Clinical trial results:
A 28-Week, Prospective, Single-Arm, Open Label Phase 4 Study to Evaluate Treatment Optimization With Once-Daily Insulin Glargine HOE901-300 IU/Ml In Combination With Prandial Rapid-Acting Insulin Analogue In Patients With Type 1 Diabetes Previously Uncontrolled on Twice Daily Basal Insulin as Part of Basal-Bolus Therapy

Summary

EudraCT number	2015-001186-46
Trial protocol	BE
Global end of trial date	10 May 2018

Results information

Result version number	v1 (current)
This version publication date	09 May 2019
First version publication date	09 May 2019

Trial information

Trial identification

Sponsor protocol code	GLARGL07699

Additional study identifiers

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

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	28 August 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of optimizing treatment from twice-daily (BID) basal to once-daily (OD) insulin glargine HOE901-300 IU/mL as part of basal bolus regime in terms of improving Hemoglobin A1c (HbA1c) by at least 0.3% in uncontrolled type 1 diabetes mellitus subjects.

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 was 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	17 December 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 48
Country: Number of subjects enrolled	Canada: 46
Worldwide total number of subjects	94
EEA total number of subjects	48

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)	82
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were involved in the study from 17 December 2015 to 10 May 2018 at 25 centers in Belgium and Canada.

Pre-assignment

Screening details:

A total of 130 subjects were screened, of which 36 subjects had screening failure. After a 4 week run-in period, 94 subjects who met all of the inclusion criteria and none of the exclusion criteria were enrolled and switched from their basal insulin treatment to HOE901-U300.

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	HOE901-U300

Arm description:

Subjects received insulin glargine HOE901-300 IU/mL, once daily, subcutaneous (SC) injection for 24 weeks.

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:

1.5 mL, subcutaneous, self administered using a prefilled disposable SoloSTAR® pen once daily in the morning for 24 weeks.

Number of subjects in period 1	HOE901-U300
Started	94
Completed	94

Baseline characteristics

Reporting groups	
Reporting group title	HOE901-U300
Reporting group description:	
Subjects received insulin glargine HOE901-300 IU/mL, once daily, subcutaneous (SC) injection for 24 weeks.	

Reporting group values	HOE901-U300	Total	
Number of subjects	94	94	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 49.4 ± 13.1	 -	
Gender categorical Units: Subjects			
Female Male	50 44	50 44	
Body mass index (BMI) Units: kg/m^2 arithmetic mean standard deviation	 27.8 ± 4.7	 -	
Duration of disease Units: years arithmetic mean standard deviation	 27.3 ± 12.9	 -	

End points

End points reporting groups

Reporting group title	HOE901-U300

Reporting group description:

Subjects received insulin glargine HOE901-300 IU/mL, once daily, subcutaneous (SC) injection for 24 weeks.

Primary: Change From Baseline in HbA1c at Week 24

End point title	Change From Baseline in HbA1c at Week 24[1]

End point description:

Change in HbA1c was calculated by subtracting baseline value from Week 24 value. Missing data was imputed using last on-treatment observation carried forward (LOCF). Baseline was defined as the last available value prior to the first dose of investigational medicinal product (IMP). The analysis was performed on intent-to-treat (ITT) population, which included all evaluable subjects for the 24 week treatment period, regardless of whether the IMP was taken or not and whatever the duration of their follow-up period.

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

End point values	HOE901-U300			
Subject group type	Reporting group			
Number of subjects analysed	94			
Units: Percentage of HbA1c				
arithmetic mean (confidence interval 95%)	0.2745 (0.1507 to 0.3982)			

Statistical analyses

No statistical analyses for this end point

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 24 value. The 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 12

End point values	HOE901-U300			
Subject group type	Reporting group			
Number of subjects analysed	90			
Units: Percentage of HbA1c				
arithmetic mean (confidence interval 95%)	0.4011 (0.2862 to 0.5160)			

Statistical analyses

No statistical analyses for this end point

Secondary: Evolution of Fasting Plasma Glucose (FPG)

End point title	Evolution of Fasting Plasma Glucose (FPG)

End point description:

The analysis was performed on ITT population. Here, 'number of subjects analysed' = total number of subjects with available data for this endpoint and 'n' = number of subjects with available data for specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and Week 24

End point values	HOE901-U300			
Subject group type	Reporting group			
Number of subjects analysed	93			
Units: mg/dL				
arithmetic mean (standard error)				
Baseline (n= 93)	217.783 (± 91.6753)			
Week 12 (n = 86)	191.748 (± 68.6914)			
Week 24 (n= 85)	208.132 (± 82.3453)			

Statistical analyses

No statistical analyses for this end point

Secondary: Evolution in Fasting Self-Monitored Plasma Glucose (SMBG)

End point title	Evolution in Fasting Self-Monitored Plasma Glucose (SMBG)

End point description:

The analysis was performed on ITT population. Here, 'number of subjects analysed' = total number of subjects with available data for this endpoint and 'n' = number of subjects with available data for specified categories.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and Week 24

End point values	HOE901-U300			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline (n= 88)	198.454 (± 90.0085)			
Week 12 (n= 84)	172.826 (± 86.7930)			
Week 24 (n= 83)	181.786 (± 79.2007)			

Statistical analyses

No statistical analyses for this end point

Secondary: Evolution of SMBG Between 3 AM And Bedtime at Baseline and Week 24

End point title	Evolution of SMBG Between 3 AM And Bedtime at Baseline and Week 24

End point description:

SMBG profiles measured at the following 8 points: pre-breakfast, 2-hour post-breakfast, pre-lunch, 2-hour post-lunch, pre-dinner, 2-hour post-dinner, bedtime, and at 3:00 am. Subjects were requested to perform 8-point SMBG profiles over a single 24-hour period on one day during the week before baseline, Week 4, Week 8, Week 12, and Week 24. On days when 8-point profiles were done, 03.00 AM was considered as the first point of measurement, i.e. “night” time point. The analysis was performed on ITT population. Here, 'n' = number of subjects with available data for specified time points.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	HOE901-U300			
Subject group type	Reporting group			
Number of subjects analysed	94			
Units: mg/dL				
arithmetic mean (standard deviation)				
Pre-breakfast: Baseline (n= 88)	198.454 (± 90.0085)			
Pre-breakfast: Week 24 (n= 83)	181.786 (± 79.2007)			

Attachments (see zip file)	Mean SMBG (mg/dL) ± SE/Evolution of 8 point SMBG.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieved HbA1c target of <7.0% at Week 12 and Week 24

End point title	Percentage of Subjects Achieved HbA1c target of <7.0% at Week 12 and Week 24

End point description:

Percentage of subjects achieving HbA1c target of <7.0% at Week 12 and Week 24 were calculated by 95% Clopper-Pearson confidence intervals (CIs). The analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Week 12 and Week 24

End point values	HOE901-U300			
Subject group type	Reporting group			
Number of subjects analysed	94			
Units: Percentage of Subjects				
number (not applicable)				
Week 12	0			
Week 24	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving HbA1c Improvement From Baseline to Week 24 of At Least 0.3% Without Nocturnal Hypoglycemia (Documented <= 70 mg/dL or 3.9 mmol/L) and/or Severe Confirmed Hypoglycemia

End point title	Percentage of Subjects Achieving HbA1c Improvement From Baseline to Week 24 of At Least 0.3% Without Nocturnal Hypoglycemia (Documented <= 70 mg/dL or 3.9 mmol/L) and/or Severe Confirmed Hypoglycemia

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). Nocturnal hypoglycemia was hypoglycemia that occurred between 00:00 and 05:59 hours (clock time). Documented symptomatic hypoglycemia was an event during which typical symptoms of

hypoglycemia were accompanied by a measured plasma glucose concentration of =<3.9 mmol/L (=<70 mg/dL). Analysis was performed on ITT population. Here, number of subjects analysed=subjects with available data for this end point.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	HOE901-U300			
Subject group type	Reporting group			
Number of subjects analysed	92			
Units: Percentage of subjects				
number (not applicable)	5.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Hypoglycemic Events Per Patient Year During Run-in Period and Last 4 weeks of Treatment

End point title	Number of Hypoglycemic Events Per Patient Year During Run-in Period and Last 4 weeks of Treatment

End point description:

Number of hypoglycemia per patient-year was computed per patient as: 365.25 x (number of episodes of hypoglycemia / number of days exposed) and summarized by observation period (i.e., 4-week run-in period, last 4 weeks on-treatment period). Run-in period was defined as the time between the date of the informed consent and the first insulin glargine HOE901-300 IU/mL injection. Last 4-weeks on-treatment period defined by the last 4-weeks preceding the last injection of insulin glargine HOE901-300 IU/mL. Here, 'n' = number of subjects with available data for specified time points.

End point type	Secondary

End point timeframe:

Run-in period (Week -4 to Week 0), last 4 weeks of treatment (Week 20 to 24)

End point values	HOE901-U300			
Subject group type	Reporting group			
Number of subjects analysed	94			
Units: Events per patient-year				
arithmetic mean (standard deviation)				
Nocturnal: Run-in period (n= 70)	16.40 (± 20.38)			
Nocturnal:Last 4 weeks of treatment (n= 70)	13.66 (± 23.79)			
Severe: Run-in period (n= 69)	1.04 (± 3.42)			
Severe: Last 4 weeks of treatment (n= 69)	1.95 (± 7.52)			
Confirmed (<=70 mg/dL):Run-in period (n= 69)	93.17 (± 67.22)			

Confirmed<=70 mg/dL Last 4 weeks of treatment n=69	97.83 (± 75.45)			
Confirmed (<54mg/dL):Run-in period (n= 70)	33.40 (± 31.04)			
Confirmed<54mg/dL: Last 4 weeks of treatment n=70	37.14 (± 39.85)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were collected from signature of the informed consent form up to the last visit (Week 25) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs are TEAEs that is AEs that developed/worsened from first study drug intake up to Week 25. Analysis was performed on safety population which included subjects who were exposed to at least one dose of IMP, regardless of the amount of treatment administered.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	HOE901-U300

Reporting group description:

Subjects received insulin glargine HOE901-300 IU/mL, once daily, SC injection for 24 weeks.

Serious adverse events	HOE901-U300		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 94 (4.26%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine Leiomyoma			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thrombosis			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Hypoglycaemic Coma			
subjects affected / exposed	1 / 94 (1.06%)		
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 / 94 (1.06%)		
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	HOE901-U300		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 94 (28.72%)		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 94 (5.32%)		
occurrences (all)	5		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 94 (6.38%)		
occurrences (all)	8		
Vomiting			
subjects affected / exposed	5 / 94 (5.32%)		
occurrences (all)	7		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 94 (5.32%)		
occurrences (all)	5		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	15 / 94 (15.96%)		
occurrences (all)	17		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 September 2016	Following amendments were added: -Sanofi-aventis Canada was added to Sanofi Belgium to ensure sufficient subjects recruitment. -Sample size was reduced from 119 to 102, to accept a global power of 85% instead of 90%. -Estimated centers number was increased to 30. Specialty and experience of the investigators (endocrinologists) was removed. -Recommended starting dose of insulin glargine HOE901-300 IU/mL was amended. -Dose adjustment was amended to modify proposed dose by adding more than 1U if value of median fasting SMBG from the last 3 days was >130 mg/dL. -Dose adjustment was amended to harmonize with Table 1 of protocol. -A "x" was added at Visit V0 in the flow chart to measure and record the vital signs (BP, weight and heart rate). The sentence "An HbA1c value from just before the run-in period should be available" was removed. -Pen needle length was clarified to allow another length of needle than 5 mm. -Canada and Belgium storage conditions text wash modified according the country regulations. -The text was modified to allow nurses to perform the tracking and reconciliation of the NIMP. -The HbA1c testing "National Glycohemoglobin Standardization Program" (NGSP) method was allowed. -Subjects were allowed to use their blood glucose system with the exception of five 8-point SMBG analysis. -Laboratory tests for inclusion & exclusion criterias were allowed to perform within 72 hours before visits 0 & 1. -Pregnancy check by serum or urine pregnancy testing was added. -Obligation of sponsor to be reported in an expedited manner was added and was applicable only for Canada. -Record retention was adapted to different retention times for Belgium (20 years) & Canada (25 years) after completion or discontinuation of the clinical trial.
04 July 2017	- The total expected number of subjects was fixed to 90 and the required power to 80%. - An interim analysis was performed to assess the Belgian data. - A partial database lock was done after the last subject in Belgium had completed the last visit. - The planned database lock date was fixed 3 months after last patient last visit. - The sentence: "Once in use, replace pre-filled pen if not completely used within the period allowed by the regulating authorities applicable in the country (4 weeks in Belgium; 42 days in Canada)" was replaced by "Once in use, replace pre-filled pen if not completely used within the period allowed by the regulating authorities applicable in the country". - The sentence: "All hypoglycemia episodes will be documented on the "hypoglycemia specific form" and on an AE form in the e-CRF. This includes all symptomatic hypoglycemia events and asymptomatic hypoglycemia. A SAE complementary form in the e-CRF will be completed in addition to the AE form "hypoglycemia specific form" for Hypoglycemia events fulfilling the criteria of an SAE" was replaced by "All hypoglycemia episodes will be documented on the "hypoglycemia specific form" in the e-CRF. This included all symptomatic hypoglycemia events and asymptomatic hypoglycemia. A serious adverse event (SAE) complementary form in the e-CRF would be completed in addition to the "hypoglycemia specific form" for Hypoglycemia events fulfilling the criteria of an SAE.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported