Weeks SMPG Pre-Midday Meal

|   |   |
|---|---|
| Comparison groups                       | Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine |
| Number of subjects included in analysis | 300   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| P-value                                 | < 0.001   |
| Method                                  | Mixed models analysis                                       |
| Parameter estimate                      | LS Mean Diff  |
| Point estimate                          | -15.55  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -23.58  |
| upper limit                             | -7.52   |
| Variability estimate                    | Standard error of the mean                                  |
| Dispersion value                        | 4.08  |

**Statistical analysis title**

BL to 28 Weeks SMPG Midday Meal 2-hr Postprandial

Statistical analysis description:

Change from Baseline to 28 Weeks SMPG Midday Meal 2-Hour Postprandial

|   |   |
|---|---|
| Comparison groups                       | Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine |
| Number of subjects included in analysis | 300   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| P-value                                 | < 0.001   |
| Method                                  | Mixed models analysis                                       |
| Parameter estimate                      | LS Mean Diff  |
| Point estimate                          | -18.15  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -27.18  |
| upper limit                             | -9.12   |
| Variability estimate                    | Standard error of the mean                                  |
| Dispersion value                        | 4.58  |

**Statistical analysis title**

BL to 28 Weeks SMPG Pre-Evening Meal

Statistical analysis description:

Change from Baseline to 28 Weeks SMPG Pre-Evening Meal

|                   |   |
|-------------------|---|
| Comparison groups | Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine |
|-------------------|---|

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 300                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           |                            |
| P-value                                 | = 0.001                    |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | LS Mean Diff               |
| Point estimate                          | -14.96                     |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -23.93                     |
| upper limit                             | -5.99                      |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 4.55                       |

|  |   |
|--|---|
| <b>Statistical analysis title</b>                                      | BL to 28 Weeks SMPG Evening Meal 2-hr Postprandial          |
| Statistical analysis description:                                      |   |
| Change from Baseline to 28 Weeks SMPG Evening Meal 2-Hour Postprandial |   |
| Comparison groups  | Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine |
| Number of subjects included in analysis                                | 300   |
| Analysis specification   | Pre-specified   |
| Analysis type  |   |
| P-value  | < 0.001   |
| Method   | Mixed models analysis                                       |
| Parameter estimate   | LS Mean Diff  |
| Point estimate   | -21.28  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | -32.46  |
| upper limit  | -10.1   |
| Variability estimate   | Standard error of the mean                                  |
| Dispersion value   | 5.68  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>               | BL to 28 Weeks SMPG at 3:00AM                               |
| Statistical analysis description:               |   |
| Change from Baseline to 28 Weeks SMPG at 3:00AM |   |
| Comparison groups                               | Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine |
| Number of subjects included in analysis         | 300   |
| Analysis specification                          | Pre-specified   |
| Analysis type                                   |   |
| P-value   | < 0.001   |
| Method  | Mixed models analysis                                       |
| Parameter estimate                              | LS Mean Diff  |
| Point estimate                                  | -19.48  |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -28.77                     |
| upper limit          | -10.18                     |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 4.72                       |

## Secondary: Change from Baseline to 28 Weeks in Body Weight

|   |   |
|---|---|
| End point title   | Change from Baseline to 28 Weeks in Body Weight |
| End point description:  |   |
| LS means of the body weight change from baseline to primary endpoint at week 28 was adjusted by treatment, country, metformin use, week, treatment-by-week interaction, and baseline body weight as covariate, via a MMRM analysis. |   |
| End point type  | Secondary                                       |
| End point timeframe:  |   |
| Baseline, 28 Weeks  |   |

| End point values                    | Dulaglutide +<br>Insulin<br>Glargine | Placebo +<br>Insulin<br>Glargine |  |  |
|-------------------------------------|--------------------------------------|----------------------------------|--|--|
| Subject group type                  | Reporting group                      | Reporting group                  |  |  |
| Number of subjects analysed         | 150                                  | 150                              |  |  |
| Units: kg                           |                                      |                                  |  |  |
| least squares mean (standard error) | -1.91 (± 0.3)                        | 0.5 (± 0.3)                      |  |  |

## Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | Change From Baseline to 28 Wks Body Weight MMRM             |
| Comparison groups                       | Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine |
| Number of subjects included in analysis | 300   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| P-value                                 | < 0.001   |
| Method                                  | Mixed models analysis                                       |
| Parameter estimate                      | LS Means Difference   |
| Point estimate                          | -2.41   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -3.19   |
| upper limit                             | -1.64   |
| Variability estimate                    | Standard error of the mean                                  |
| Dispersion value                        | 0.39  |

---

**Secondary: Change from Baseline to 28 Weeks in Daily Mean Insulin Glargine Dose**

---

|                 |  |
|-----------------|--|
| End point title | Change from Baseline to 28 Weeks in Daily Mean Insulin Glargine Dose |
|-----------------|--|

End point description:

LS means of the insulin dose change from baseline to primary endpoint at week 28 was adjusted by treatment, country, metformin use, week, treatment-by-week interaction, and baseline insulin dose as covariate, via a MMRM analysis.

---

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

---

End point timeframe:

Baseline, 28 Weeks

---

| End point values                    | Dulaglutide +<br>Insulin<br>Glargine | Placebo +<br>Insulin<br>Glargine |  |  |
|-------------------------------------|--------------------------------------|----------------------------------|--|--|
| Subject group type                  | Reporting group                      | Reporting group                  |  |  |
| Number of subjects analysed         | 150                                  | 150                              |  |  |
| Units: units (u)                    |                                      |                                  |  |  |
| least squares mean (standard error) |                                      |                                  |  |  |
| Units (U)                           | 12.75 (± 2.27)                       | 25.94 (± 2.3)                    |  |  |

**Statistical analyses**

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Change From Baseline to 28 Wks Insulin Glargine             |
| Comparison groups                       | Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine |
| Number of subjects included in analysis | 300   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| P-value                                 | < 0.001   |
| Method                                  | Mixed models analysis                                       |
| Parameter estimate                      | LS Means Diff   |
| Point estimate                          | -13.19  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -19.55  |
| upper limit                             | -6.84   |
| Variability estimate                    | Standard error of the mean                                  |
| Dispersion value                        | 3.21  |

---

**Secondary: Number of Participants with Investigator Reported and Adjudicated**

---



## Cardiovascular Events

|                 |   |
|-----------------|---|
| End point title | Number of Participants with Investigator Reported and Adjudicated Cardiovascular Events |
|-----------------|---|

End point description:

Cardiovascular (CV) adverse events (AEs) were adjudicated by an independent committee of physicians with cardiology expertise external to the sponsor. Deaths occurring during the study treatment period and nonfatal CV AEs were to be adjudicated. Nonfatal CV events that were to be adjudicated were myocardial infarction; hospitalization for unstable angina; hospitalization for heart failure; coronary interventions (such as coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI); and cerebrovascular events, including cerebrovascular accident (CVA/stroke), and transient ischemic attack (TIA).

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

End point timeframe:

Baseline through 28 Weeks

| End point values            | Dulaglutide +<br>Insulin<br>Glargine | Placebo +<br>Insulin<br>Glargine |  |  |
|-----------------------------|--------------------------------------|----------------------------------|--|--|
| Subject group type          | Reporting group                      | Reporting group                  |  |  |
| Number of subjects analysed | 150                                  | 150                              |  |  |
| Units: participants         |                                      |                                  |  |  |
| number (not applicable)     | 3                                    | 1                                |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with Self-Reported Events of Hypoglycemia

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants with Self-Reported Events of Hypoglycemia |
|-----------------|--|

End point description:

Hypoglycemic events (HE) were classified as severe (defined as episodes requiring the assistance of another person to actively administer resuscitative actions), documented symptomatic (defined as any time a participant feels that he/she is experiencing symptoms and/or signs associated with hypoglycemia, and has a plasma glucose level of  $\leq 3.9$  mmol/L), asymptomatic (defined as events not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose of  $\leq 3.9$  mmol/L), nocturnal (defined as any hypoglycemic event that occurred between bedtime and waking), or probable symptomatic (defined as events during which symptoms of hypoglycemia were not accompanied by a plasma glucose determination). The percentage of participants with self-reported hypoglycemic events is presented. The percentage of participants with self-reported hypoglycemic events is presented.

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

End point timeframe:

Baseline through 28 Weeks

| End point values                  | Dulaglutide +<br>Insulin<br>Glargine | Placebo +<br>Insulin<br>Glargine |  |  |
|-----------------------------------|--------------------------------------|----------------------------------|--|--|
| Subject group type                | Reporting group                      | Reporting group                  |  |  |
| Number of subjects analysed       | 150                                  | 150                              |  |  |
| Units: percentage of participants |                                      |                                  |  |  |
| number (not applicable)           |                                      |                                  |  |  |
| Symptomatic                       | 35.3                                 | 30                               |  |  |
| Asymptomatic                      | 42.7                                 | 39.3                             |  |  |
| Severe                            | 0.7                                  | 0                                |  |  |
| Nocturnal                         | 28                                   | 28.7                             |  |  |
| Probable Symptomatic              | 2.7                                  | 2                                |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants Discontinuing the Study Due to Severe, Persistent Hyperglycemia

|                        |  |
|------------------------|--|
| End point title        | Percentage of Participants Discontinuing the Study Due to Severe, Persistent Hyperglycemia         |
| End point description: | Percentage of participants who discontinued due to severe, persistent hyperglycemia are presented. |
| End point type         | Secondary  |
| End point timeframe:   | Baseline through 28 Weeks  |

| End point values                  | Dulaglutide +<br>Insulin<br>Glargine | Placebo +<br>Insulin<br>Glargine |  |  |
|-----------------------------------|--------------------------------------|----------------------------------|--|--|
| Subject group type                | Reporting group                      | Reporting group                  |  |  |
| Number of subjects analysed       | 150                                  | 150                              |  |  |
| Units: percentage of participants |                                      |                                  |  |  |
| number (not applicable)           | 0                                    | 0                                |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Adjudicated Acute Pancreatitis Events

|                        |   |
|------------------------|---|
| End point title        | Number of Participants with Adjudicated Acute Pancreatitis Events   |
| End point description: | The number of cases of acute pancreatitis confirmed by adjudication. A summary of serious and other non-serious AEs, regardless of causality, is located in the Reported Adverse Events module. |
| End point type         | Secondary   |

End point timeframe:  
Baseline through 28 Weeks

| End point values            | Dulaglutide +<br>Insulin<br>Glargine | Placebo +<br>Insulin<br>Glargine |  |  |
|-----------------------------|--------------------------------------|----------------------------------|--|--|
| Subject group type          | Reporting group                      | Reporting group                  |  |  |
| Number of subjects analysed | 150                                  | 150                              |  |  |
| Units: participants         |                                      |                                  |  |  |
| number (not applicable)     | 0                                    | 0                                |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Thyroid Tumors/Neoplasms (Including C-Cell Hyperplasia)

|                 |   |
|-----------------|---|
| End point title | Number of Participants With Thyroid Tumors/Neoplasms (Including C-Cell Hyperplasia) |
|-----------------|---|

End point description:

Number of participants with one or more thyroid tumors/neoplasms of any type, including C-cell hyperplasia and thyroid cysts, is presented.

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

End point timeframe:

Baseline through 28 Weeks

| End point values            | Dulaglutide +<br>Insulin<br>Glargine | Placebo +<br>Insulin<br>Glargine |  |  |
|-----------------------------|--------------------------------------|----------------------------------|--|--|
| Subject group type          | Reporting group                      | Reporting group                  |  |  |
| Number of subjects analysed | 150                                  | 150                              |  |  |
| Units: participants         |                                      |                                  |  |  |
| number (not applicable)     | 1                                    | 0                                |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with Dulaglutide Anti-Drug Antibodies

|                 |  |
|-----------------|--|
| End point title | Number of Participants with Dulaglutide Anti-Drug Antibodies |
|-----------------|--|

End point description:

Dulaglutide anti-drug antibodies (ADA) were assessed at baseline, Weeks 12 and 28. A participant was considered to have treatment-emergent (TE) dulaglutide ADAs if the participant had at least 1 titer that was TE relative to baseline, defined as a 4-fold or greater increase in titer from baseline measurement.

|                               |           |
|-------------------------------|-----------|
| End point type                | Secondary |
| End point timeframe:          |           |
| Baseline, Week 12 and Week 28 |           |

| End point values            | Dulaglutide +<br>Insulin<br>Glargine | Placebo +<br>Insulin<br>Glargine |  |  |
|-----------------------------|--------------------------------------|----------------------------------|--|--|
| Subject group type          | Reporting group                      | Reporting group                  |  |  |
| Number of subjects analysed | 149 <sup>[1]</sup>                   | 149 <sup>[2]</sup>               |  |  |
| Units: participants         |                                      |                                  |  |  |
| number (not applicable)     | 0                                    | 2                                |  |  |

Notes:

[1] - Participants receiving at least 1 dose of study drug and had at least 1 Dulaglutide ADA test result.

[2] - Participants receiving at least 1 dose of study drug and had at least 1 Dulaglutide ADA test result.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants Achieving HbA1c Targets of <7.0% or ≤6.5%

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants Achieving HbA1c Targets of <7.0% or ≤6.5% |
|-----------------|--|

End point description:

Percentage of participants who achieved a target HbA1c target of <7%, without weight gain and without documented symptomatic hypoglycemia at 28 weeks were analyzed using regression model, controlling for treatment, pre-treatment, baseline HbA1c and country.

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

End point timeframe:

28 Weeks

| End point values                  | Dulaglutide +<br>Insulin<br>Glargine | Placebo +<br>Insulin<br>Glargine |  |  |
|-----------------------------------|--------------------------------------|----------------------------------|--|--|
| Subject group type                | Reporting group                      | Reporting group                  |  |  |
| Number of subjects analysed       | 150                                  | 150                              |  |  |
| Units: percentage of participants |                                      |                                  |  |  |
| number (not applicable)           |                                      |                                  |  |  |
| HbA1c ≤ 6.5                       | 50.7                                 | 16.7                             |  |  |
| HbA1c < 7.0                       | 69.3                                 | 35.3                             |  |  |

### Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | Participants Achieving HbA1c Targets ≤6.5%                  |
| Comparison groups          | Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine |

|   |                      |
|---|----------------------|
| Number of subjects included in analysis | 300                  |
| Analysis specification                  | Pre-specified        |
| Analysis type                           |                      |
| P-value                                 | < 0.001              |
| Method                                  | Regression, Logistic |
| Parameter estimate                      | Odds ratio (OR)      |
| Point estimate                          | 6.66                 |
| Confidence interval                     |                      |
| level                                   | 95 %                 |
| sides                                   | 2-sided              |
| lower limit                             | 3.7                  |
| upper limit                             | 12                   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Participants Achieving HbA1c Targets of <7.0%               |
| Comparison groups                       | Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine |
| Number of subjects included in analysis | 300   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| P-value                                 | < 0.001   |
| Method                                  | Regression, Logistic  |
| Parameter estimate                      | Log odds ratio  |
| Point estimate                          | 5.71  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 3.35  |
| upper limit                             | 9.73  |

**Secondary: Percentage of Participants Achieving HbA1c Target of <7.0% and Without Weight Gain (<0.1 kilograms [kg]) at 28 Weeks and Without Documented Symptomatic Hypoglycemia During the Maintenance Period (Weeks 12-28)**

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants Achieving HbA1c Target of <7.0% and Without Weight Gain (<0.1 kilograms [kg]) at 28 Weeks and Without Documented Symptomatic Hypoglycemia During the Maintenance Period (Weeks 12-28) |
|-----------------|--|

End point description:

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

End point timeframe:

28 Weeks

| End point values                  | Dulaglutide +<br>Insulin<br>Glargine | Placebo +<br>Insulin<br>Glargine |  |  |
|-----------------------------------|--------------------------------------|----------------------------------|--|--|
| Subject group type                | Reporting group                      | Reporting group                  |  |  |
| Number of subjects analysed       | 150                                  | 150                              |  |  |
| Units: percentage of participants |                                      |                                  |  |  |
| number (not applicable)           | 40.7                                 | 16.7                             |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | HbA1c Target <7.0% w/o Wt Gain and Hypoglycemia             |
| Comparison groups                       | Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine |
| Number of subjects included in analysis | 300   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| P-value                                 | < 0.001   |
| Method                                  | Regression, Logistic  |
| Parameter estimate                      | Odds ratio (OR)   |
| Point estimate                          | 4.17  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 2.32  |
| upper limit                             | 7.47  |

## Secondary: Percentage of Participants Achieving HbA1c Target of <7.0% at 28 Weeks and Without Documented Symptomatic Hypoglycemia during the Maintenance Period (Weeks 12-28)

|                        |  |
|------------------------|--|
| End point title        | Percentage of Participants Achieving HbA1c Target of <7.0% at 28 Weeks and Without Documented Symptomatic Hypoglycemia during the Maintenance Period (Weeks 12-28)   |
| End point description: | Percentage of participants achieving target HbA1c of <7.0% at 28 weeks without documented symptomatic hypoglycemia are presented. Documented symptomatic hypoglycemia is defined as any time a participant experienced symptoms and or signs associated with hypoglycemia and had a plasma glucose of ≤70 mg/dL. |
| End point type         | Secondary  |
| End point timeframe:   |  |
| 28 Weeks               |  |

| End point values                  | Dulaglutide +<br>Insulin<br>Glargine | Placebo +<br>Insulin<br>Glargine |  |  |
|-----------------------------------|--------------------------------------|----------------------------------|--|--|
| Subject group type                | Reporting group                      | Reporting group                  |  |  |
| Number of subjects analysed       | 150                                  | 150                              |  |  |
| Units: percentage of participants |                                      |                                  |  |  |
| number (not applicable)           | 52                                   | 28                               |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | HbA1c Target of <7.0% w/o Symptom Hypoglycemia              |
| Comparison groups                       | Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine |
| Number of subjects included in analysis | 300   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| P-value                                 | < 0.001   |
| Method                                  | Regression, Logistic  |
| Parameter estimate                      | Odds ratio (OR)   |
| Point estimate                          | 3.61  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 2.09  |
| upper limit                             | 6.23  |

## Secondary: Percentage of Participants Achieving HbA1c Target of <7.0% and Without Weight Gain (<0.1 kg)

|                        |  |
|------------------------|--|
| End point title        | Percentage of Participants Achieving HbA1c Target of <7.0% and Without Weight Gain (<0.1 kg)       |
| End point description: | The percentage of participants achieving a target HbA1c of <7.0% without weight gain is presented. |
| End point type         | Secondary  |
| End point timeframe:   | 28 Weeks   |

|                                   |                                      |                                  |  |  |
|-----------------------------------|--------------------------------------|----------------------------------|--|--|
| <b>End point values</b>           | Dulaglutide +<br>Insulin<br>Glargine | Placebo +<br>Insulin<br>Glargine |  |  |
| Subject group type                | Reporting group                      | Reporting group                  |  |  |
| Number of subjects analysed       | 150                                  | 150                              |  |  |
| Units: percentage of participants |                                      |                                  |  |  |
| number (not applicable)           | 52.7                                 | 20                               |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Achieving HbA1c Target of <7.0% W/O Weight Gain             |
| Comparison groups                       | Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine |
| Number of subjects included in analysis | 300   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| P-value                                 | < 0.001   |
| Method                                  | Regression, Logistic  |
| Parameter estimate                      | Odds ratio (OR)   |
| Point estimate                          | 5.6   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 3.26  |
| upper limit                             | 9.62  |

### Secondary: Rate of Hypoglycemic Events up to 28 Weeks

|   |  |
|---|--|
| End point title   | Rate of Hypoglycemic Events up to 28 Weeks |
| End point description:  |  |
| The rate of total hypoglycemic events any type per 30 days is presented. The hypoglycemia rate per 30 days during defined period is calculated by the number of hypoglycemia events within the period/number of days participant at risk within the period*30 days. |  |
| End point type  | Secondary                                  |
| End point timeframe:  |  |
| Baseline through 28 Weeks   |  |

| End point values                     | Dulaglutide +<br>Insulin<br>Glargine | Placebo +<br>Insulin<br>Glargine |  |  |
|--------------------------------------|--------------------------------------|----------------------------------|--|--|
| Subject group type                   | Reporting group                      | Reporting group                  |  |  |
| Number of subjects analysed          | 150                                  | 150                              |  |  |
| Units: Rate                          |                                      |                                  |  |  |
| arithmetic mean (standard deviation) | 0.63 (± 1.24)                        | 0.7 (± 1.32)                     |  |  |

### Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Entire Study

Adverse event reporting additional description:

H9X-MC-GBDI

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

### Reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | Dula_1.5 |
|-----------------------|----------|

Reporting group description: -

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events  | Dula_1.5        | Placebo         |  |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events                   |                 |                 |  |
| subjects affected / exposed   | 9 / 150 (6.00%) | 7 / 150 (4.67%) |  |
| number of deaths (all causes)                                       | 0               | 0               |  |
| number of deaths resulting from adverse events                      | 0               | 0               |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                 |  |
| hepatic cancer  |                 |                 |  |
| alternative dictionary used: MedDRA 18.1                            |                 |                 |  |
| subjects affected / exposed   | 0 / 150 (0.00%) | 1 / 150 (0.67%) |  |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 1           |  |
| Injury, poisoning and procedural complications                      |                 |                 |  |
| lower limb fracture   |                 |                 |  |
| alternative dictionary used: MedDRA 18.1                            |                 |                 |  |
| subjects affected / exposed   | 1 / 150 (0.67%) | 0 / 150 (0.00%) |  |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Cardiac disorders   |                 |                 |  |
| angina unstable   |                 |                 |  |
| alternative dictionary used: MedDRA 18.1                            |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 150 (0.67%) | 1 / 150 (0.67%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| atrial fibrillation                             |                 |                 |  |
| alternative dictionary used: MedDRA 18.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 150 (0.67%) | 0 / 150 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| bradycardia                                     |                 |                 |  |
| alternative dictionary used: MedDRA 18.1        |                 |                 |  |
| subjects affected / exposed                     | 2 / 150 (1.33%) | 0 / 150 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| coronary artery disease                         |                 |                 |  |
| alternative dictionary used: MedDRA 18.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 150 (0.67%) | 0 / 150 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| myocardial infarction                           |                 |                 |  |
| alternative dictionary used: MedDRA 18.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 150 (0.67%) | 0 / 150 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| carotid artery stenosis                         |                 |                 |  |
| alternative dictionary used: MedDRA 18.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 150 (0.67%) | 0 / 150 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| cerebral infarction                             |                 |                 |  |
| alternative dictionary used: MedDRA 18.1        |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 150 (0.67%) | 0 / 150 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| transient ischaemic attack                           |                 |                 |  |
| alternative dictionary used: MedDRA 18.1             |                 |                 |  |
| subjects affected / exposed                          | 2 / 150 (1.33%) | 0 / 150 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| non-cardiac chest pain                               |                 |                 |  |
| alternative dictionary used: MedDRA 18.1             |                 |                 |  |
| subjects affected / exposed                          | 0 / 150 (0.00%) | 1 / 150 (0.67%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                              |                 |                 |  |
| granulomatous liver disease                          |                 |                 |  |
| alternative dictionary used: MedDRA 18.1             |                 |                 |  |
| subjects affected / exposed                          | 1 / 150 (0.67%) | 0 / 150 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders               |                 |                 |  |
| skin ulcer   |                 |                 |  |
| alternative dictionary used: MedDRA 18.1             |                 |                 |  |
| subjects affected / exposed                          | 0 / 150 (0.00%) | 1 / 150 (0.67%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders      |                 |                 |  |
| intervertebral disc protrusion                       |                 |                 |  |
| alternative dictionary used: MedDRA 18.1             |                 |                 |  |
| subjects affected / exposed                          | 0 / 150 (0.00%) | 1 / 150 (0.67%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| osteoarthritis                                       |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| alternative dictionary used:<br>MedDRA 18.1        |                 |                 |  |
| subjects affected / exposed                        | 0 / 150 (0.00%) | 1 / 150 (0.67%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Infections and infestations</b>                 |                 |                 |  |
| gastroenteritis                                    |                 |                 |  |
| alternative dictionary used:<br>MedDRA 18.1        |                 |                 |  |
| subjects affected / exposed                        | 1 / 150 (0.67%) | 0 / 150 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>viral infection</b>                             |                 |                 |  |
| alternative dictionary used:<br>MedDRA 18.1        |                 |                 |  |
| subjects affected / exposed                        | 0 / 150 (0.00%) | 1 / 150 (0.67%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Metabolism and nutrition disorders</b>          |                 |                 |  |
| hypoglycaemia                                      |                 |                 |  |
| alternative dictionary used:<br>MedDRA 18.1        |                 |                 |  |
| subjects affected / exposed                        | 1 / 150 (0.67%) | 0 / 150 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                        | Dula_1.5          | Placebo           |  |
|--|-------------------|-------------------|--|
| Total subjects affected by non-serious<br>adverse events |                   |                   |  |
| subjects affected / exposed                              | 51 / 150 (34.00%) | 29 / 150 (19.33%) |  |
| <b>Gastrointestinal disorders</b>                        |                   |                   |  |
| diarrhoea  |                   |                   |  |
| alternative dictionary used:<br>MedDRA 18.1              |                   |                   |  |
| subjects affected / exposed                              | 17 / 150 (11.33%) | 6 / 150 (4.00%)   |  |
| occurrences (all)  | 19                | 6                 |  |
| dyspepsia  |                   |                   |  |
| alternative dictionary used:<br>MedDRA 18.1              |                   |                   |  |

|   |                                   |  |
|---|-----------------------------------|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>9 / 150 (6.00%)</p> <p>9</p>   | <p>0 / 150 (0.00%)</p> <p>0</p>   |  |
| <p>nausea</p> <p>alternative dictionary used:<br/>MedDRA 18.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>18 / 150 (12.00%)</p> <p>23</p>  | <p>2 / 150 (1.33%)</p> <p>3</p>   |  |
| <p>vomiting</p> <p>alternative dictionary used:<br/>MedDRA 18.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>9 / 150 (6.00%)</p> <p>11</p>  | <p>0 / 150 (0.00%)</p> <p>0</p>   |  |
| <p>Infections and infestations</p> <p>nasopharyngitis</p> <p>alternative dictionary used:<br/>MedDRA 18.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>6 / 150 (4.00%)</p> <p>7</p>             | <p>14 / 150 (9.33%)</p> <p>19</p> |  |
| <p>upper respiratory tract infection</p> <p>alternative dictionary used:<br/>MedDRA 18.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>11 / 150 (7.33%)</p> <p>18</p>                            | <p>10 / 150 (6.67%)</p> <p>10</p> |  |
| <p>Metabolism and nutrition disorders</p> <p>decreased appetite</p> <p>alternative dictionary used:<br/>MedDRA 18.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>10 / 150 (6.67%)</p> <p>11</p> | <p>0 / 150 (0.00%)</p> <p>0</p>   |  |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

---

### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported