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 Transition to Toujeo® Compared to Standard of Care Insulin, in Basal Insulin Treated Patients With Uncontrolled Type 2 Diabetes Mellitus, With Six Month Extension

Summary

EudraCT number	2015-001832-39
Trial protocol	GB IE FI ES IT
Global end of trial date	20 October 2017

Results information

Result version number	v1 (current)
This version publication date	04 November 2018
First version publication date	04 November 2018

Trial information

Trial identification

Sponsor protocol code	LPS14060

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02967211
WHO universal trial number (UTN)	U1111-1170-8132
Other trial identifiers	Study Name: Regain 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	20 December 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 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 as measured by glycated hemoglobin (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	21 December 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	Romania: 82
Country: Number of subjects enrolled	Spain: 165
Country: Number of subjects enrolled	United Kingdom: 68
Country: Number of subjects enrolled	Finland: 42
Country: Number of subjects enrolled	France: 37
Country: Number of subjects enrolled	Brazil: 102
Country: Number of subjects enrolled	Italy: 111
Country: Number of subjects enrolled	Switzerland: 2
Worldwide total number of subjects	609
EEA total number of subjects	505

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)	356
From 65 to 84 years	253
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 98 active sites in 8 countries. A total of 795 subjects were screened between 21 December 2015 and 7 October 2016, of which 186 were screen failures. Screen failures were mainly due to HbA1c <=7.0% at screening visit.

Pre-assignment

Screening details:

A total of 609 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%, >=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.

Number of subjects in period 1	Toujeo	Standard of Care
Started	305	304
Treated	304	304
Completed	289	291
Not completed	16	13
Consent withdrawn by subject	7	7
Randomized but not treated	1	-
Adverse event	-	2
Other than specified	5	4
Lost to follow-up	1	-
Protocol deviation	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Toujeo
Reporting group 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.	
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.	

Reporting group values	Toujeo	Standard of Care	Total
Number of subjects	305	304	609
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	62.1	62.0	
standard deviation	± 10.1	± 9.6	-
Gender categorical Units: Subjects			
Female	142	136	278
Male	163	168	331
Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean	32.03	32.02	
standard deviation	± 6.06	± 6.05	-
Duration of Type 2 Diabetes Mellitus Units: years			
arithmetic mean	13.78	13.61	
standard deviation	± 7.38	± 7.82	-
Baseline HbA1c Units: percentage of HbA1c			
arithmetic mean	8.58	8.51	
standard deviation	± 1.10	± 1.18	-
Basal Insulin Daily Dose			
Data for daily basal insulin dose (U/kg) was reported for a total of 608 subjects (Toujeo: 304 and Standard of Care: 304).			
Units: U/kg			
arithmetic mean	0.406	0.406	
standard deviation	± 0.209	± 0.226	-

End points

End points reporting groups

Reporting group title	Toujeo
Reporting group 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.	
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.	

Primary: Change From Baseline in HbA1c to Month 6

End point title	Change From Baseline in HbA1c to Month 6
End point description:	
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:	
Baseline, Month 6	

End point values	Toujeo	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	296		
Units: percentage of HbA1c				
least squares mean (standard error)	-0.23 (± 0.056)	-0.41 (± 0.056)		

Statistical analyses

Statistical analysis title	Toujeo vs. Standard of Care
Statistical analysis description:	
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, multicountry 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	587
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.0554 [2]
Method	Mixed models analysis
Parameter estimate	Least Square (LS) Mean difference
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.015
upper limit	0.329
Variability estimate	Standard error of the mean
Dispersion value	0.08

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.

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 postbaseline 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	281	287		
Units: percentage of HbA1c				
least squares mean (standard error)	-0.37 (± 0.062)	-0.35 (± 0.062)		

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	305	304		
Units: percentage of subjects				
number (not applicable)				
At Month 6	8.5	14.5		
At Month 12	11.1	10.2		

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 <=70 mg/dL [<=3.9 mmol/L]) and <54 mg/dL [<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 <=70 mg/dL [<=3.9 mmol/L]) and <54 mg/dL [<3.0 mmol/L]) at Month 6 and Month 12

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 <=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	305	304		
Units: percentage of subjects				
number (not applicable)				
At (<=70 mg/dL [3.9 mmol/L]): Month 6	5.6	11.2		
At (<54 mg/dL [3.0 mmol/L]): Month 6	7.2	12.5		

At (<=70 mg/dL [3.9 mmol/L]): Month 12	6.6	6.3		
At (<54 mg/dL [3.0 mmol/L]): Month 12	9.2	7.9		

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	305	304		
Units: percentage of subjects				
number (not applicable)				
At Month 6	79.7	79.9		
At Month 12	66.6	71.4		

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 of ITT population 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). 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	293	295		
Units: mmol/L				
least squares mean (standard error)				
Change At Month 6 (n = 289, 290)	-0.72 (± 0.156)	-1.21 (± 0.155)		
Change At Month 12 (n = 281, 286)	-1.30 (± 0.177)	-1.26 (± 0.176)		

Statistical analyses

No statistical analyses for this end point

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

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 =<70 mg/dL (=<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.

End point type	Secondary

End point timeframe:

Baseline up to Month 12

End point values	Toujeo	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	304	304		
Units: percentage of subjects				
number (not applicable)				
At <=70 mg/dL	33.9	33.9		
At <54 mg/dL	15.1	13.2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Week 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 Units 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	41 / 304 (13.49%)	36 / 304 (11.84%)	
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 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast Neoplasm			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial Cancer Stage Iii			

subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Carcinoma			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases To Lung			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophageal Carcinoma			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic Carcinoma Metastatic			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic Neoplasm			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Adenocarcinoma			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian Cyst			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic Pain			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial Lung Disease			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			

subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Oedema			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
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	3 / 304 (0.99%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide Attempt			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 304 (0.33%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Brain Contusion			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fall			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral Neck Fracture			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand Fracture			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip Fracture			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus Injury			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal Injury			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Fracture			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity To Various Agents			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Acute Myocardial Infarction			
subjects affected / exposed	1 / 304 (0.33%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Angina Pectoris			
subjects affected / exposed	1 / 304 (0.33%)	3 / 304 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial Fibrillation			
subjects affected / exposed	0 / 304 (0.00%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Flutter			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular Block			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular Block Complete			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (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 / 304 (0.33%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Chronic			

subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	2 / 304 (0.66%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiorenal Syndrome			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
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 / 304 (0.33%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left Ventricular Dysfunction			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral Valve Stenosis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyrotoxic Cardiomyopathy			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dementia Alzheimer's Type			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Unconsciousness			

subjects affected / exposed	2 / 304 (0.66%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-Ischaemic Encephalopathy			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
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	1 / 304 (0.33%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar Infarction			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar Stroke			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (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	0 / 304 (0.00%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Haemorrhagic Anaemia			

subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypochromic Anaemia			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo Positional			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal Artery Thrombosis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Obstruction			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis Chronic			

subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Steato-Fibrosis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Steatosis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (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 / 304 (0.33%)	0 / 304 (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			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	1 / 304 (0.33%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Kidney Disease			
subjects affected / exposed	2 / 304 (0.66%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Detrusor Sphincter Dyssynergia			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic Syndrome			

subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Impairment			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Retention			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
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			
Gouty Tophus			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral Disc Protrusion			
subjects affected / exposed	2 / 304 (0.66%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterial Prostatitis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter Gastroenteritis			
subjects affected / exposed	2 / 304 (0.66%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 304 (0.33%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Erysipelas			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia Sepsis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingivitis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (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	2 / 304 (0.66%)	2 / 304 (0.66%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Pneumococcal			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Viral			

subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis Chronic			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Infection			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes Mellitus Inadequate Control			
subjects affected / exposed	0 / 304 (0.00%)	1 / 304 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic Ketoacidosis			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 304 (0.33%)	0 / 304 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Toujeo	Standard of Care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 304 (5.26%)	18 / 304 (5.92%)	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	16 / 304 (5.26%)	18 / 304 (5.92%)	
occurrences (all)	16	20	

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 the 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, - removed the value "self-monitored plasma glucose (SMPG) <=70 mg/dL" in order to collect probable symptomatic and relative hypoglycaemia, - clarified the responsibilities of reporting AEs by the Investigators or third party, - extended the period between last subject last visit and database lock, - clarified the origin of the hypoglycemic 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 AE reporting instructions for alanine aminotransferase (ALT) increase, - clarified the definition of procedure and consequence for subjects who withdrew from the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported