



## Clinical trial results:

### A Twenty Six Week, Randomized, Open-label, 2-Arm, Parallel Group Real World Pragmatic Trial to Assess the Clinical and Health Outcomes Benefit of Toujeo® Compared to Standard of Care Insulin for Initiating Basal Insulin in Insulin Naïve Patients With Uncontrolled Type 2 Diabetes Mellitus, With 6-Month Extension

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2015-001831-18    |
| Trial protocol           | GB DE IE ES FR IT |
| Global end of trial date | 16 October 2017   |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 31 October 2018 |
| First version publication date | 31 October 2018 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | LPS13931 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |                           |
|------------------------------------|---------------------------|
| ISRCTN number                      | -                         |
| ClinicalTrials.gov id (NCT number) | NCT02967224               |
| WHO universal trial number (UTN)   | U1111-1170-8104           |
| Other trial identifiers            | Study Name: Reach-Control |

Notes:

#### Sponsors

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

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 14 December 2017 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 16 October 2017  |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate non-inferiority of Toujeo versus standard of care basal insulin therapy measured as glycosylated haemoglobin (HbA1c) change from baseline to Month 6.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy:

Subjects received oral anti diabetic drugs (OADs), glucagon-like peptide 1 receptor agonist (GLP1-RA) as background therapy at the discretion of the investigator and consistent with local labeling guidelines for use with insulin.

Evidence for comparator:

Standard of care basal insulin i.e., any commercially available long-acting or intermediate insulins, or any basal insulins (except Toujeo) including biosimilars was used as comparator.

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 05 November 2015 |
| 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 | Brazil: 102        |
| Country: Number of subjects enrolled | Italy: 95          |
| Country: Number of subjects enrolled | Romania: 87        |
| Country: Number of subjects enrolled | Spain: 104         |
| Country: Number of subjects enrolled | United Kingdom: 69 |
| Country: Number of subjects enrolled | France: 83         |
| Country: Number of subjects enrolled | Germany: 161       |
| Country: Number of subjects enrolled | Ireland: 2         |
| Worldwide total number of subjects   | 703                |
| EEA total number of subjects         | 601                |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|-------------------------------------------|-----|
| 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)                      | 428 |
| From 65 to 84 years                       | 272 |
| 85 years and over                         | 3   |

## Subject disposition

### Recruitment

#### Recruitment details:

The study was conducted at 127 active sites in 8 countries. A total of 798 subjects were screened between 05 November 2015 and 6 October 2016, of which 95 were screen failures. Screen failures were mainly due to HbA1c  $\leq 7.0\%$  at screening visit.

### Pre-assignment

#### Screening details:

A total of 703 subjects were randomized, stratified by GLP1-RA use in 6 months prior to randomization (yes, no), sulfonylurea (SU) use at the time of randomization (yes, no), and screening HbA1c category ( $< 9.0\%$ ,  $\geq 9.0\%$ ). Assignment to arms was done centrally using interactive response technology (IRT) in 1:1 ratio (Toujeo: Standard of care).

### Period 1

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

### Arms

|                              |        |
|------------------------------|--------|
| Are arms mutually exclusive? | Yes    |
| Arm title                    | Toujeo |

#### Arm description:

Toujeo® (Insulin glargine, 300 Units [U]/mL) subcutaneous (SC) injection once daily up to Month 12 on top of non-insulin anti-diabetic treatment.

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

#### Dosage and administration details:

Insulin glargine, 300 U/mL (dose range of 1 Unit to 80 Units) was self-administered by deep SC injection at any time of the day according to the local label and titration was performed according to local guidelines and/or the investigator's discretion.

|           |                  |
|-----------|------------------|
| Arm title | Standard of Care |
|-----------|------------------|

#### Arm description:

"Standard of care" commercially available basal insulin SC injection administered according to local label up to Month 12 on top of non-insulin anti-diabetic treatment.

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

#### Dosage and administration details:

Long acting or intermediate insulins, or any basal insulins (except Toujeo) including biosimilars with an appropriate pen device was self-administered by deep SC injection according to local label and titration was performed according to local guidelines and/or the investigator's discretion.

| <b>Number of subjects in period 1</b> | Toujeo | Standard of Care |
|---------------------------------------|--------|------------------|
| Started                               | 352    | 351              |
| Treated                               | 350    | 350              |
| Completed                             | 334    | 336              |
| Not completed                         | 18     | 15               |
| Consent withdrawn by subject          | 7      | 8                |
| Randomized and not treated            | 2      | 1                |
| Adverse event                         | 1      | -                |
| Other than specified                  | 5      | 4                |
| Lost to follow-up                     | 1      | 1                |
| Protocol deviation                    | 2      | 1                |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                          |                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| Reporting group title                                                                                                                                                                                    | Toujeo           |
| Reporting group description:<br>Toujeo® (Insulin glargine, 300 Units [U]/mL) subcutaneous (SC) injection once daily up to Month 12 on top of non-insulin anti-diabetic treatment.                        |                  |
| Reporting group title                                                                                                                                                                                    | Standard of Care |
| Reporting group description:<br>"Standard of care" commercially available basal insulin SC injection administered according to local label up to Month 12 on top of non-insulin anti-diabetic treatment. |                  |

| Reporting group values                                                                                                     | Toujeo           | Standard of Care | Total |
|----------------------------------------------------------------------------------------------------------------------------|------------------|------------------|-------|
| Number of subjects                                                                                                         | 352              | 351              | 703   |
| Age categorical<br>Units: Subjects                                                                                         |                  |                  |       |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation                                                    | 61.4<br>± 9.9    | 61.4<br>± 10.0   | -     |
| Gender categorical<br>Units: Subjects                                                                                      |                  |                  |       |
| Female                                                                                                                     | 147              | 152              | 299   |
| Male                                                                                                                       | 205              | 199              | 404   |
| Body Mass Index (BMI)                                                                                                      |                  |                  |       |
| Data for BMI was reported for a total of 699 subjects (Toujeo: 349 and Standard of Care: 350).                             |                  |                  |       |
| Units: kg/m <sup>2</sup><br>arithmetic mean<br>standard deviation                                                          | 31.15<br>± 6.06  | 31.13<br>± 5.76  | -     |
| Duration of Type 2 Diabetes Mellitus<br>Units: years<br>arithmetic mean<br>standard deviation                              | 11.16<br>± 7.37  | 10.88<br>± 7.10  | -     |
| Baseline HbA1c<br>Units: percentage of HbA1c<br>arithmetic mean<br>standard deviation                                      | 8.99<br>± 1.40   | 9.08<br>± 1.49   | -     |
| Basal Insulin Daily Dose                                                                                                   |                  |                  |       |
| Data for daily basal insulin dose (U/kg) was reported for a total of 699 subjects (Toujeo: 350 and Standard of Care: 349). |                  |                  |       |
| Units: U/kg<br>arithmetic mean<br>standard deviation                                                                       | 0.176<br>± 0.073 | 0.173<br>± 0.065 | -     |

## End points

### End points reporting groups

|                                                                                                                                                                                                          |                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| Reporting group title                                                                                                                                                                                    | Toujeo           |
| Reporting group description:<br>Toujeo® (Insulin glargine, 300 Units [U]/mL) subcutaneous (SC) injection once daily up to Month 12 on top of non-insulin anti-diabetic treatment.                        |                  |
| Reporting group title                                                                                                                                                                                    | Standard of Care |
| Reporting group description:<br>"Standard of care" commercially available basal insulin SC injection administered according to local label up to Month 12 on top of non-insulin anti-diabetic treatment. |                  |

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

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                          |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Change From Baseline in HbA1c to Month 6 |
| End point description:<br>Change in HbA1c was calculated by subtracting baseline value from Month 6 value. Adjusted least square means and standard errors were obtained from a mixed-effect model with repeated measures (MMRM) to account for missing data, using all post-baseline HbA1c data available during the 6 month randomized period (defined as the time from randomization up to Day 180) regardless of study drug discontinuation or intensification. Analysis was performed on Intent-to-treat (ITT) population which included all randomized subjects who received at least 1 dose of IMP, regardless of whether treatment was actually being received & analysed as per allocated treatment group. Number of subjects analysed=subjects with at least 1 baseline & 1 post-baseline HbA1c assessment during the 6 month randomized period. |                                          |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Primary                                  |
| End point timeframe:<br>Baseline, Month 6                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                          |

| End point values                    | Toujeo          | Standard of Care |  |  |
|-------------------------------------|-----------------|------------------|--|--|
| Subject group type                  | Reporting group | Reporting group  |  |  |
| Number of subjects analysed         | 342             | 339              |  |  |
| Units: percentage of HbA1c          |                 |                  |  |  |
| least squares mean (standard error) | -1.38 (± 0.059) | -1.50 (± 0.059)  |  |  |

### Statistical analyses

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                             |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Statistical analysis title                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Toujeo vs. Standard of Care |
| Statistical analysis description:<br>A hierarchical step-down testing procedure was used to control type 1 error. Analysis was performed using a MMRM approach with fixed categorical effects of treatment arm, visit, treatment-by-visit interaction, multi-country organization (MCO), randomization strata of SU use (yes/no), randomization strata of GLP-1 receptor agonist use (yes/no), as well as continuous fixed covariates of baseline HbA1c and baseline HbA1c value-by-visit interaction. |                             |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Toujeo v Standard of Care   |

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| Number of subjects included in analysis | 681                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | non-inferiority <sup>[1]</sup>    |
| P-value                                 | = 0.0145 <sup>[2]</sup>           |
| Method                                  | Mixed models analysis             |
| Parameter estimate                      | Least Square (LS) Mean difference |
| Point estimate                          | 0.12                              |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -0.046                            |
| upper limit                             | 0.281                             |
| Variability estimate                    | Standard error of the mean        |
| Dispersion value                        | 0.083                             |

Notes:

[1] - Non-inferiority of Toujeo vs. Standard of Care was demonstrated if the upper bound of the two-sided 95% confidence interval (CI) for the difference between groups was <0.3%.

[2] - Threshold for significance at 0.025 level.

|                                         |                             |
|-----------------------------------------|-----------------------------|
| <b>Statistical analysis title</b>       | Toujeo vs. Standard of Care |
| Comparison groups                       | Toujeo v Standard of Care   |
| Number of subjects included in analysis | 681                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[3]</sup>  |
| P-value                                 | = 0.1585                    |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LS Mean Difference          |
| Point estimate                          | 0.12                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -0.046                      |
| upper limit                             | 0.281                       |
| Variability estimate                    | Standard deviation          |
| Dispersion value                        | 0.083                       |

Notes:

[3] - Superiority of Toujeo over 'standard of care' was demonstrated if the upper bound of the two-sided 95% CI for the difference between groups was <0 (zero).

## Secondary: Change From Baseline in HbA1c to Month 12

|                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                           |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                              | Change From Baseline in HbA1c to Month 12 |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                           |
| Change in HbA1c was calculated by subtracting baseline value from Month 12 value. Adjusted least square means and standard errors were obtained from a mixed-effect model with repeated measurements. Analysis was performed on ITT population. Here, number of subjects analysed = subjects with at least one baseline and one post-baseline HbA1c assessment during the 12 month randomized period (defined as the time from randomization up to Day 360). |                                           |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                               | Secondary                                 |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                           |
| Baseline, Month 12                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                           |

| End point values                    | Toujeo               | Standard of Care     |  |  |
|-------------------------------------|----------------------|----------------------|--|--|
| Subject group type                  | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed         | 330                  | 333                  |  |  |
| Units: percentage of HbA1c          |                      |                      |  |  |
| least squares mean (standard error) | -1.39 ( $\pm$ 0.057) | -1.46 ( $\pm$ 0.056) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects Who Achieved a Target HbA1c of < 7% at Month 6 and Month 12

|                 |                                                                                    |
|-----------------|------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Who Achieved a Target HbA1c of < 7% at Month 6 and Month 12 |
|-----------------|------------------------------------------------------------------------------------|

End point description:

Measurements at Month 6 and Month 12 were considered in the analysis. Analysis was performed on ITT population.

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

End point timeframe:

Month 6 and Month 12

| End point values              | Toujeo          | Standard of Care |  |  |
|-------------------------------|-----------------|------------------|--|--|
| Subject group type            | Reporting group | Reporting group  |  |  |
| Number of subjects analysed   | 352             | 351              |  |  |
| Units: percentage of subjects |                 |                  |  |  |
| number (not applicable)       |                 |                  |  |  |
| At Month 6                    | 29.0            | 30.5             |  |  |
| At Month 12                   | 24.1            | 29.1             |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects Who Achieved a Target HbA1c of <7% Without Severe and/or Symptomatic Documented Hypoglycaemia (Blood Glucose $\leq$ 70 mg/dL [ $\leq$ 3.9 mmol/L]) and <54 mg/dL [ $\leq$ 3.0 mmol/L]) at Month 6 and Month 12

|                 |                                                                                                                                                                           |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Who Achieved a Target HbA1c of <7% Without Severe and/or Symptomatic Documented Hypoglycaemia (Blood Glucose $\leq$ 70 mg/dL [ $\leq$ 3.9 mmol/L]) |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

## End point description:

Severe hypoglycaemia was an event in which the subject required the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Documented symptomatic hypoglycaemia was an event during which typical symptoms of hypoglycaemia were accompanied by a measured plasma glucose concentration of  $\leq 70$  mg/dL (3.9 mmol/L) or <54 mg/dL (3.0 mmol/L). Analysis was performed on ITT population.

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

End point timeframe:

Month 6 and Month 12

| End point values                             | Toujeo          | Standard of Care |  |  |
|----------------------------------------------|-----------------|------------------|--|--|
| Subject group type                           | Reporting group | Reporting group  |  |  |
| Number of subjects analysed                  | 352             | 351              |  |  |
| Units: percentage of subjects                |                 |                  |  |  |
| number (not applicable)                      |                 |                  |  |  |
| At ( $\leq 70$ mg/dL [3.9 mmol/L]): Month 6  | 21.0            | 24.2             |  |  |
| At (<54 mg/dL [3.0 mmol/L]): Month 6         | 25.9            | 27.4             |  |  |
| At ( $\leq 70$ mg/dL [3.9 mmol/L]): Month 12 | 16.2            | 22.8             |  |  |
| At (<54 mg/dL [3.0 mmol/L]): Month 12        | 21              | 26.2             |  |  |

## Statistical analyses

No statistical analyses for this end point

**Secondary: Percentage of Subjects Who Remained on Assigned Basal Insulin Therapy Without Intensification at Month 6 and Month 12**

|                 |                                                                                                                       |
|-----------------|-----------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Who Remained on Assigned Basal Insulin Therapy Without Intensification at Month 6 and Month 12 |
|-----------------|-----------------------------------------------------------------------------------------------------------------------|

## End point description:

Intensification was defined by: addition of an OAD or GLP-1 RA, addition of a rapid acting insulin, increase in dose of any of their background anti-diabetes medications. Remaining on assigned therapy was defined by - subjects who neither permanently withdraw nor switch from Toujeo to "standard of care" basal insulin or from "standard of care" basal insulin to Toujeo. Analysis was performed on ITT population.

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

End point timeframe:

Month 6 and Month 12

| End point values              | Toujeo          | Standard of Care |  |  |
|-------------------------------|-----------------|------------------|--|--|
| Subject group type            | Reporting group | Reporting group  |  |  |
| Number of subjects analysed   | 352             | 351              |  |  |
| Units: percentage of subjects |                 |                  |  |  |
| number (not applicable)       |                 |                  |  |  |
| At Month 6                    | 82.1            | 80.1             |  |  |
| At Month 12                   | 73.6            | 72.1             |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Fasting Plasma Glucose (FPG) to Month 6 and Month 12

|                 |                                                                              |
|-----------------|------------------------------------------------------------------------------|
| End point title | Change From Baseline in Fasting Plasma Glucose (FPG) to Month 6 and Month 12 |
|-----------------|------------------------------------------------------------------------------|

End point description:

Change in FPG was calculated by subtracting baseline value from Month 6 and Month 12 value. Adjusted least squares means and standard errors were obtained from a MMRM approach including all post-baseline FPG data available during the 12 month randomized period. Analysis was run on subjects with at least one baseline and one post-baseline FPG assessment during the 12 month randomized period (defined as the time from randomization up to Day 360) . Analysis was performed on ITT population. Here 'n' signifies subjects with at least one baseline and one post baseline FPG values at specified time points.

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

End point timeframe:

Baseline, Month 6 and Month 12

| End point values                    | Toujeo          | Standard of Care |  |  |
|-------------------------------------|-----------------|------------------|--|--|
| Subject group type                  | Reporting group | Reporting group  |  |  |
| Number of subjects analysed         | 352             | 351              |  |  |
| Units: mmol/L                       |                 |                  |  |  |
| least squares mean (standard error) |                 |                  |  |  |
| Change At Month 6 (n = 328, 330)    | -2.92 (± 0.134) | -3.22 (± 0.134)  |  |  |
| Change At Month 12 (n = 320, 325)   | -3.32 (± 0.136) | -3.27 (± 0.135)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With At Least One Hypoglycaemic Event (Severe and/or Confirmed Hypoglycaemia [ $\leq 70$ mg/dL and $< 54$ mg/dL]) During 12 Month On-Treatment Period

|                 |                                                              |
|-----------------|--------------------------------------------------------------|
| End point title | Percentage of Subjects With At Least One Hypoglycaemic Event |
|-----------------|--------------------------------------------------------------|

End point description:

Severe hypoglycaemia was an event in which the subject required the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Severe and/or confirmed hypoglycaemia event was a severe event or an event confirmed with plasma glucose  $\leq 70$  mg/dL ( $\leq 3.9$  mmol/L), or  $< 54$  mg/dL ( $< 3.0$  mmol/L). Assessment was done during 12-month on-treatment period i.e. time from the first study drug intake up to 1 day after last injection of study drug. Analysis was performed on safety population defined as all randomized subjects who received at least one dose of Toujeo or "standard of care" basal insulin, regardless of the study drug administered.

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

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End point timeframe:

Baseline up to Month 12

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| End point values              | Toujeo          | Standard of Care |  |  |
|-------------------------------|-----------------|------------------|--|--|
| Subject group type            | Reporting group | Reporting group  |  |  |
| Number of subjects analysed   | 350             | 350              |  |  |
| Units: percentage of subjects |                 |                  |  |  |
| number (not applicable)       |                 |                  |  |  |
| At $\leq 70$ mg/dL            | 30.6            | 28.3             |  |  |
| At $< 54$ mg/dL               | 10.0            | 9.1              |  |  |

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Week 52) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Treatment-emergent AEs were AEs that developed or worsened or became serious during the 12-month on-treatment period i.e. time from the first study drug intake up to 1 day after last injection of study drug. Treatment-emergent AEs leading to death were analysed. Analysis was performed on safety population.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 20.1   |

### Reporting groups

|                       |        |
|-----------------------|--------|
| Reporting group title | Toujeo |
|-----------------------|--------|

Reporting group description:

Toujeo® (Insulin glargine, 300 U/mL) SC injection once daily up to Month 12 on top of non-insulin anti-diabetic treatment.

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Standard of Care |
|-----------------------|------------------|

Reporting group description:

"Standard of care" commercially available basal insulin SC injection administered according to local label up to Month 12 on top of non-insulin anti-diabetic treatment.

| Serious adverse events                                              | Toujeo            | Standard of Care  |  |
|---------------------------------------------------------------------|-------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                   |                   |  |
| subjects affected / exposed                                         | 43 / 350 (12.29%) | 41 / 350 (11.71%) |  |
| number of deaths (all causes)                                       | 2                 | 1                 |  |
| number of deaths resulting from adverse events                      |                   |                   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |  |
| Basal Cell Carcinoma                                                |                   |                   |  |
| subjects affected / exposed                                         | 0 / 350 (0.00%)   | 1 / 350 (0.29%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| Breast Cancer Recurrent                                             |                   |                   |  |
| subjects affected / exposed                                         | 0 / 350 (0.00%)   | 1 / 350 (0.29%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| Invasive Lobular Breast Carcinoma                                   |                   |                   |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung Neoplasm Malignant                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Metastases To Central Nervous System            |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metastases To Lung                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metastatic Gastric Cancer                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ovarian Germ Cell Teratoma                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatic Carcinoma Stage Iv                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Papillary Cystadenoma Lymphomatosum             |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |

|                                                      |                 |                 |  |
|------------------------------------------------------|-----------------|-----------------|--|
| Aortic Stenosis                                      |                 |                 |  |
| subjects affected / exposed                          | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Arterial Occlusive Disease                           |                 |                 |  |
| subjects affected / exposed                          | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Extremity Necrosis                                   |                 |                 |  |
| subjects affected / exposed                          | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Hypertension                                         |                 |                 |  |
| subjects affected / exposed                          | 1 / 350 (0.29%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Peripheral Arterial Occlusive Disease                |                 |                 |  |
| subjects affected / exposed                          | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Face Oedema                                          |                 |                 |  |
| subjects affected / exposed                          | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Injection Site Reaction                              |                 |                 |  |
| subjects affected / exposed                          | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Non-Cardiac Chest Pain                               |                 |                 |  |
| subjects affected / exposed                          | 1 / 350 (0.29%) | 2 / 350 (0.57%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Reproductive system and breast disorders        |                 |                 |  |
| Breast Fibrosis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| 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                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Alveolitis Allergic                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Dyspnoea                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural Effusion                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumothorax                                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 350 (0.57%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Pulmonary Embolism                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory Failure                             |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Psychiatric disorders                           |                 |                 |  |
| Confusional State                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| 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  |                 |                 |  |
| Abdominal Injury                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chest Injury                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Contusion                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Craniocerebral Injury                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fall                                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Incisional Hernia                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Ligament Rupture                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Periprosthetic Fracture                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tendon Rupture                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Acute Coronary Syndrome                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute Myocardial Infarction                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina Pectoris                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 2 / 350 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina Unstable                                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 350 (0.57%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial Fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac Failure                                 |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 350 (0.29%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac Failure Congestive                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiogenic Shock                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary Artery Disease                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 2 / 350 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary Artery Stenosis                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial Ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 350 (0.57%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Embolitic Stroke                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Hypoglycaemic Unconsciousness                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 2 / 350 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoxic-Ischaemic Encephalopathy                |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ischaemic Stroke                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sciatica                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (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 / 350 (0.29%) | 2 / 350 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Anaemia                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anaemia Of Malignant Disease                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Anal Fistula                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric Fistula                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrooesophageal Reflux Disease                |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Incarcerated Inguinal Hernia                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper Gastrointestinal Haemorrhage              |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Bile Duct Stone                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholelithiasis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Jaundice Cholestatic                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (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          |                 |                 |  |
| Diabetic Foot                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin Ulcer                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Acute Kidney Injury                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic Kidney Disease                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cystitis Noninfective                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypertensive Nephropathy                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Iga Nephropathy                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nephrotic Syndrome                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal Failure                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urethral Polyp                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endocrine disorders                             |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Goitre                                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| 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 |                 |                 |  |
| Back Pain                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal Pain                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal Stiffness                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteoarthritis                                  |                 |                 |  |
| subjects affected / exposed                     | 4 / 350 (1.14%) | 5 / 350 (1.43%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Polyarthritis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rotator Cuff Syndrome                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Anal Abscess                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| 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 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Escherichia Bacteraemia                                       |                 |                 |  |
| subjects affected / exposed                                   | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Escherichia Pyelonephritis                                    |                 |                 |  |
| subjects affected / exposed                                   | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Infective Exacerbation Of Chronic Obstructive Airways Disease |                 |                 |  |
| subjects affected / exposed                                   | 0 / 350 (0.00%) | 2 / 350 (0.57%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Intervertebral Discitis                                       |                 |                 |  |
| subjects affected / exposed                                   | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Osteomyelitis                                                 |                 |                 |  |
| subjects affected / exposed                                   | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Periodontitis                                                 |                 |                 |  |
| subjects affected / exposed                                   | 1 / 350 (0.29%) | 0 / 350 (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                                   | 3 / 350 (0.86%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all               | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Postoperative Wound Infection                                 |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Septic Shock                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin Infection                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tooth Abscess                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary Tract Infection                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Viral Infection                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Hyperglycaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 350 (0.29%) | 0 / 350 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperkalaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypokalaemia                                    |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 350 (0.00%) | 1 / 350 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| 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>                     | Toujeo           | Standard of Care |  |
|-------------------------------------------------------|------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                  |                  |  |
| subjects affected / exposed                           | 29 / 350 (8.29%) | 20 / 350 (5.71%) |  |
| Infections and infestations                           |                  |                  |  |
| Nasopharyngitis                                       |                  |                  |  |
| subjects affected / exposed                           | 29 / 350 (8.29%) | 20 / 350 (5.71%) |  |
| occurrences (all)                                     | 32               | 22               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 18 December 2015 | Following changes were made: - Added exclusion criterion for subjects with hypersensitivity to Toujeo or excipients - added a sensitivity analysis for the primary endpoint on per-protocol population instead of the 6-month completer population - clarified the definition of the per-protocol population and the 6-month completer population - added the $\alpha$ -glucosidase inhibitor class to the list of oral agents as part of inclusion criterion - removed the value "self-monitored plasma glucose (SMPG) $\leq 70$ mg/dL" in order to collect probable symptomatic and relative hypoglycaemia - clarified the responsibilities of reporting adverse events by the Investigators or third party - extended the period between last subject last visit and database lock - added decision tree for neutropenia - clarified the origin of the hypoglycaemic control subscale - clarified that the standard of care basal insulin could be provided by the site or dispensing pharmacy, - removed the term "country" as an effect in statistical models in order to prevent convergence issues - clarified that laboratory testing could be performed during the entire screening period - clarified contraceptive methods for subjects in the United Kingdom - clarified adverse event reporting instructions for alanine aminotransferase (ALT) increase - clarified the definition of procedure and consequence for subjects who withdrew from the study. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported