Clinical trial results:
Phase IV Study to Evaluate the Safety and Efficacy of the Treatment of Hyperglycemia with Gla-300 in Basal-Bolus Regimen in Hospitalised Type 2 Diabetes Mellitus (T2D) Patients Poorly Controlled with Basal Insulin and/or Non-Insulin Treatments and Therapy Intensification at Discharge with Basal Insulin

Summary

EudraCT number	2015-004715-20
Trial protocol	ES
Global end of trial date	17 July 2018

Results information

Result version number	v1 (current)
This version publication date	01 August 2019
First version publication date	01 August 2019

Trial information

Trial identification

Sponsor protocol code	GLARGL07710

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	STUDY NAME: COBALTA

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	01 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of therapy intensification on discharge with basal insulin in hospitalized type 2 diabetes subjects poorly controlled with basal insulin and/or non-insulin antidiabetic agents (glycated hemoglobin [HbA1c] >= 8.0% on admission) measured by the decrease in HbA1c at 6 months post-discharge.

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:

During hospitalization, the treatment regimen consisted of a basal-bolus-correction (BBC) insulin therapy. The initial total daily insulin dose was calculated according to the site protocol and distributed 50% as bolus insulin and 50% as basal insulin (Gla-300). Both insulins were titrated according to a pre-defined titration algorithm. Non-insulin antidiabetic drugs (NIADs) were retired during hospitalization and re-established at hospital discharge according to clinical criteria.

Evidence for comparator: -

Actual start date of recruitment	10 June 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	Spain: 112
Worldwide total number of subjects	112
EEA total number of subjects	112

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)	27
From 65 to 84 years	71
85 years and over	14

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 15 sites in Spain. A total of 115 subjects were screened between 10 June 2016 and 20 December 2017, of which 3 subjects were screening failure. Screen failures were mainly due to exclusion criteria met.

Pre-assignment

Screening details:

A total of 112 subjects were included in the study.

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 300 U/mL

Arm description:

Subjects received Insulin glargine 300 U/mL once daily for around 26 weeks (maximum 2 weeks hospitalization and 6 months follow-up).

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 once daily in the evening using a pre-filled pen. The dose was self-titrated every 3-4 days to achieve fasting blood glucose levels in the target range of 90-140mg/dL.

Number of subjects in period 1	Insulin glargine 300 U/mL
Started	112
Completed	93
Not completed	19
Death	6
Discontinuation of study treatment	1
Adverse event	2
Not allowed concomitant medication	1
Revocation of informed consent	2
Posterior diagnose of cancer	1
Lost to follow-up	4
Exclusion criteria	1

Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study
Reporting group description:	
Subjects received Insulin glargine 300 U/mL once daily for around 26 weeks (maximum 2 weeks hospitalization and 6 months follow-up).	

Reporting group values	Overall Study	Total	
Number of subjects	112	112	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	72.3		
standard deviation	± 10.8	-	
Gender categorical			
Units: Subjects			
Female	44	44	
Male	68	68	
Body Weight			
Units: kilogram (kg)			
arithmetic mean	80.1		
standard deviation	± 16.6	-	
Body Mass Index			
Units: kilogram per square meter (kg/m^2)			
arithmetic mean	30.1		
standard deviation	± 5.9	-	
Hemoglobin A1C (HbA1C)			
Units: percentage of hemoglobin			
arithmetic mean	8.9		
standard deviation	± 0.7	-	
Fasting Blood Glucose			
Units: milligrams per deciliter (mg/dL)			
arithmetic mean	205.4		
standard deviation	± 83.9	-	

End points

End points reporting groups

Reporting group title	Insulin glargine 300 U/mL

Reporting group description:

Subjects received Insulin glargine 300 U/mL once daily for around 26 weeks (maximum 2 weeks hospitalization and 6 months follow-up).

Primary: Change From Discharge in Glycated Hemoglobin (HbA1c) to Month 6

End point title	Change From Discharge in Glycated Hemoglobin (HbA1c) to Month 6[1]

End point description:

Change in HbA1c was calculated by subtracting discharge value from Month 6 value. Analysis was performed on intent-to-treat (ITT) population that included all subjects who received at least one dose of Gla-300 study insulin and had a primary or secondary measure of effectiveness evaluation both at baseline and in at least one follow-up visit.

End point type	Primary

End point timeframe:

Discharge, Month 6 (post discharge)

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: As the endpoint contains single arm, no statistical analysis is provided.

End point values	Insulin glargine 300 U/mL			
Subject group type	Reporting group			
Number of subjects analysed	94			
Units: percentage of HbA1c				
arithmetic mean (standard deviation)	1.6 (± 1.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Hospital Admission in 7-Point Capillary Glycaemia to Hospital Discharge

End point title	Mean Change From Hospital Admission in 7-Point Capillary Glycaemia to Hospital Discharge

End point description:

7-Point Capillary blood glucose were measured at the following 7 time points at baseline (hospital admission) and hospital discharge: before breakfast, 2 hours after breakfast, before lunch, 2 hours after lunch, before dinner, 2 hours after dinner, at bedtime. Analysis was performed on ITT population. Here, "n"signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline (hospital admission), discharge

End point values	Insulin glargine 300 U/mL			
Subject group type	Reporting group			
Number of subjects analysed	94			
Units: mg/dL				
arithmetic mean (standard deviation)				
Glycaemia before breakfast (n= 87)	25.1 (± 66.6)			
Glycaemia 2 hours after breakfast (n=61)	44.0 (± 87.3)			
Food glucose before lunch (n=90)	43.6 (± 70.6)			
Glycaemia 2 hours after lunch (n= 68)	63.0 (± 85.4)			
Glycaemia before dinner (n= 91)	53.8 (± 83.4)			
Glycaemia 2 hours after dinner (n= 66)	43.4 (± 81.1)			
Glycaemia at bedtime (n= 76)	47.9 (± 78.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Hospital Admission in Fasting Plasma Glucose (FPG) to Discharge, Month 3 and Month 6

End point title	Mean Change From Hospital Admission in Fasting Plasma Glucose (FPG) to Discharge, Month 3 and Month 6

End point description:

Mean Change in FPG was calculated by subtracting baseline (hospital admission) value from hospital discharge value, Month 3 value and Month 6 value. Analysis was performed on ITT population. Here, 'n' signifies number of subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline (hospital admission), discharge, Month 3, Month 6 (post discharge)

End point values	Insulin glargine 300 U/mL			
Subject group type	Reporting group			
Number of subjects analysed	94			
Units: mg/dL				
arithmetic mean (standard deviation)				
Discharge (n= 94)	51.5 (± 90.9)			
Month 3 (n=92)	68.2 (± 96.0)			
Month 6 (n=93)	77.6 (± 86.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Diabetes Treatment Satisfaction Questionnaire (DTSQ) Mean Score at Month 6

End point title	Diabetes Treatment Satisfaction Questionnaire (DTSQ) Mean Score at Month 6

End point description:

The DTSQs is a validated questionnaire to assess subject's satisfaction with their diabetes treatment. Total DTSQ score consists of the sum of 6 items (Q1 and Q4 - Q8), each rated on a 7-point scale (from 0 to 6). Total DTSQ score ranged from 0 (very dissatisfied) to 36 (very satisfied); higher score = more satisfaction. Analysis was performed on ITT population. Here, subjects analysed signifies subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Month 6 (post discharge)

End point values	Insulin glargine 300 U/mL			
Subject group type	Reporting group			
Number of subjects analysed	91			
Units: score on a scale				
arithmetic mean (standard deviation)	31.0 (± 4.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Body Weight From Discharge to Month 6

End point title	Change in Body Weight From Discharge to Month 6

End point description:

Change in body weight was calculated by subtracting discharge value from Month 6 value. Analysis was performed on safety population that consisted of all included all subjects who received at least one dose of the Gla-300 study insulin. Here, subjects analysed signifies number of subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Discharge, Month 6 (post discharge)

End point values	Insulin glargine 300 U/mL			
Subject group type	Reporting group			
Number of subjects analysed	86			
Units: kilogram (Kg)				
arithmetic mean (standard deviation)	0.0 (± 6.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Confirmed or Severe Hypoglycemia During Hospitalisation and at Month 6 After Discharge

End point title	Number of Subjects With Confirmed or Severe Hypoglycemia During Hospitalisation and at Month 6 After Discharge

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. Analysis was performed on safety population. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

From Baseline to discharge, Month 6 (post discharge)

End point values	Insulin glargine 300 U/mL			
Subject group type	Reporting group			
Number of subjects analysed	112			
Units: subjects				
number (not applicable)				
During hospitalization (n=112)	28			
Month 6 (n=93)	55			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Re-hospitalisations or Emergency Visits at Month 6 After Discharge

End point title	Number of Re-hospitalisations or Emergency Visits at Month 6 After Discharge

End point description:

Analysis was performed on safety population. Here, subjects analysed signifies number of subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Month 6 (post discharge)

End point values	Insulin glargine 300 U/mL			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: number of visits				
number (not applicable)				
Re-hospitalization	46			
Emergency visits	64			

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 (Month 6) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs and deaths are treatment-emergent AEs that developed/worsened and deaths that occurred during the time from first study drug intake up to Month 6. Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Insulin glargine 300 U/mL

Reporting group description:

Subjects received Insulin glargine 300 U/mL 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.

Serious adverse events	Insulin glargine 300 U/mL		
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 112 (33.04%)		
number of deaths (all causes)	6		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder Neoplasm			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Colon Cancer			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung Neoplasm			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			

Peripheral Ischaemia				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pulmonary Embolism				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Varicose Ulceration				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Asthma				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower Respiratory Tract Infection				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	7 / 112 (6.25%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Pulmonary Mass				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Respiratory Failure				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory Tract Infection				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tonsillar Hypertrophy				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Intervertebral Discitis				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute Myocardial Infarction				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Angina Pectoris				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac Failure				
subjects affected / exposed	4 / 112 (3.57%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Cardiac Failure Acute				
subjects affected / exposed	2 / 112 (1.79%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Cardiac Failure Chronic				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac Failure Congestive				
subjects affected / exposed	2 / 112 (1.79%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac Tamponade				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiogenic Shock				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Left Ventricular Failure				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Myocardial Ischaemia				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Brain Stem Stroke				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic Stroke				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxic-Ischaemic Encephalopathy				

subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lacunar Infarction			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Plasma Cell Myeloma			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Colitis Ischaemic			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enteritis Infectious			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Diabetic Ulcer			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Skin Ulcer			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Chronic Kidney Disease			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary Tract Infection			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary Tract Infection Fungal			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral Discitis			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic Fracture			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Klebsiella Sepsis			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Stoma Site Infection			

subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Insulin glargine 300 U/mL		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 112 (28.57%)		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	9 / 112 (8.04%)		
occurrences (all)	10		
Renal and urinary disorders			
Urinary Tract Infection			
subjects affected / exposed	14 / 112 (12.50%)		
occurrences (all)	18		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	11 / 112 (9.82%)		
occurrences (all)	16		
Vitamin D Deficiency			
subjects affected / exposed	6 / 112 (5.36%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 January 2016	Following changes were made: Change in exclusion criteria: Following criteria added: - Subjects that required intensification with rapid-acting insulin at discharge. - Pregnant, lactating women or fertile women not using contraceptive methods during study. - Subjects unable or unwilling to sign informed consent.
04 October 2016	- Change in inclusion criteria: -Minimum expected hospitalization length moved from 7 to 5 days. - Criteria removed: Maximum age of 75 years. - Change in exclusion criteria:- Criteria added: subjects who were unable to titrate or manage correctly the insulin treatment due to their medical condition. - Non-allowed treatments: -Corticosteroid treatment limitations were clarified: Oral or parenteral corticosteroids were not allowed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported