Clinical trial results:
An interventional, Open-Label, Single-Arm, Multicenter, 24 Weeks Phase 4 Study Assessing the Efficacy and Safety of Toujeo in Patients with Type 2 Diabetes Inadequately Controlled with Basal Insulin

Summary

EudraCT number	2015-002416-33
Trial protocol	FR
Global end of trial date	24 July 2017

Results information

Result version number	v1 (current)
This version publication date	03 August 2018
First version publication date	03 August 2018

Trial information

Trial identification

Sponsor protocol code	GLARGL07667

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02967237
WHO universal trial number (UTN)	U1111-1176-6203

Notes:

Sponsors

Sponsor organisation name	Sanofi Aventis France
Sponsor organisation address	82, avenue Raspail, Gentilly Cedex, France, 94255
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	27 November 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To describe the effect of HOE901-U300 in subjects with type 2 diabetes inadequately controlled by their basal insulin and eligible for a change of basal insulin, according to the investigator's judgement, in terms of improvement of glycated hemoglobin (HbA1c).

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: -	
Evidence for comparator: -	
Actual start date of recruitment	04 January 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	France: 140
Worldwide total number of subjects	140
EEA total number of subjects	140

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)	79
From 65 to 84 years	60
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted in France. A total of 194 subjects were screened between 04 January 2016 and 29 December 2016, of which 54 subjects were screen failures. Screen failures were mainly due to inclusion criteria not met. A total of 140 subjects were included.

Pre-assignment

Screening details:

Among 140 subjects, 3 subjects did not receive any dose of investigational medicinal product (IMP) and 137 subjects were included in the safety population.

Period 1

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

Arms

Arm title	Insulin glargine: HOE901-U300

Arm description:

Subjects received HOE901-U300 (Insulin glargine, 300 U/mL) once daily for 24 weeks. The dose was adjusted every 3-4 days to achieve fasting self-measured plasma glucose (SMPG) in the target range of 80-130 mg/dL, as recommended by the American diabetes association/ European association for the Study of Diabetes (ADA/EASD).

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

Dosage and administration details:

HOE901-U300 was administered by subcutaneous injection at approximately the same time every day (i.e., without exceeding ± 3 hours compared to the usual time).

Number of subjects in period 1	Insulin glargine: HOE901-U300
Started	140
Treated (Safety population)	137
Completed	129
Not completed	11
Consent withdrawn by subject	2
Adverse event	5
Included but not treated	3
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study
Reporting group description:	
Subjects received HOE901-U300 (Insulin glargine, 300 U/mL) once daily for 24 weeks. The dose was adjusted every 3-4 days to achieve fasting self-measured plasma glucose (SMPG) in the target range of 80-130 mg/dL, as recommended by the American diabetes association/ European association for the study of Diabetes (ADA/EASD).	

Reporting group values	Overall Study	Total	
Number of subjects	140	140	
Age categorical Units: Subjects			
Adults (18-64 years)	79	79	
From 65-84 years	60	60	
85 years and over	1	1	
Gender categorical Units: Subjects			
Female	50	50	
Male	90	90	

End points

End points reporting groups

Reporting group title	Insulin glargine: HOE901-U300

Reporting group description:

Subjects received HOE901-U300 (Insulin glargine, 300 U/mL) once daily for 24 weeks. The dose was adjusted every 3-4 days to achieve fasting self-measured plasma glucose (SMPG) in the target range of 80-130 mg/dL, as recommended by the American diabetes association/ European association for the Study of Diabetes (ADA/EASD).

Primary: Change From Baseline in Glycated Hemoglobin (HbA1c) to Week 24

End point title	Change From Baseline in Glycated Hemoglobin (HbA1c) to Week 24[1]

End point description:

Change in HbA1c was calculated by subtracting baseline value from Week 24 value. Analysis was performed on modified intention-to-treat population (mITT) population that included all subjects in the study who received at least one dose of IMP and were assessable for the primary endpoint. Here, "subjects analysed" = subjects with available data for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Week 24

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The study consisted of single-arm hence, no comparative analysis was performed. The 95% CI is given adjusted by baseline value.

End point values	Insulin glargine: HOE901-U300			
Subject group type	Reporting group			
Number of subjects analysed	132			
Units: HbA1c (%)				
least squares mean (confidence interval 95%)	-0.64 (-0.81 to -0.46)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reaching Fasting Self-monitored Plasma Glucose (SMPG) Target Range of 90-130 mg/dL at Week 12 and Week 24

End point title	Percentage of Subjects Reaching Fasting Self-monitored Plasma Glucose (SMPG) Target Range of 90-130 mg/dL at Week 12 and Week 24

End point description:

Fasting SMPG values at Week 24 time-point was calculated by the mean of the last 3 readings in the week prior to the specified week visit. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:
Week 12 and Week 24

End point values	Insulin glargine: HOE901-U300			
Subject group type	Reporting group			
Number of subjects analysed	136			
Units: percentage of subjects				
number (not applicable)				
At Week 12	35.0			
At Week 24	38.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with HbA1c <7.0%, <7.5% and <8% at Week 24

End point title	Percentage of Subjects with HbA1c <7.0%, <7.5% and <8% at Week 24

End point description:
Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:
Week 24

End point values	Insulin glargine: HOE901-U300			
Subject group type	Reporting group			
Number of subjects analysed	136			
Units: percentage of subjects				
number (not applicable)				
HbA1c <7.0%	11.4			
HbA1c <7.5%	29.5			
HbA1c <8.0%	50.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HbA1c Across HbA1c Subgroups Categories (=<8%, >8 to 9%, and >9%) at Week 12 and Week 24

End point title	Change From Baseline in HbA1c Across HbA1c Subgroups Categories (=<8%, >8 to 9%, and >9%) at Week 12 and Week 24

End point description:

Change in HbA1c was calculated by subtracting baseline value from Week 12 and Week 24 time point value for each subgroup category at baseline. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and Week 24

End point values	Insulin glargine: HOE901-U300			
Subject group type	Reporting group			
Number of subjects analysed	136			
Units: HbA1c (%)				
arithmetic mean (standard deviation)				
Change in HbA1c for <=8% level at Week 12 (n=43)	-0.22 (± 0.57)			
Change in HbA1c for <=8% level at Week 24 (n=41)	-0.19 (± 0.66)			
Change in HbA1c for 8%-9% level at Week 12 (n=57)	-0.45 (± 0.71)			
Change in HbA1c for 8%-9% level at Week 24 (n=56)	-0.56 (± 1.01)			
Change in HbA1c for >9% level at Week 12 (n=36)	-0.95 (± 0.89)			
Change in HbA1c for >9% level at Week 24 (n=35)	-1.35 (± 0.97)			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Change in FPG was calculated by subtracting baseline value from Week 12 and Week 24 time point value. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and Week 24

End point values	Insulin glargine: HOE901-U300			
Subject group type	Reporting group			
Number of subjects analysed	136			
Units: mg/dL				
arithmetic mean (standard deviation)				
Change at Week 12	-21.0 (± 58.9)			
Change at Week 24	-24.9 (± 61.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Diabetes Treatment Satisfaction Questionnaire (DTSQ) Score at Week 24

End point title	Change From Baseline in Diabetes Treatment Satisfaction Questionnaire (DTSQ) Score at Week 24

End point description:

The DTSQs is a validated questionnaire to assess subject's satisfaction with their diabetes treatment. It consisted of 8 questions (Q1- Q8), each item is rated on a 7-point scale ranged from 0 to 6 (0 [never] to 6 [most of the time]). Treatment satisfaction score consists of the sum of 6 items (Q1 and Q4 - Q8). Total DTSQ score ranged from 0 (very dissatisfied) to 36 (very satisfied); higher score = more satisfaction. Q2 and Q3 are related to blood glucose and rated separately from the satisfaction-related items. Question 2 gives an indication on the perception of frequency of hyperglycemias and question 3 gives an indication on the perception of frequency of hypoglycaemia. Each question was rated on a 7-point scale ranges from 0 (never) to 6 (most of the time), where higher score indicates higher recurrence. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Insulin glargine: HOE901-U300			
Subject group type	Reporting group			
Number of subjects analysed	136			
Units: units on a scale				
arithmetic mean (standard deviation)				
Perception of frequency of hyperglycemia	-1.4 (± 2.3)			
Perception of frequency of hypoglycemia	0.2 (± 2.2)			
Treatment Satisfaction	4.3 (± 9.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With At Least One Hypoglycemia Event (Any Hypoglycemia, Symptomatic Documented Hypoglycemia, Severe Hypoglycemia) During On-Treatment Period

End point title	Percentage of Subjects With At Least One Hypoglycemia Event (Any Hypoglycemia, Symptomatic Documented Hypoglycemia, Severe Hypoglycemia) During On-Treatment Period

End point description:

Categories of hypoglycaemia event were based on ADA classification. Severe hypoglycemia was an event in which the subject required the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Documented symptomatic hypoglycemia was an event during which subjects didn't need assistance to treat the hypoglycemia but had at least one symptom (tremor, perspiration, dizziness, hunger sensation, headaches, weakness, irritability, palpitations, loss of consciousness, convulsions, other) with measured plasma glucose concentration of <=70 mg/dL. Percentage of subjects with symptomatic documented, severe and any hypoglycaemia (severe or symptomatic) were reported. On-treatment period was defined as the time from first dose of IMP up to 24 weeks of treatment period. Analysis was performed on safety population that consisted of all included subjects in the study and who had received at least one treatment dose.

End point type	Secondary

End point timeframe:

First dose of study drug up to 24 weeks

End point values	Insulin glargine: HOE901-U300			
Subject group type	Reporting group			
Number of subjects analysed	137			
Units: percentage of subjects				
number (not applicable)				
Any hypoglycemia	45.99			
Severe hypoglycemia	2.19			
Documented symptomatic hypoglycemia	31.39			

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 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 adverse events that is AEs that developed/worsened during the 'on treatment period' (from the first dose IMP up to 24 weeks of treatment period). Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Insulin glargine: HOE901-U300

Reporting group description:

Subjects received HOE901-U300 (Insulin glargine, 300 U/mL) once daily for 24 weeks. The dose was adjusted every 3-4 days to achieve fasting SMPG in the target range of 80-130 mg/dL, as recommended by the ADA/EASD.

Serious adverse events	Insulin glargine: HOE901-U300		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 137 (9.49%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Nasal Cavity Cancer			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Phlebitis			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocardial Infarction			

subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis Acute			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal Failure			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal Injury			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes Mellitus Inadequate Control			
subjects affected / exposed	4 / 137 (2.92%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			

subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Insulin glargine: HOE901-U300		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 137 (12.41%)		
Infections and infestations			
Bronchitis			
subjects affected / exposed	9 / 137 (6.57%)		
occurrences (all)	10		
Nasopharyngitis			
subjects affected / exposed	8 / 137 (5.84%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 June 2016	Following amendment were made: Selection criteria was modified and updated as: - subjects treated or not treated with oral antidiabetic agents (including metformin, sulfonylureas, glinides, DPP-4 inhibitors, SGLT2 inhibitors…) in the 8 weeks prior to the screening visit. Inclusion criteria was modified and updated as: - Mean of the last 3 fasting plasma glucose values measured in the week prior to the inclusion visit of >130 mg/dl or at least 2 fasting plasma glucose values in the week prior to the inclusion visit >130 mg/dl. - "The last 3 measurements" was replaced by "these measurements" and text was updated as: these measurements before the V1 will allow to evaluate the corresponding inclusion criterion.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported