Clinical trial results:
National, Randomized, Controlled, Open-label, Parallel-Group Study Comparing the Efficacy and Safety of Two Different Titration Algorithm Approaches (Physician Managed Versus Patient Managed) for New Insulin Glargine U300 Therapy in Type 2 Diabetes Patients

Summary

EudraCT number	2015-001167-39
Trial protocol	IT
Global end of trial date	05 October 2017

Results information

Result version number	v1 (current)
This version publication date	19 October 2018
First version publication date	19 October 2018

Trial information

Trial identification

Sponsor protocol code	GLARGL07537

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Study Name: Italian Titration Approach Study

Notes:

Sponsors

Sponsor organisation name	Sanofi S.p.A
Sponsor organisation address	Viale L. Bodio 37/b, Milano, Italy, 20158
Public contact	Sanofi aventis recherche & développement, Trial Transparency Team, contact-US@sanofi.com
Scientific contact	Sanofi aventis recherche & développement, Trial Transparency Team, 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	06 February 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority, in terms of glycemic control, of a subject-managed (nurse assisted) versus a physician-managed algorithm for titrating Insulin glargine 300 U/ml (HOE901-U300) in insulin naïve type 2 diabetes mellitus (T2DM) subjects inadequately controlled with oral antidiabetic agents.

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) at a stable dose in accordance to the authorized local labelling for use with insulin.

Evidence for comparator: -

Actual start date of recruitment	28 August 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	Italy: 359
Worldwide total number of subjects	359
EEA total number of subjects	359

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)	163
From 65 to 84 years	196
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 46 centres in Italy. A total of 458 subjects were screened between 28 August 2015 and 23 March 2017, of which 99 subjects were screen failures. Screen failures were mainly due to inclusion criteria not met.

Pre-assignment

Screening details:

A total of 359 subjects were randomized in 1:1 ratio to either of the 2 titration modality arms.

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	Physician-Managed Titration

Arm description:

Subjects received HOE901-U300 once daily for 24 weeks. The dose was titrated by physician at each study visit according to study design (weekly for the first 12 weeks, bi-weekly until Week 24) to achieve fasting Self-Measured Plasma Glucose (SMPG) in the target range of 80-110 mg/dL.

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 subcutaneous (SC) injection once in the evening, at approximately the same time every day (i.e., without exceeding +/- 3 hours compared to the usual time) in the abdominal wall, the deltoid or the thigh. Within a given area, location should be changed (rotated) each time to prevent injection-site skin reactions.

Arm title	Subject-Managed Titration

Arm description:

Subjects received HOE901-U300 once daily for 24 weeks. The dose was self-titrated every 3-4 days to achieve fasting SMPG in the target range of 80-110 mg/dL.

Arm type	Active comparator
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 SC injection once in the evening, at approximately the same time every day (i.e., without exceeding +/- 3 hours compared to the usual time) in the abdominal wall, the deltoid or the thigh. Within a given area, location should be changed (rotated) each time to prevent injection-site skin reactions.

Number of subjects in period 1	Physician-Managed Titration	Subject-Managed Titration
Started	181	178
Treated	180	175
Completed	169	170
Not completed	12	8
Consent withdrawn by subject	5	4
Adverse event	1	1
Other than specified	3	2
Lost to follow-up	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Physician-Managed Titration
Reporting group description:	
Subjects received HOE901-U300 once daily for 24 weeks. The dose was titrated by physician at each study visit according to study design (weekly for the first 12 weeks, bi-weekly until Week 24) to achieve fasting Self-Measured Plasma Glucose (SMPG) in the target range of 80-110 mg/dL.	
Reporting group title	Subject-Managed Titration
Reporting group description:	
Subjects received HOE901-U300 once daily for 24 weeks. The dose was self-titrated every 3-4 days to achieve fasting SMPG in the target range of 80-110 mg/dL.	

Reporting group values	Physician-Managed Titration	Subject-Managed Titration	Total
Number of subjects	181	178	359
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	63.71	64.04	
standard deviation	± 9.87	± 9.76	-
Gender categorical			
Units: Subjects			
Female	71	66	137
Male	110	112	222
Body mass index (BMI)			
Data for BMI was reported for a total of 355 subjects (Physician-Managed: 180 and Subject-Managed of Care: 175).			
Units: Kg/m^2			
arithmetic mean	30.11	30.54	
standard deviation	± 5.02	± 6.18	-
Duration of T2DM			
Units: Years			
arithmetic mean	11.57	11.59	
standard deviation	± 7.82	± 7.40	-
Glycated Haemoglobin (HbA1c %)			
Data for Glycated Haemoglobin was reported for a total of 355 subjects (Physician-Managed: 180 and Subject-Managed: 175).			
Units: percentage of HbA1c			
arithmetic mean	8.82	8.77	
standard deviation	± 0.64	± 0.67	-

End points

End points reporting groups

Reporting group title	Physician-Managed Titration

Reporting group description:

Subjects received HOE901-U300 once daily for 24 weeks. The dose was titrated by physician at each study visit according to study design (weekly for the first 12 weeks, bi-weekly until Week 24) to achieve fasting Self-Measured Plasma Glucose (SMPG) in the target range of 80-110 mg/dL.

Reporting group title	Subject-Managed Titration

Reporting group description:

Subjects received HOE901-U300 once daily for 24 weeks. The dose was self-titrated every 3-4 days to achieve fasting SMPG in the target range of 80-110 mg/dL.

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. Analysis was performed on ITT population that included all randomized subjects who received at least one dose of study drug and had a baseline assessment of primary efficacy variable. Subjects were analysed as per allocated treatment group.

End point type	Primary

End point timeframe:

Baseline, Week 24

End point values	Physician-Managed Titration	Subject-Managed Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	175		
Units: percentage of HbA1c				
least squares mean (standard error)	-1.49 (± 0.06)	-1.60 (± 0.06)		

Statistical analyses

Statistical analysis title	Subject-Managed Titration vs Physician-Managed

Statistical analysis description:

Analysis was performed using a linear mixed-effect model approach with titration approach and center as fixed effects and the HbA1c baseline value as covariate.

Comparison groups	Subject-Managed Titration v Physician-Managed Titration

Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	0.08

Notes:

[1] - Non-inferiority of subject-managed titration versus physician-managed titration was demonstrated if the upper bound of the two-sided 95% confidence interval (CI) for the difference between groups was <0.3%.

Secondary: Percentage of Subjects With At Least One Confirmed and/or Severe Nocturnal Hypoglycemic Events (Hypoglycemia <=70 mg/dL [3.9 mmol/L]) From Baseline to Week 24

End point title	Percentage of Subjects With At Least One Confirmed and/or Severe Nocturnal Hypoglycemic Events (Hypoglycemia <=70 mg/dL [3.9 mmol/L]) From Baseline to Week 24

End point description:

Severe hypoglycemia is an event requiring assistance of another person to actively administer carbohydrate, glucagon, or perform 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). Nocturnal hypoglycemia was hypoglycemia that occurred between 00:00 and 05:59 hours (clock time). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Physician-Managed Titration	Subject-Managed Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	175		
Units: percentage of subjects				
number (not applicable)	4.44	3.43		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Change in FPG was calculated by subtracting baseline value from Week 24 value. Analysis was

performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Physician-Managed Titration	Subject-Managed Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	175		
Units: mg/dL				
least squares mean (standard error)	-60.93 (± 2.49)	-60.89 (± 2.34)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Changes in insulin dose were based on the median of the fasting SMPG values measured on 3 consecutive days, the last being the day of titration. Change in daily insulin dose was calculated by subtracting baseline value from Week 24 value. Analysis was performed on ITT population. Here, number of subjects analysed=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Physician-Managed Titration	Subject-Managed Titration		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	165		
Units: U/kg				
arithmetic mean (standard deviation)	0.16 (± 0.14)	0.19 (± 0.17)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All adverse events (AEs) were collected from signature of the informed consent form up to the final visit (Week 24) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs are treatment-emergent AEs that developed/worsened or became serious during on-treatment period from first dose of the study drug up to two days after the last dose of study drug for both titration groups. Analysis was performed on safety population that included all randomized subjects who have taken at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Physician managed titration

Reporting group description:

Subjects received HOE901-U300 once daily for 24 weeks. The dose was titrated by physician at each study visit according to study design (weekly for the first 12 weeks, bi-weekly until Week 24 to achieve fasting SMPG in the target range of 80-110 mg/dL.

Reporting group title	Subject managed titration

Reporting group description:

Subjects received HOE901-U300 once daily for 24 weeks. The dose was self-titrated every 3-4 days to achieve fasting self-measured plasma glucose (SMPG) in the target range of 80-110 mg/dL.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: There were no non-serious adverse events at 5% frequency threshold.

Serious adverse events	Physician managed titration	Subject managed titration	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 180 (6.11%)	3 / 175 (1.71%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Rib Fracture			
subjects affected / exposed	1 / 180 (0.56%)	0 / 175 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	1 / 180 (0.56%)	0 / 175 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			

subjects affected / exposed	1 / 180 (0.56%)	0 / 175 (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 / 180 (0.56%)	0 / 175 (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	0 / 180 (0.00%)	1 / 175 (0.57%)	
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	2 / 180 (1.11%)	0 / 175 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Ischaemia			
subjects affected / exposed	1 / 180 (0.56%)	0 / 175 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid Artery Disease			
subjects affected / exposed	0 / 180 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 180 (0.56%)	0 / 175 (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			
Acute Pulmonary Oedema			
subjects affected / exposed	1 / 180 (0.56%)	0 / 175 (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 / 180 (0.56%)	0 / 175 (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	0 / 180 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Osteomyelitis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 180 (0.56%)	0 / 175 (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			
Hypoglycaemia			
subjects affected / exposed	1 / 180 (0.56%)	0 / 175 (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	Physician managed titration	Subject managed titration	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 180 (0.00%)	0 / 175 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2016	Following amendment changes were made: The sample size was changed to 354 randomized subjects. Per protocol population was added to the analysis populations in order to provide supportive information for the analysis of the primary variable.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported