Clinical trial results:
6-Month, Multicenter, Randomized, Open-label, 2-Arm, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus® Injected Once Daily in Children and Adolescents age 6 - 17 Years with Type 1 Diabetes Mellitus with a 6-month Safety Extension Period

Summary

EudraCT number	2015-002084-42
Trial protocol	GB HU LV IT DE CZ FR ES PL SE DK BG Outside EU/EEA
Global end of trial date	20 December 2018

Results information

Result version number	v1 (current)
This version publication date	04 July 2019
First version publication date	04 July 2019

Trial information

Trial identification

Sponsor protocol code	EFC13957

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02735044
WHO universal trial number (UTN)	U1111-1168-4546

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly, 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 January 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of a new formulation of insulin glargine (HOE901-U300) to Lantus in terms of change of HbA1c from baseline to endpoint (month 6) in children and adolescents with type 1 diabetes mellitus.

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:

Fast acting mealtime insulin analogs were required to be used 6 months prior screening visit. The type of insulin were to remain unchanged during the study.

Evidence for comparator: -

Actual start date of recruitment	14 April 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	Argentina: 31
Country: Number of subjects enrolled	Brazil: 27
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	Chile: 22
Country: Number of subjects enrolled	Israel: 15
Country: Number of subjects enrolled	Japan: 14
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 10
Country: Number of subjects enrolled	Mexico: 50
Country: Number of subjects enrolled	Russian Federation: 35
Country: Number of subjects enrolled	Serbia: 11
Country: Number of subjects enrolled	United States: 35
Country: Number of subjects enrolled	Poland: 20
Country: Number of subjects enrolled	Romania: 28
Country: Number of subjects enrolled	Spain: 15

Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Bulgaria: 20
Country: Number of subjects enrolled	Czech Republic: 9
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 39
Country: Number of subjects enrolled	Italy: 26
Country: Number of subjects enrolled	Latvia: 15
Worldwide total number of subjects	463
EEA total number of subjects	192

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)	143
Adolescents (12-17 years)	320
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 105 centers in 24 countries. A total of 616 subjects were screened between 14 April 2016 and 31 October 2017, of which 153 were screen failures. Screen failures were mainly due to glycated hemoglobin (HbA1c) level outside of defined ranges per eligibility criteria.

Pre-assignment

Screening details:

A total of 463 subjects were randomized in the study. Randomization was stratified by age group (<12 years and >=12 years) and by HbA1c (<8.5% and >=8.5%). Assignment to arms was done centrally using interactive voice system in 1:1 ratio.

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	HOE901-U300

Arm description:

Insulin glargine 300 Units/milliliter (U/mL) Subcutaneous (SC) injection once daily in the morning or evening for 12 months.

Arm type	Experimental
Investigational medicinal product name	Insulin glargine
Investigational medicinal product code	
Other name	Toujeo
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin glargine 300 U/mL SC injection using a prefilled pen. Dose titration to achieve fasting self-monitored plasma glucose (SMPG) from 90 to 130 milligram/deciliter (mg/dL) (5.0 to 7.2 millimol per liter [mmol/L]).

Arm title	Lantus

Arm description:

Insulin glargine 100 U/mL SC injection once daily in the morning or evening for 12 months.

Arm type	Experimental
Investigational medicinal product name	Insulin glargine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin glargine 100 U/mL SC injection using a prefilled pen. Dose titration to achieve fasting SMPG from 90 to 130 mg/dL (5.0 to 7.2 mmol/L).

Number of subjects in period 1	HOE901-U300	Lantus
Started	233	230
Completed	217	207
Not completed	16	23
Adverse Event	3	3
Randomized and not treated	-	2
Other than specified	5	11
Poor compliance to protocol	7	7
Lack of efficacy	1	-

Baseline characteristics

Reporting groups	
Reporting group title	HOE901-U300
Reporting group description:	
Insulin glargine 300 Units/milliliter (U/mL) Subcutaneous (SC) injection once daily in the morning or evening for 12 months.	
Reporting group title	Lantus
Reporting group description:	
Insulin glargine 100 U/mL SC injection once daily in the morning or evening for 12 months.	

Reporting group values	HOE901-U300	Lantus	Total
Number of subjects	233	230	463
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	12.9	12.9	
standard deviation	± 2.9	± 2.9	-
Gender categorical			
Units: Subjects			
Female	105	121	226
Male	128	109	237
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	11	6	17
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	8	6	14
White	211	211	422
More than one race	2	2	4
Unknown or Not Reported	0	1	1
Not recorded	1	4	5
Body Mass Index (BMI)			
Units: BMI percentile			
arithmetic mean	67.52	69.13	
standard deviation	± 26.62	± 26.64	-
Hemoglobin A1C (HbA1C)			
Units: percentage of A1C			
arithmetic mean	8.65	8.61	
standard deviation	± 0.88	± 0.87	-

End points

End points reporting groups

Reporting group title	HOE901-U300
Reporting group description:	
Insulin glargine 300 Units/milliliter (U/mL) Subcutaneous (SC) injection once daily in the morning or evening for 12 months.	
Reporting group title	Lantus
Reporting group description:	
Insulin glargine 100 U/mL SC injection once daily in the morning or evening for 12 months.	

Primary: Change From Baseline in HbA1c to Month 6

End point title	Change From Baseline in HbA1c to Month 6
End point description:	
Change in HbA1c was calculated by subtracting baseline value from Month 6 value. Adjusted least-square (LS) means and standard errors (SE) were obtained using analysis of covariance (ANCOVA) after multiple imputations of missing data using post-baseline HbA1c data available on the main 6-month randomized period. Analysis was performed on intent-to-treat (ITT) population that included all randomized subjects, regardless of whether the treatment kit was used, and was analysed according to the allocated treatment group. Here, number of subjects analysed signified number of subjects with available data for the endpoint.	
End point type	Primary
End point timeframe:	
Baseline to Month 6	

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	232	230		
Units: Percentage of HbA1c				
arithmetic mean (standard deviation)	-0.399 (± 0.063)	-0.402 (± 0.064)		

Statistical analyses

Statistical analysis title	HOE901-U300, Lantus
Statistical analysis description:	
Analysis was performed using ANCOVA models which included the treatment group, the randomization stratum of age group at screening visit (<12 years and >=12 years), and the continuous fixed covariates of the baseline HbA1c value.	
Comparison groups	HOE901-U300 v Lantus

Number of subjects included in analysis	462
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	LS Mean difference
Point estimate	0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.172
upper limit	0.179
Variability estimate	Standard error of the mean
Dispersion value	0.09

Notes:

[1] - Non-inferiority of HOE901-U300 versus Lantus was demonstrated if the upper bound of the two-sided 95% confidence interval (CI) for the difference in the mean change in HbA1c from baseline to month 6 was <0.3%.

Statistical analysis title	HOE901-U300, Lantus

Statistical analysis description:

A step-wise closed testing approach was used to control the type I error. Analysis was performed using ANCOVA models which included the treatment group, the randomization stratum of age group at screening visit (<12 years and >=12 years), and the continuous fixed covariates of the baseline HbA1c value.

Comparison groups	HOE901-U300 v Lantus
Number of subjects included in analysis	462
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.965 [3]
Method	ANCOVA

Notes:

[2] - Superiority of HOE901-U300 versus Lantus was demonstrated if the upper bound of the two-sided 95% CI for the difference between treatment groups was <0 (zero).

[3] - Threshold for significance at 0.025 level.

Secondary: Change From Baseline in Fasting Plasma Glucose (FPG) to Month 6

End point title	Change From Baseline in Fasting Plasma Glucose (FPG) to Month 6

End point description:

Change in FPG was calculated by subtracting baseline value from Month 6 value. Adjusted LS means and SE were obtained using ANCOVA after multiple imputation to address missing data in the main 6 month randomized period. Analysis was performed on ITT population. Here, number of subjects analysed signified number of subjects with available data for the endpoint.

End point type	Secondary

End point timeframe:

Baseline to Month 6

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	232	230		
Units: millimole per liter (mmol/L)				
least squares mean (standard deviation)	-0.563 (± 0.372)	-0.549 (± 0.372)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With HbA1c Values of <7.5% at Month 6

End point title	Percentage of Subjects With HbA1c Values of <7.5% at Month 6

End point description:

Subjects without any available HbA1c assessment at month 6 and/or with a premature study discontinuation during the main 6-month randomized period were considered as a failure (non-responders) in the analysis. Analysis was performed using Cochran-Mantel-Haenszel (CMH) method with randomization strata of screening HbA1c (<8.5%; >=8.5%) and randomization strata of age at screening (<12 years, >=12 years). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Month 6

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233	230		
Units: percentage of subjects				
number (not applicable)	26.18	23.48		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With HbA1c Values of <7.5% Without Any Episode of Severe and/or Documented Self- Monitored Plasma Glucose ([SMPG] <54 mg/dL [3.0 mmol/L]) Symptomatic Hypoglycemia During the Last 3 Months of the Main 6-month Randomized Period

End point title	Percentage of Subjects With HbA1c Values of <7.5% Without Any Episode of Severe and/or Documented Self- Monitored Plasma Glucose ([SMPG] <54 mg/dL [3.0 mmol/L]) Symptomatic Hypoglycemia During the Last 3 Months of the Main 6-month Randomized Period

End point description:

Subjects without any available HbA1c assessment at month 6 and/or with a premature study discontinuation during the main 6-month randomized period were considered as a failure (non-responders) in the analysis. Analysis was performed using Cochran-Mantel-Haenszel (CMH) method with

randomization strata of screening HbA1c (<8.5%; >=8.5%) and randomization strata of age at screening (<12 years, >=12 years). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

upto Month 6

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233	230		
Units: percentage of subjects				
number (not applicable)	4.29	4.78		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With FPG of <=130 mg/dL (7.2 mmol/L) at Month 6

End point title	Percentage of Subjects With FPG of <=130 mg/dL (7.2 mmol/L) at Month 6

End point description:

Subjects without any available FPG assessment at month 6 and/or with a premature study discontinuation during the main 6-month randomized period were considered as a failure (non-responders) in the analysis. Analysis was performed using CMH method with randomization strata of screening HbA1c (<8.5%; >=8.5%) and randomization strata of age at screening (<12 years, >=12 years). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Month 6

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233	230		
Units: percentage of subjects				
number (not applicable)	27.47	26.52		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With FPG of <=130 mg/dL (7.2 mmol/L) Without Any Episode of Severe and/or Documented (SMPG <54 mg/dL [3.0 mmol/L]) Symptomatic Hypoglycemia During the Last 3 Months of the Main 6-

month Randomized Period

End point title	Percentage of Subjects With FPG of <=130 mg/dL (7.2 mmol/L) Without Any Episode of Severe and/or Documented (SMPG <54 mg/dL [3.0 mmol/L]) Symptomatic Hypoglycemia During the Last 3 Months of the Main 6-month Randomized Period

End point description:

Subjects without any available HbA1c assessment at month 6 and/or with a premature study discontinuation during the main 6-month randomized period were considered as a failure (non-responders) in the analysis. Analysis was performed using CMH method with randomization strata of screening HbA1c (<8.5%; >=8.5%) and randomization strata of age at screening (<12 years, >=12 years). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

upto Month 6

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233	230		
Units: percentage of subjects				
number (not applicable)	9.44	7.39		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in 24-Hour Mean Plasma Glucose Based on 8-point SMPG Profiles to Month 6

End point title	Change From Baseline in 24-Hour Mean Plasma Glucose Based on 8-point SMPG Profiles to Month 6

End point description:

8-point SMPG profiles were measured at the following 8 points: between 01:00 and 04:00 AM 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 using a ANCOVA model including the fixed categorical effects of treatment group, randomization strata of screening HbA1c (<8.5%; >=8.5%), randomization strata of age at screening (<12 years, >=12 years) and the baseline 24-hour average 8-point profile SMPG. Analysis was performed on ITT population. Here, number of subjects analysed signified number of subjects with available data for the endpoint.

End point type	Secondary

End point timeframe:

Baseline to Month 6

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	146		
Units: mmol/L				
least squares mean (standard error)	0.139 (± 0.249)	-0.266 (± 0.250)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Variability of 24-Hour Mean Plasma Glucose Based on 8-point SMPG Profiles at Month 6

End point title	Change From Baseline in Variability of 24-Hour Mean Plasma Glucose Based on 8-point SMPG Profiles at Month 6

End point description:

8-point SMPG profiles were measured at the following 8 points: between 01:00 and 04:00 (clock time) at night, pre-breakfast, 2 hours after breakfast, pre-lunch, 2 hours after lunch, pre-dinner, 2 hours after dinner, and bedtime. Variability was the mean of coefficient of variation calculated over the 8-point SMPG. Analysis was performed using a ANCOVA model including the fixed categorical effects of treatment group, randomization strata of screening HbA1c (<8.5%; >=8.5%) and randomization strata of age at screening (<12 years, >=12 years). Analysis was performed on ITT population. Here, number of subjects analysed signified number of subjects with available data for the endpoint.

End point type	Secondary

End point timeframe:

Baseline, Month 6

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	146		
Units: percentage of mean variability				
least squares mean (standard error)	1.469 (± 1.409)	0.789 (± 1.415)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Month 6 in 8-Point SMPG Profile Per Time Point

End point title	Change From Baseline to Month 6 in 8-Point SMPG Profile Per Time Point

End point description:

8-point SMPG profiles were measured for following 8 time points at Baseline and Month 6: between 01:00 and 04:00 (clock time) 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 available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline to Month 6

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233	230		
Units: mmol/L				
arithmetic mean (standard deviation)				
Between 01:00 and 04:00 at night (n=109,116)	0.84 (± 6.94)	-0.60 (± 7.08)		
Pre-breakfast (n=141,142)	-0.41 (± 5.48)	-1.71 (± 6.56)		
2 hours after breakfast (n=135,128)	-0.26 (± 7.18)	-0.62 (± 6.78)		
Pre-lunch (n=144,140)	0.43 (± 6.99)	1.11 (± 6.85)		
2 hours after lunch (n=131, 129)	0.49 (± 7.64)	-0.55 (± 7.20)		
Pre-dinner (n=141, 126)	0.29 (± 8.05)	-0.02 (± 6.78)		
2 hours after dinner (n= 125, 124)	0.51 (± 8.53)	0.60 (± 6.86)		
Bedtime (n=114,117)	0.86 (± 7.60)	-0.60 (± 7.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With at Least One Hypoglycemic Events (Any Hypoglycemia, Severe Hypoglycemia, Documented Symptomatic, Probable Symptomatic, Asymptomatic Hypoglycemia, Pseudo-hypoglycemia and Severe and/or Confirmed Hypoglycemia) at Month 12

End point title	Percentage of Subjects With at Least One Hypoglycemic Events (Any Hypoglycemia, Severe Hypoglycemia, Documented Symptomatic, Probable Symptomatic, Asymptomatic Hypoglycemia, Pseudo-hypoglycemia and Severe and/or Confirmed Hypoglycemia) at Month 12

End point description:

Severe hypoglycemia: an event in which the child/adolescent having altered mental status and cannot assist in their care, is semiconscious or unconscious, or in coma ± convulsions and may require parenteral therapy (glucagon or glucose). Documented symptomatic hypoglycemia: an event during which typical symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of <=70 mg/dL (3.9 mmol/L). Asymptomatic hypoglycemia: an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration <=70 mg/dL. Probable symptomatic hypoglycemia: an event during which symptoms of hypoglycemia were not accompanied by plasma glucose determination but was presumably caused by a plasma glucose concentration <=70 mg/dL. Pseudo-hypoglycemia:an event with any of the typical symptoms of hypoglycaemia with plasma glucose concentration >70 mg/dL. Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

Month 12

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233	228		
Units: percentage of subjects				
number (not applicable)				
Any hypoglycemia	99.1	98.7		
Severe Hypoglycemia	8.6	11.0		
Documented Symptomatic Hypoglycemia	94.8	93.9		
Probable Symptomatic Hypoglycemia	10.3	13.6		
Asymptomatic Hypoglycemia	88.4	89.5		
Pseudo-hypoglycemia	15.9	14.5		
Severe and/or documented hypoglycemia	99.1	98.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Any Hyperglycemia With Ketosis at Month 12

End point title	Percentage of Subjects With Any Hyperglycemia With Ketosis at Month 12

End point description:

Hyperglycemia with ketosis was defined as SMPG >=252 mg/dL (14 mmol/L) with accompanying self-measured blood ketones >=1.5 mmol/L. Analysis was performed on the safety population which included all randomized subjects who actually received at least 1 dose or part of a dose of investigational medicinal product (IMP) and was analysed according to treatment received.

End point type	Secondary

End point timeframe:

Month 12

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233	228		
Units: percentage of subjects				
number (not applicable)	9.9	13.6		

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 the end of the study (Week 58) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs and deaths are treatment-emergent adverse events that is AEs that developed, worsened or became serious during the 'on treatment period' (time from first dose of IMP up to 2 days after last injection of IMP). Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	HOE901-U300

Reporting group description:

Insulin glargine 300 U/mL SC injection once daily in the morning or evening for 12 months.

Reporting group title	Lantus

Reporting group description:

Insulin glargine 100 U/mL SC injection once daily in the morning or evening for 12 months.

Serious adverse events	HOE901-U300	Lantus	
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 233 (15.02%)	31 / 228 (13.60%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	3 / 233 (1.29%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	1 / 233 (0.43%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electric Shock			

subjects affected / exposed	0 / 233 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 233 (0.43%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Radius Fracture			
subjects affected / exposed	1 / 233 (0.43%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib Fracture			
subjects affected / exposed	1 / 233 (0.43%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Limb Fracture			
subjects affected / exposed	1 / 233 (0.43%)	0 / 228 (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			
Autonomic Nervous System Imbalance			
subjects affected / exposed	1 / 233 (0.43%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 233 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Coma			
subjects affected / exposed	1 / 233 (0.43%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Seizure			

subjects affected / exposed	8 / 233 (3.43%)	10 / 228 (4.39%)	
occurrences causally related to treatment / all	3 / 11	4 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Unconsciousness			
subjects affected / exposed	6 / 233 (2.58%)	10 / 228 (4.39%)	
occurrences causally related to treatment / all	4 / 10	4 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 233 (0.43%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 233 (0.43%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Anembryonic Gestation			
subjects affected / exposed	1 / 233 (0.43%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Testicular Torsion			
subjects affected / exposed	0 / 233 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermal Cyst			
subjects affected / exposed	1 / 233 (0.43%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed Suicide			

subjects affected / exposed	1 / 233 (0.43%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Confusional State			
subjects affected / exposed	0 / 233 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal Insufficiency			
subjects affected / exposed	0 / 233 (0.00%)	1 / 228 (0.44%)	
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	1 / 233 (0.43%)	2 / 228 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 233 (0.43%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Viral			
subjects affected / exposed	1 / 233 (0.43%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningococcal Infection			
subjects affected / exposed	0 / 233 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic Shock			
subjects affected / exposed	0 / 233 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			

subjects affected / exposed	0 / 233 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	1 / 233 (0.43%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvitis			
subjects affected / exposed	0 / 233 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes Mellitus Inadequate Control			
subjects affected / exposed	2 / 233 (0.86%)	2 / 228 (0.88%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic Ketoacidosis			
subjects affected / exposed	5 / 233 (2.15%)	6 / 228 (2.63%)	
occurrences causally related to treatment / all	1 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic Metabolic Decompensation			
subjects affected / exposed	1 / 233 (0.43%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 233 (0.43%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	2 / 233 (0.86%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ketosis			

subjects affected / exposed	1 / 233 (0.43%)	0 / 228 (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	HOE901-U300	Lantus	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	105 / 233 (45.06%)	118 / 228 (51.75%)	
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 233 (8.15%)	15 / 228 (6.58%)	
occurrences (all)	38	23	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	14 / 233 (6.01%)	9 / 228 (3.95%)	
occurrences (all)	20	10	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal Pain			
subjects affected / exposed	15 / 233 (6.44%)	7 / 228 (3.07%)	
occurrences (all)	17	7	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	12 / 233 (5.15%)	10 / 228 (4.39%)	
occurrences (all)	14	14	
Influenza			
subjects affected / exposed	14 / 233 (6.01%)	19 / 228 (8.33%)	
occurrences (all)	17	25	
Nasopharyngitis			
subjects affected / exposed	37 / 233 (15.88%)	39 / 228 (17.11%)	
occurrences (all)	57	60	
Pharyngitis			
subjects affected / exposed	14 / 233 (6.01%)	22 / 228 (9.65%)	
occurrences (all)	18	29	
Upper Respiratory Tract Infection			

subjects affected / exposed	20 / 233 (8.58%)	18 / 228 (7.89%)	
occurrences (all)	28	21	
Metabolism and nutrition disorders			
Ketosis			
subjects affected / exposed	19 / 233 (8.15%)	30 / 228 (13.16%)	
occurrences (all)	50	52	
Overweight			
subjects affected / exposed	2 / 233 (0.86%)	13 / 228 (5.70%)	
occurrences (all)	2	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 January 2016	Following protocol changes were implemented before the study was initiated. - Primary and secondary efficacy analyses were modified to include all post-baseline data regardless of treatment discontinuation. - Change to the minimum rate of subjects to be randomized from the age range < 12 years. - Standard deviation assumption for sample size determination was modified. - Removal of sampling for hematology and clinical chemistry at baseline visit. - Change to the dose adjustment rules of the IMP to provide more structured guidance for adjustment of the IMP dose. - Change to the prohibited concomitant therapy by clarifying that short-term use of non-study antihyperglycemic agents other than the IMP or non-investigational medicinal product (NIMP) was not considered as a prohibited therapy and that use of prohibited therapy would result in the subject's withdrawal from the study treatment rather than from the study. - Change specifying the descriptive purpose of secondary efficacy analyses.
23 August 2016	Following protocol changes were made: - Change to statistical methodology in primary and secondary endpoint analyses was made to replace the the mixed-effect model with repeated measures (MMRM) by a multiple imputation approach. - Change in eligibility criteria to lift the upper limit of the HbA1c range from 10% to 11%. - Change to instructions for hyperglycemia with ketosis. - Change to instructions for glucose meter by providing recommendations for tests with the control solution. - Change to instructions for handling of subjects after permanent treatment discontinuation by highlighting importance of collecting key parameters at scheduled study endpoint. - Change to utilization of Pharmacokinetic data by removing objective of comparison with historical data in adults.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported