EU Clinical Trials Register

Clinical trial results:

A 24-Week, Multicenter, Randomized, Open-Label, Parallel-group Study Comparing the Efficacy and Safety of Toujeo® and Tresiba® in Insulin-Naive Patients with Type 2 Diabetes Mellitus not Adequately Controlled with Oral Antihyperglycemic Drug(s) ± GLP-1 Receptor Agonist

Summary

EudraCT number	2015-005101-36
Trial protocol	DK SE GR HU CZ SK FR GB SI BG HR IT
Global end of trial date	15 August 2017

Results information

Result version number	v1 (current)
This version publication date	30 August 2018
First version publication date	30 August 2018

Trial information

Trial identification

Sponsor protocol code	LPS14584

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02738151
WHO universal trial number (UTN)	U1111-1177-6327
Other trial identifiers	STUDY NAME: BRIGHT

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette,, Chilly-Mazarin, France,
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	29 September 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority of Toujeo to Tresiba in glycated hemoglobin (HbA1c) change from baseline to Week 24.

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:

Oral Anti diabetic Drugs (OADs), glucagon–like peptide-1 (GLP-1) receptor agonist according to local labelling. Dose remained unchanged during the study unless there was a specific safety issue related to these treatments.

Evidence for comparator: -

Actual start date of recruitment	19 May 2016
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	Israel: 26
Country: Number of subjects enrolled	Italy: 43
Country: Number of subjects enrolled	Serbia: 31
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	United States: 462
Country: Number of subjects enrolled	Romania: 112
Country: Number of subjects enrolled	Slovakia: 35
Country: Number of subjects enrolled	Sweden: 16
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	Croatia: 10
Country: Number of subjects enrolled	Bulgaria: 24
Country: Number of subjects enrolled	Czech Republic: 60
Country: Number of subjects enrolled	Denmark: 19
Country: Number of subjects enrolled	France: 18

Country: Number of subjects enrolled	Greece: 21
Country: Number of subjects enrolled	Hungary: 32
Worldwide total number of subjects	929
EEA total number of subjects	406

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)	596
From 65 to 84 years	329
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 158 study centers across 16 countries. A total of 1376 subjects were screened between 19 May 2016 and 19 February 2017, of whom 447 were screen failures.

Pre-assignment

Screening details:

A total of 929 subjects were randomized in 1:1 ratio to either Toujeo or Tresiba, stratified by screening glycated hemoglobin A1c (HbA1c) values (<8% or >=8%); and use of sulfonylurea (SU) or meglitinides at screening ('yes' versus 'no').

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 Unit [U]/mL) subcutaneous (SC) injection once daily up to Week 24 on top of non-insulin antidiabetic 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 self-administered by subcutaneous (SC) injection in the evening using a pre-filled pen. Dose titration to achieve fasting self-monitored plasma glucose (SMPG) from 80 to 100 mg/dL (4.4 to 5.6 mmol/L).

Arm title	Tresiba

Arm description:

Tresiba® (Insulin Degludec, 100 U/mL) SC injection once daily up to Week 24 on top of non-insulin antidiabetic treatment.

Arm type	Active comparator
Investigational medicinal product name	Insulin degludec
Investigational medicinal product code	
Other name	Tresiba®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin degludec, 100U/ml self-administered by subcutaneous (SC) injection in the evening using a pre-filled pen. Dose titration to achieve fasting self-monitored plasma glucose (SMPG) from 80 to 100 mg/dL (4.4 to 5.6 mmol/L).

Number of subjects in period 1	Toujeo	Tresiba
Started	466	463
Treated	462	462
Completed	443	432
Not completed	23	31
Randomized but not treated	4	1
Adverse event	4	5
Other than specified	11	21
Poor Compliance to Protocol	4	3
Hypoglycemia	-	1

Baseline characteristics

Reporting groups

Reporting group title	Toujeo
Reporting group description:	
Toujeo® (Insulin glargine, 300 Unit [U]/mL) subcutaneous (SC) injection once daily up to Week 24 on top of non-insulin antidiabetic treatment.	
Reporting group title	Tresiba
Reporting group description:	
Tresiba® (Insulin Degludec, 100 U/mL) SC injection once daily up to Week 24 on top of non-insulin antidiabetic treatment.	

Reporting group values	Toujeo	Tresiba	Total
Number of subjects	466	463	929
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	60.6	60.5	
standard deviation	± 9.6	± 9.8	-
Gender categorical			
Units: Subjects			
Female	219	211	430
Male	247	252	499
Body Mass Index (BMI)			
Units: Kg/m^2			
arithmetic mean	31.7	31.3	
standard deviation	± 4.3	± 4.4	-
Duration of Type 2 Diabetes Mellitus			
Units: years			
arithmetic mean	10.5	10.7	
standard deviation	± 6.1	± 6.5	-
Baseline HbA1c			
Units: Percentage of HbA1c			
arithmetic mean	8.71	8.57	
standard deviation	± 0.83	± 0.80	-
Basal Insulin Daily Dose			
Number of subjects analysed = subjects with available data for specified measure. (461 for both Toujeo and Tresiba arm)			
Units: Units per kilogram (U/kg)			
arithmetic mean	0.19	0.12	
standard deviation	± 0.04	± 0.03	-

End points

End points reporting groups

Reporting group title	Toujeo

Reporting group description:

Toujeo® (Insulin glargine, 300 Unit [U]/mL) subcutaneous (SC) injection once daily up to Week 24 on top of non-insulin antidiabetic treatment.

Reporting group title	Tresiba

Reporting group description:

Tresiba® (Insulin Degludec, 100 U/mL) SC injection once daily up to Week 24 on top of non-insulin antidiabetic treatment.

Primary: Change From Baseline in HbA1c to Week 24

End point title	Change From Baseline in HbA1c to Week 24

End point description:

Change in HbA1c was calculated by subtracting baseline value from Week 24 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 24-week on-treatment period. 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. Overall number of subjects analysed=subjects with at least 1 baseline & 1 post-baseline HbA1c assessment during 24 week on-treatment period.

End point type	Primary

End point timeframe:

Baseline, Week 24

End point values	Toujeo	Tresiba		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	430	425		
Units: percentage of HbA1c				
least squares mean (standard error)				
Week 24	-1.64 (± 0.037)	-1.59 (± 0.037)		

Statistical analyses

Statistical analysis title	Toujeo vs Tresiba

Statistical analysis description:

A hierarchical step-down testing procedure was used to control type 1 error. Analysis was performed using a MMRM approach with treatment groups, randomization strata, visit, and treatment-by-visit interaction as fixed categorical effects and baseline HbA1c value and baseline HbA1c value-by-visit interaction as continuous fixed covariates.

Comparison groups	Toujeo v Tresiba

Number of subjects included in analysis	855
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.0001 [2]
Method	Mixed models analysis
Parameter estimate	Least Square (LS) Mean difference
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.152
upper limit	0.051
Variability estimate	Standard error of the mean
Dispersion value	0.052

Notes:

[1] - Non-inferiority of Toujeo vs Tresiba 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.

Statistical analysis title	Toujeo vs. Tresiba
Comparison groups	Toujeo v Tresiba
Number of subjects included in analysis	855
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.3302
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.152
upper limit	0.051
Variability estimate	Standard error of the mean
Dispersion value	0.052

Notes:

[3] - Superiority of Toujeo over Tresiba was demonstrated if the upper bound of the two-sided 95% CI for the difference in the mean change in HbA1c from baseline to Week 24 between Toujeo over Tresiba on ITT population was <0 (zero).

Secondary: Change From Baseline in HbA1c to Week 12

End point title	Change From Baseline in HbA1c to Week 12

End point description:

Change in HbA1c was calculated by subtracting baseline value from Week 12 value. Adjusted least square means and standard errors were obtained from a mixed-effect model with MMRM. Analysis was performed on ITT population. Here, overall number of subjects analysed = subjects with at least one baseline and one post-baseline HbA1c assessment during the 12 week on-treatment period.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Toujeo	Tresiba		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	448	445		
Units: percentage of HbA1c				
least squares mean (standard error)				
Week 12	-1.37 (± 0.036)	-1.39 (± 0.036)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Fasting Plasma Glucose (FPG) to Week 12 and Week 24

End point title	Change From Baseline in Fasting Plasma Glucose (FPG) to Week 12 and Week 24
End point description:	

Change in FPG was calculated by subtracting baseline value from Week 12 and Week 24 value. Adjusted LS means were obtained from MMRM including post baseline values during the 24-week on-treatment period. Analysis was performed on ITT population. Here, n = subjects with at least one baseline and one post baseline FPG values at specified timepoints.

End point type	Secondary
End point timeframe:	

Baseline, Week 12 and Week 24

End point values	Toujeo	Tresiba		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	462		
Units: mmol/L				
least squares mean (standard error)				
Week 12 (n=442, 441)	-3.64 (± 0.099)	-3.89 (± 0.100)		
Week 24 (n=417, 408)	-3.52 (± 0.109)	-3.95 (± 0.110)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Fasting Self-Monitoring Plasma Glucose (SMPG) to Week 12 and Week 24

End point title	Change From Baseline in Fasting Self-Monitoring Plasma Glucose (SMPG) to Week 12 and Week 24
End point description:	

Fasting SMPG was measured by the subject before breakfast and before the administration of the glucose-lowering agents once a day during the study. Adjusted LS means were obtained from MMRM including post baseline values during the 24 week on-treatment period. Analysis was performed on ITT

population. Here, n = subjects with at least one baseline and one post baseline fasting SMPG values at specified timepoints.

End point type	Secondary
End point timeframe:	
Baseline, Week 12 and Week 24	

End point values	Toujeo	Tresiba		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	462		
Units: mmol/L				
least squares mean (standard error)				
Week 12 (n=430, 431)	-3.26 (± 0.067)	-3.25 (± 0.067)		
Week 24 (n=421, 416)	-3.23 (± 0.067)	-3.29 (± 0.068)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in 8 Point SMPG Profile to Week 12 and Week 24 Per Time Point

End point title	Change From Baseline in 8 Point SMPG Profile to Week 12 and Week 24 Per Time Point
End point description:	

8-point SMPG profiles were measured at the following 8 points: 03:00 at night, pre-breakfast, 2 hours after breakfast, pre-lunch, 2 hours after lunch, pre-dinner, 2 hours after dinner, and bedtime. Analysis was performed on ITT population. Here, n = subjects with at least one baseline and one post baseline SMPG values at specified timepoints.

End point type	Secondary
End point timeframe:	
Baseline, Week 12 and Week 24	

End point values	Toujeo	Tresiba		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	462		
Units: mmol/L				
arithmetic mean (standard deviation)				
Week 12: 03:00 at night (n=342, 334)	-2.77 (± 3.16)	-2.28 (± 3.49)		
Week 12: Pre-breakfast (n=378, 371)	-3.42 (± 2.79)	-3.00 (± 2.63)		
Week 12: 2 hours after breakfast (n=365, 351)	-3.20 (± 4.02)	-3.23 (± 3.92)		
Week 12: Pre-lunch (n=365, 358)	-2.64 (± 3.90)	-2.50 (± 3.65)		
Week 12: 2 hours after lunch (n=365, 367)	-2.51 (± 4.15)	-1.99 (± 3.94)		
Week 12: Pre-dinner (n=366, 363)	-2.04 (± 3.63)	-1.93 (± 3.74)		

Week 12: 2 hours after dinner (n=355, 352)	-2.32 (± 4.20)	-1.76 (± 3.87)		
Week 12: Bedtime (n=344, 331)	-2.44 (± 4.07)	-2.08 (± 3.95)		
Week 24: 03:00 at night (n=331, 305)	-2.65 (± 3.43)	-2.43 (± 3.51)		
Week 24: Pre-breakfast (n=363, 341)	-3.37 (± 2.81)	-3.03 (± 2.85)		
Week 24: 2 hours after breakfast (n=346, 326)	-3.30 (± 3.68)	-3.50 (± 4.00)		
Week 24: Pre-lunch (n=350, 331)	-2.81 (± 3.67)	-2.29 (± 3.93)		
Week 24: 2 hours after lunch (n=350, 338)	-2.74 (± 3.73)	-1.93 (± 3.91)		
Week 24: Pre-dinner (n=350, 333)	-1.87 (± 3.78)	-1.86 (± 4.01)		
Week 24: 2 hours after dinner (n=338, 326)	-2.28 (± 4.19)	-2.07 (± 4.00)		
Week 24: Bedtime (n=315, 286)	-2.52 (± 3.87)	-2.09 (± 3.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in 4-point SMPG Profile to Week 12 and Week 24 Per Time Point

End point title	Change From Baseline in 4-point SMPG Profile to Week 12 and Week 24 Per Time Point

End point description:

4-point SMPG profiles were measured at the following 4 points: prebreakfast, prelunch, predinner and bedtime. Analysis was performed on ITT population. Here, n = subjects with at least one baseline and one post baseline SMPG values at specified timepoints.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and Week 24

End point values	Toujeo	Tresiba		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	462		
Units: mmol/L				
arithmetic mean (standard deviation)				
Week 12: Pre-breakfast (n=380, 374)	-3.41 (± 2.75)	-2.97 (± 2.62)		
Week 12: Pre-lunch (n=369, 362)	-2.63 (± 3.88)	-2.44 (± 3.65)		
Week 12: Pre-dinner (n=371, 370)	-2.03 (± 3.64)	-1.92 (± 3.76)		
Week 12: Bedtime (n=346, 336)	-2.41 (± 4.10)	-2.11 (± 3.96)		
Week 24: Pre-breakfast (n=363, 341)	-3.38 (± 2.81)	-2.99 (± 2.81)		
Week 24: Pre-lunch (n=351, 332)	-2.81 (± 3.67)	-2.26 (± 3.92)		
Week 24: Pre-dinner (n=353, 335)	-1.88 (± 3.79)	-1.86 (± 4.01)		
Week 24: Bedtime (n=314, 289)	-2.51 (± 3.87)	-2.10 (± 4.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in 24-hour Average 8-point SMPG Profile to Week 12 and Week 24

End point title	Change From Baseline in 24-hour Average 8-point SMPG Profile to Week 12 and Week 24

End point description:

The 8-point SMPG profile was measured at the following 8 points: 03:00 at night, pre-breakfast, 2 hours after breakfast, pre-lunch, 2 hours after lunch, pre-dinner, 2 hours after dinner, and bedtime. Adjusted LS means were obtained from MMRM. Analysis was performed on ITT population. Here, n = subjects with at least one baseline and one post-baseline 24-hour average SMPG values at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and Week 24

End point values	Toujeo	Tresiba		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	462		
Units: mmol/L				
least squares mean (standard error)				
Week 12 (n= 379,375)	-2.57 (± 0.092)	-2.50 (± 0.093)		
Week 24 (n=363, 345)	-2.62 (± 0.094)	-2.53 (± 0.096)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Variability of Fasting SMPG to Week 12 and Week 24

End point title	Change From Baseline in Variability of Fasting SMPG to Week 12 and Week 24

End point description:

Adjusted LS means were obtained from MMRM. Variability was assessed by the mean of coefficient of variation calculated over at least 3 SMPG measured during the 7 days preceding the given visit. Analysis was performed on ITT population. Here, n = subjects with at least one baseline and one post baseline Fasting SMPG values at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and Week 24

End point values	Toujeo	Tresiba		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	462		
Units: percentage of mean variability				
least squares mean (standard error)				
Week 12 (n=430, 431)	2.38 (± 0.418)	2.62 (± 0.416)		
Week 24 (n=421, 416)	1.49 (± 0.391)	1.97 (± 0.390)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Variability of 24-Hour 8-Point SMPG Profiles at Week 12 and Week 24

End point title	Change From Baseline in Variability of 24-Hour 8-Point SMPG Profiles at Week 12 and Week 24

End point description:

Adjusted LS means were obtained from MMRM. Data was presented in form of percentage of SMPG profile. Analysis was performed on ITT population. Here, n = subjects with at least one baseline and one post-baseline 24-hour average SMPG values at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and Week 24

End point values	Toujeo	Tresiba		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	462		
Units: percentage of mean variability				
least squares mean (standard error)				
Week 12 (n=379,375)	4.08 (± 0.562)	4.73 (± 0.561)		
Week 24 (n=363, 345)	3.70 (± 0.588)	3.95 (± 0.599)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reaching Target HbA1c of < 7% and =<6.5% at Week 12 and Week 24

End point title	Percentage of Subjects Reaching Target HbA1c of < 7% and =<6.5% at Week 12 and Week 24

End point description:

Only the post-baseline HbA1c measurements before rescue and during the 12 week and 24-week on-treatment period were considered in the analysis. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Week 12, and Week 24

End point values	Toujeo	Tresiba		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	462		
Units: percentage of subjects				
number (not applicable)				
Subjects who reached the target <7% at Week 12	34.63	36.15		
Subjects who reached target <=6.5% at Week 12	11.47	14.29		
Subjects who reached the target <7% at Week 24	48.70	44.59		
Subjects who reached target <=6.5% at Week 24	21.21	19.70		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reaching Target HbA1c <7% and =<6.5% at Week 12 and Week 24 Without Severe and/or Confirmed Hypoglycemia (70 mg/dL) Event

End point title	Percentage of Subjects Reaching Target HbA1c <7% and =<6.5% at Week 12 and Week 24 Without Severe and/or Confirmed Hypoglycemia (70 mg/dL) Event

End point description:

Severe hypoglycemia 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 hypoglycemia event was a severe event or an event confirmed by plasma glucose =<3.9 mmol/L (=<70 mg/dL). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Week 12, and Week 24

End point values	Toujeo	Tresiba		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	462		
Units: percentage of subjects				
number (not applicable)				
Week 12: Subjects who reached the target <7%	16.45	13.64		
Week 12: Subjects who reached target <=6.5%	4.11	4.55		
Week 24: Subjects who reached the target <7%	13.42	12.99		

Week 24: Subjects who reached target <=6.5%	5.84	5.19		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Sulphonylurea or Meglitinide Dose Reduction/ Discontinuation Due to Hypoglycemia

End point title	Percentage of Subjects With Sulphonylurea or Meglitinide Dose Reduction/ Discontinuation Due to Hypoglycemia

End point description:

Percentage of subjects With Sulphonylurea or Meglitinide dose reduction/ discontinuation due to Hypoglycemia during 24 Week treatment period were reported. Only subjects with Sulphonylurea or meglitinides at Screening as per actual strata were taken into account in this analysis. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Toujeo	Tresiba		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	462		
Units: percentage of subjects				
number (not applicable)	4.98	4.76		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Requiring a Rescue Therapy During 24 Weeks Treatment Period

End point title	Percentage of Subjects Requiring a Rescue Therapy During 24 Weeks Treatment Period

End point description:

Routine fasting SMPG and central laboratory FPG (and HbA1c after Week 12) values were used to determine the requirement of rescue medication. Threshold values at Week 12: FPG >200 mg/dL (11 mmol/L), or HbA1c >8.5%. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Toujeo	Tresiba		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	462		
Units: percentage of subjects				
number (not applicable)	1.30	1.30		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Basal Insulin Dose (U/kg Body Weight) to Week 12 and Week 24

End point title	Change From Baseline in Basal Insulin Dose (U/kg Body Weight) to Week 12 and Week 24

End point description:

Only the insulin dose measurements performed before initiation of rescue therapy and during the on-treatment period were considered in the analysis. Analysis was performed on Safety Population which included all randomized subjects who did actually receive at least one dose of IMP, regardless of the amount of treatment administered.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and Week 24

End point values	Toujeo	Tresiba		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	462		
Units: Units per kilogram (U/kg)				
arithmetic mean (standard deviation)				
Week 12 (n=450, 445)	0.289 (± 0.200)	0.255 (± 0.195)		
Week 24 (n=436, 425)	0.357 (± 0.253)	0.309 (± 0.241)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With At Least One Hypoglycemic Events (Any, Severe and/or Confirmed Hypoglycemia: Any Time of the Day) by Study Period

End point title	Percentage of Subjects With At Least One Hypoglycemic Events (Any, Severe and/or Confirmed Hypoglycemia: Any Time of the Day) by Study Period

End point description:

Severe hypoglycemia 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 hypoglycemia 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 by treatment period (for =<12

for >12 weeks to =<24 weeks (24W)). Percentage of subjects with at least one hypoglycemia (hypo) event at any time of the day were reported. Analysis was performed on Safety Population.

End point type	Secondary
End point timeframe:	
Day 1-Week 12, Week 13-Week 24, and 24 Week Period	

End point values	Toujeo	Tresiba		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	462		
Units: percentage of subjects				
number (not applicable)				
Any hypo Day1-Week 12	53.0	58.4		
Any hypo Week13-14	57.2	57.4		
Any hypo 24 week period	70.1	71.2		
Severe and/or confirmed hypo (=<70mg/dL) D1–W12	47.4	54.3		
Severe and/or confirmed hypo (=<70mg/dL) W13-14	54.1	55.8		
Severe and/or confirmed hypo(=<70mg/dL) 24W period	66.5	69.0		
Severe and/or confirmed hypo (< 54mg/dL) D1–W12	7.8	11.7		
Severe and/or confirmed hypo(<54 mg/dL) W13-14	9.8	11.2		
Severe and/or confirmed hypo (<54mg/dL) 24W period	14.7	18.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With At Least One Hypoglycemic Events (Any, Severe and/or Confirmed Hypoglycemia: Nocturnal) by Study Period

End point title	Percentage of Subjects With At Least One Hypoglycemic Events (Any, Severe and/or Confirmed Hypoglycemia: Nocturnal) by Study Period

End point description:

Severe hypoglycemia 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). Nocturnal hypoglycemia was hypoglycemia that occurred between 00:00 and 05:59 hours (clock time). Assessment was done by treatment period (for =<12 weeks, for >12 weeks to =<24 weeks). Safety population included all randomized subjects who did actually receive at least one dose of IMP, regardless of the amount of treatment administered.

End point type	Secondary
End point timeframe:	
Day 1-Week 12, Week 13-Week 24, and 24 Week Period	

End point values	Toujeo	Tresiba		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	462		
Units: percentage of subjects				
number (not applicable)				
Any hypo D1-W12	18.4	21.0		
Any hypo W13-14	22.7	21.2		
Any hypo 24W period	31.2	30.3		
Severe and/or confirmed hypo (=<70mg/dL) D1-W12	15.2	18.8		
Severe and/or confirmed hypo (=<70mg/dL) W13-14	21.4	21.0		
Severe and/or confirmed hypo(=<70mg/dL) 24W Period	28.6	28.8		
Severe and/or confirmed hypo (< 54mg/dL) D1-W12	2.8	3.5		
Severe and/or confirmed hypo (< 54mg/dL) W13-14	4.5	3.8		
Severe and/or confirmed hypo(< 54mg/dL) 24W Period	6.1	6.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Hypoglycemia (Any, Severe and/or Confirmed Hypoglycemia: Any Time of the Day) Event Rate Per Subject Year During Study Period

End point title	Hypoglycemia (Any, Severe and/or Confirmed Hypoglycemia: Any Time of the Day) Event Rate Per Subject Year During Study Period

End point description:

Severe hypoglycemia 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 hypoglycemia 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). Analysis was performed on Safety population.

End point type	Secondary

End point timeframe:

Day 1-Week 12, Week 13-Week 24, and 24 Week Period

End point values	Toujeo	Tresiba		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	462		
Units: Events per subject year				
number (not applicable)				
Any hypo D1-W12	8.93	11.31		
Any hypo W13-14	11.28	11.60		
Any hypo 24W period	10.09	11.45		
Severe and/or confirmed hypo (=<70mg/dL) D1-W12	8.08	10.47		

Severe and/or confirmed hypo (=<70mg/dL) W13-14	10.64	11.21		
Severe and/or confirmed hypo (≤70mg/dL) 24W period	9.34	10.83		
Severe and/or confirmed hypo (< 54mg/dL) D1-W12	0.49	0.86		
Severe and/or confirmed hypo(<54 mg/dL) W13-14	0.73	0.91		
Severe and/or confirmed hypo (<54mg/dL) 24W period	0.61	0.88		

Statistical analyses

No statistical analyses for this end point

Secondary: Hypoglycemia (Any, Severe and/or Confirmed Hypoglycemia: Nocturnal) Event Rate Per subject Year During Study Period

End point title	Hypoglycemia (Any, Severe and/or Confirmed Hypoglycemia: Nocturnal) Event Rate Per subject Year During Study Period

End point description:

Severe hypoglycemia 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 hypoglycemia 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). Nocturnal hypoglycemia was hypoglycemia that occurred between 00:00 and 05:59 hours (clock time). Analysis was performed on Safety Population.

End point type	Secondary

End point timeframe:

Day 1-Week 12, Week 13-Week 24, and 24 Week Period

End point values	Toujeo	Tresiba		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	462		
Units: Events per Subject year				
number (not applicable)				
Any hypo D1-W12	1.65	2.36		
Any hypo W13-14	2.32	2.39		
Any hypo 24W period	1.98	2.38		
Severe and/or confirmed hypo (=<70mg/dL) D1-W12	1.42	2.20		
Severe and/or confirmed hypo (=<70mg/dL) W13-14	2.24	2.33		
Severe and/or confirmed hypo (=<70mg/dL)24W Period	1.83	2.26		
Severe and/or confirmed hypo(< 54mg/dL) D1-W12	0.16	0.19		
Severe and/or confirmed hypo(< 54mg/dL) W13-14	0.33	0.26		
Severe and/or confirmed hypo(< 54mg/dL) 24W Period	0.24	0.22		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Total Diabetes Treatment Satisfaction Questionnaire (DTSQ) Status at Week 12 and Week 24

End point title	Change From Baseline in Total Diabetes Treatment Satisfaction Questionnaire (DTSQ) Status at Week 12 and Week 24

End point description:

The DTSQs is a validated questionnaire to assess subject's satisfaction with their diabetes treatment. It consists of 8 items that are answered on a Likert scale from 0 to 6. Total treatment satisfaction score is the sum of items 1, 4-8 scores and ranged from 0 (no satisfaction) to 36 (high satisfaction with treatment). Adjusted least square means and standard errors were obtained from a mixed-effect model with MMRM. Analysis was performed on ITT population. Here, n = subjects with at least one baseline and one post-baseline DTSQ status (DTSQs) total score.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 12 and Week 24

End point values	Toujeo	Tresiba		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	462		
Units: score on a scale				
least squares mean (standard error)				
Week 12 (n= 438, 436)	5.08 (± 0.246)	5.32 (± 0.245)		
Week 24 (n= 419, 416)	5.77 (± 0.257)	5.44 (± 0.256)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form until 7 days after last treatment administration (maximum exposure: 24 Weeks).

Adverse event reporting additional description:

Reported AEs and death were treatment-emergent AEs that is AEs that developed/worsened during the 'on-treatment period' (On-treatment period was defined as time from the first injection of open-label IMP upto 7days after the last injection of open-label IMP, regardless of introduction of rescue therapy). Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Toujeo

Reporting group description:

Toujeo® (Insulin glargine, 300 U/mL) SC injection once daily up to Week 24 on top of non-insulin antidiabetic treatment.

Reporting group title	Tresiba

Reporting group description:

Tresiba® (Insulin Degludec, 100 U/mL) SC injection once daily up to Week 24 on top of non-insulin antidiabetic treatment.

Serious adverse events	Toujeo	Tresiba	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 462 (4.55%)	20 / 462 (4.33%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acoustic Neuroma			
subjects affected / exposed	1 / 462 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma Of Colon			
subjects affected / exposed	1 / 462 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Carcinoid Tumour Pulmonary			

subjects affected / exposed	1 / 462 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pancreatic Carcinoma Metastatic		
subjects affected / exposed	0 / 462 (0.00%)	1 / 462 (0.22%)
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 / 462 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hypertensive Crisis		
subjects affected / exposed	1 / 462 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Varicose Ulceration		
subjects affected / exposed	1 / 462 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
General disorders and administration site conditions		
Non-Cardiac Chest Pain		
subjects affected / exposed	0 / 462 (0.00%)	2 / 462 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders		
Acute Respiratory Failure		
subjects affected / exposed	0 / 462 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Chronic Obstructive Pulmonary Disease		

subjects affected / exposed	1 / 462 (0.22%)	0 / 462 (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 / 462 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia Aspiration		
subjects affected / exposed	0 / 462 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary Embolism		
subjects affected / exposed	0 / 462 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Psychiatric disorders		
Alcohol Abuse		
subjects affected / exposed	1 / 462 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Drug Use Disorder		
subjects affected / exposed	1 / 462 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Major Depression		
subjects affected / exposed	0 / 462 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Injury, poisoning and procedural complications		
Meniscus Injury		
subjects affected / exposed	0 / 462 (0.00%)	1 / 462 (0.22%)
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	0 / 462 (0.00%)	3 / 462 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Flutter			
subjects affected / exposed	0 / 462 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 462 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest			
subjects affected / exposed	0 / 462 (0.00%)	1 / 462 (0.22%)	
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 / 462 (0.22%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Insufficiency			
subjects affected / exposed	0 / 462 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			
subjects affected / exposed	1 / 462 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular Tachycardia			
subjects affected / exposed	0 / 462 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Carpal Tunnel Syndrome				
subjects affected / exposed	0 / 462 (0.00%)	1 / 462 (0.22%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cerebrovascular Accident				
subjects affected / exposed	1 / 462 (0.22%)	0 / 462 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Headache				
subjects affected / exposed	1 / 462 (0.22%)	0 / 462 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Ischaemic Stroke				
subjects affected / exposed	0 / 462 (0.00%)	3 / 462 (0.65%)		
occurrences causally related to treatment / all	0 / 0	0 / 3		
deaths causally related to treatment / all	0 / 0	0 / 0		
Trigeminal Neuralgia				
subjects affected / exposed	1 / 462 (0.22%)	0 / 462 (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 Haemorrhage				
subjects affected / exposed	1 / 462 (0.22%)	0 / 462 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastrointestinal disorders				
Gastric Ulcer				
subjects affected / exposed	0 / 462 (0.00%)	1 / 462 (0.22%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Rectal Fissure				
subjects affected / exposed	1 / 462 (0.22%)	0 / 462 (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			
Nephrolithiasis			
subjects affected / exposed	0 / 462 (0.00%)	1 / 462 (0.22%)	
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			
Osteoarthritis			
subjects affected / exposed	0 / 462 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Osteoarthritis			
subjects affected / exposed	0 / 462 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 462 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial Pyelonephritis			
subjects affected / exposed	1 / 462 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 462 (0.22%)	2 / 462 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 462 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 462 (0.22%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 462 (0.22%)	0 / 462 (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	1 / 462 (0.22%)	0 / 462 (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	Tresiba	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 462 (12.12%)	58 / 462 (12.55%)	
Infections and infestations			
Upper Respiratory Tract Infection			
subjects affected / exposed	24 / 462 (5.19%)	19 / 462 (4.11%)	
occurrences (all)	25	20	
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	38 / 462 (8.23%)	40 / 462 (8.66%)	
occurrences (all)	49	45	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol?   No

Interruptions (globally)

Were there any global interruptions to the trial?   No

Limitations and caveats

 None reported