Clinical trial results:
6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus® in Insulin-Naïve Patients with Type 2 Diabetes Mellitus not Adequately Controlled with Non-Insulin Antihyperglycemic Drugs with a 6-month Safety Extension Period

Summary

EudraCT number	2012-000146-35
Trial protocol	DK SE FI EE CZ LV LT NL BG SK
Global end of trial date	26 March 2014

Results information

Result version number	v1 (current)
This version publication date	01 April 2016
First version publication date	14 June 2015

Trial information

Trial identification

Sponsor protocol code	EFC12347

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01676220
WHO universal trial number (UTN)	U1111-1124-5261

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	12 June 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 March 2014
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 and Lantus in terms of change of HbA1c from baseline to endpoint (scheduled at Month 6, Week 26) in subjects with type 2 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: -

Evidence for comparator: -

Actual start date of recruitment	31 August 2012
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	Netherlands: 7
Country: Number of subjects enrolled	Slovakia: 18
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	Bulgaria: 16
Country: Number of subjects enrolled	Czech Republic: 7
Country: Number of subjects enrolled	Denmark: 27
Country: Number of subjects enrolled	Estonia: 4
Country: Number of subjects enrolled	Finland: 18
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Latvia: 7
Country: Number of subjects enrolled	Lithuania: 20
Country: Number of subjects enrolled	Canada: 51
Country: Number of subjects enrolled	Romania: 47
Country: Number of subjects enrolled	United States: 587
Country: Number of subjects enrolled	Japan: 50

Worldwide total number of subjects	878
EEA total number of subjects	190

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)	652
From 65 to 84 years	225
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 1396 subjects were screened, of whom 518 subjects were screen failure and 878 subjects were randomized.

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:

HOE901-U300 for 12 months in combination with non-insulin antihyperglycemic drug(s).

Arm type	Experimental
Investigational medicinal product name	Insulin glargine- new formulation
Investigational medicinal product code	HOE901-U300
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

HOE901-U300 (new insulin glargine 300 units per milliliter [U/mL]) once daily (evening). Dose titration seeking fasting plasma glucose 4.4-5.6 millimole per liter (mmol/L) (80 - 100 milligram per deciliter [mg/dL]).

Arm title	Lantus

Arm description:

Lantus for 12 months in combination with non-insulin antihyperglycemic drug(s).

Arm type	Active comparator
Investigational medicinal product name	Insulin glargine
Investigational medicinal product code	HOE901-U100
Other name	Lantus
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Lantus (HOE901-U100, insulin glargine 100 U/mL) once daily (evening). Dose titration seeking fasting plasma glucose 4.4-5.6 mmol/L (80 - 100 mg/dL).

Number of subjects in period 1	HOE901-U300	Lantus
Started	439	439
Treated	435	438
Modified Intent-To-Treat Population	432	430
Completed	337	314
Not completed	102	125
Received Rescue Therapy	14	22
Adverse Event	10	8
Perceived Lack of Efficacy	3	1
Selection Criterion/Protocol Violation	9	9
No More Need of Insulin	1	-
Non Serious Hypoglycemia	2	-
Randomized But Not Treated	4	1
Protocol Violation	11	12
Personal Reason	34	45
Lost to follow-up	11	18
Site Closure/Site Withdrawal	1	4
Lack of efficacy	2	5

Baseline characteristics

Reporting groups	
Reporting group title	HOE901-U300
Reporting group description:	
HOE901-U300 for 12 months in combination with non-insulin antihyperglycemic drug(s).	
Reporting group title	Lantus
Reporting group description:	
Lantus for 12 months in combination with non-insulin antihyperglycemic drug(s).	

Reporting group values	HOE901-U300	Lantus	Total
Number of subjects	439	439	878
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 58.2 ± 9.9	 57.2 ± 10.3	 -
Gender categorical Units: Subjects			
Female	186	185	371
Male	253	254	507
Glycated Hemoglobin A1c (HbA1c) Units: Subjects			
Less Than (<) 8%	141	142	283
Greater Than or Equal to (>=) 8%	298	297	595
Body Mass Index (BMI) Units: kilogram per square meter arithmetic mean standard deviation	 32.8 ± 6.9	 33.2 ± 6.6	 -
Duration of Diabetes			
Number of subjects analyzed for this baseline characteristics = 435 and 436 in HOE901-U300 and Lantus arm, respectively.			
Units: years arithmetic mean standard deviation	 10.11 ± 6.49	 9.57 ± 6.22	 -
Basal Insulin Daily Dose			
Number of subjects analyzed for this baseline characteristics = 432 and 436 in HOE901-U300 and Lantus arm, respectively.			
Units: units per kilogram (U/kg) arithmetic mean standard deviation	 0.193 ± 0.027	 0.193 ± 0.034	 -

End points

End points reporting groups

Reporting group title	HOE901-U300
Reporting group description:	
HOE901-U300 for 12 months in combination with non-insulin antihyperglycemic drug(s).	
Reporting group title	Lantus
Reporting group description:	
Lantus for 12 months in combination with non-insulin antihyperglycemic drug(s).	

Primary: Change in HbA1c From Baseline to Month 6 Endpoint

End point title	Change in HbA1c From Baseline to Month 6 Endpoint
End point description:	
Only HbA1c measurements performed before initiation of rescue therapy were considered in the analysis. Month 6 Endpoint is either the observed value at Month 6 visit or value retrieved according to time windows. Modified Intent-to-Treat (mITT) population:randomized subjects who received at least 1 dose, had baseline and at least 1 post-baseline data of any efficacy variable, irrespective of compliance. Number of subjects analyzed=subjects included in mITT population with baseline and at least 1 post-baseline HbA1c data (Week 12 and/or Month 6).	
End point type	Primary
End point timeframe:	
Baseline, Month 6	

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	402	394		
Units: percentage of hemoglobin				
least squares mean (standard error)	-1.42 (± 0.047)	-1.46 (± 0.048)		

Statistical analyses

Statistical analysis title	HOE901-U300 vs. Lantus
Statistical analysis description:	
Analysis was performed using mixed model for repeated measurements (MMRM) with treatment groups, strata of screening HbA1c (<8.0, >=8.0%), geographical region (Non-Japan; Japan), visit and visit-by-treatment groups interaction as fixed categorical effects; baseline HbA1c and baseline HbA1c-by-visit interaction as continuous fixed covariates.	
Comparison groups	HOE901-U300 v Lantus

Number of subjects included in analysis	796
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.174
Variability estimate	Standard error of the mean
Dispersion value	0.067

Notes:

[1] - Stepwise closed testing approach was used to assess non-inferiority and superiority sequentially:
1. Non-inferiority of HOE901-U300 vs Lantus: Upper bound of two-sided 95% confidence interval (CI) of difference between HOE901-U300 and Lantus on mITT population is <0.4%.
2. Superiority (only if non-inferiority has been demonstrated): Upper bound of two-sided 95% CI for difference in mean change in HbA1c from baseline to endpoint between HOE901-U300 and Lantus on mITT population is <0.

Secondary: Percentage of Subjects With At Least One Severe and/or Confirmed Nocturnal Hypoglycemia From Start of Week 9 to Month 6

End point title	Percentage of Subjects With At Least One Severe and/or Confirmed Nocturnal Hypoglycemia From Start of Week 9 to Month 6

End point description:

Nocturnal hypoglycemia was hypoglycemia that occurred between 00:00 and 05:59 hours (clock time), regardless the subject was awake or woke up because of the event. Severe hypoglycemia was an event that required assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Confirmed hypoglycemia was an event associated with plasma glucose less than or equal to (<=) 3.9 millimoles per liter (mmol/L) (70 milligram per deciliter [mg/dL]). Only nocturnal hypoglycemia occurring before initiation of rescue therapy were considered in the analysis. Week 9 and Month 6 value correspond to the observed value at Week 9 and Month 6 visit respectively. Modified intent-to-treat population.

End point type	Secondary

End point timeframe:

Week 9 Up to Month 6

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	432	430		
Units: percentage of subjects				
number (not applicable)	15.5	17.4		

Statistical analyses

Statistical analysis title	HOE901-U300 vs. Lantus

Statistical analysis description:

A one-sided test (at alpha=0.025) for superiority of HOE901-U300 over Lantus was to be performed in case the non-inferiority of HOE901-U300 vs Lantus for the primary endpoint was demonstrated. Analysis was performed using Cochran-Mantel-Haenszel (CMH) method stratified by randomization strata of

screening HbA1c (<8.0, >=8.0%), randomization strata of geographical region (Non-Japan; Japan).

Comparison groups	HOE901-U300 v Lantus
Number of subjects included in analysis	862
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4536
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.2

Secondary: Change in Preinjection Self-Monitored Plasma Glucose (SMPG) From Baseline to Month 6 Endpoint

End point title	Change in Preinjection Self-Monitored Plasma Glucose (SMPG) From Baseline to Month 6 Endpoint

End point description:

Pre-injection SMPG was measured within 30 minutes prior to the injection of the study drug. Except for baseline value average of preinjection SMPG was assessed by the mean of at least 3 SMPG calculated over the 7 days preceding the assessment visit. Only preinjection SMPG measurements performed before initiation of rescue therapy were considered in the analysis. Month 6 Endpoint is either the observed value at Month 6 visit or value retrieved according to time windows. mITT population. Number of subjects analyzed = subjects included in the mITT population with baseline and at least one pre-injection SMPG assessment (Week 2, Week 4, Week 8, Week 12, Month 4 and/or Month 6)

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	207	222		
Units: mmol/L				
least squares mean (standard error)	-2.16 (± 0.162)	-2.33 (± 0.156)		

Statistical analyses

Statistical analysis title	HOE901-U300 vs. Lantus

Statistical analysis description:

Change in pre-injection SMPG was analyzed using MMRM model with treatment groups, strata of screening HbA1c (<8.0, >=8.0%), geographical region (Non-Japan; Japan), visit and visit-by-treatment groups interaction as fixed categorical effects; baseline preinjection SMPG value and baseline preinjection SMPG value-by-visit interaction as continuous fixed covariates.

Comparison groups	HOE901-U300 v Lantus

Number of subjects included in analysis	429
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.275
upper limit	0.605
Variability estimate	Standard error of the mean
Dispersion value	0.224

Secondary: Variability of Preinjection SMPG at Month 6 Endpoint

End point title	Variability of Preinjection SMPG at Month 6 Endpoint

End point description:

Pre-injection SMPG was measured within 30 minutes prior to the injection of the study drug. Variability was assessed by the mean of coefficient of variation calculated as 100 multiplied by (standard deviation/mean) over at least 3 SMPG measured during the 7 days preceding the assessment visit. Only preinjection SMPG measurements performed before initiation of rescue therapy were considered in the analysis. Month 6 Endpoint is either the observed value at Month 6 visit or value retrieved according to time windows. mITT population. Number of subjects analyzed = subjects included in the mITT Population with at least one pre-injection SMPG variability assessment (Week 2, Week 4, Week 8, Week 12, Month 4 and/or Month 6).

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	422	418		
Units: percentage of mean				
least squares mean (standard error)	18.7 (± 0.502)	18.33 (± 0.521)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With HbA1c <7% at Month 6

End point title	Percentage of Subjects With HbA1c <7% at Month 6

End point description:

Only HbA1c measurements performed before initiation of rescue therapy were considered in the analysis. Month 6 value corresponds to the observed value at Month 6 visit. mITT Population. Subjects without any available Month 6 HbA1C assessment were considered as failures (non-responders).

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	432	430		
Units: percentage of subjects				
number (not applicable)	43.1	42.1		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Only FPG measurements performed before initiation of rescue therapy were considered in the analysis. Month 6 Endpoint is either the observed value at Month 6 visit or value retrieved according to time windows. mITT Population. Number of subjects analyzed = subjects included in the mITT population with baseline and at least one post-baseline FPG assessment (Week 12 and/or Month 6).

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	398	387		
Units: mmol/L				
least squares mean (standard error)	-3.41 (± 0.103)	-3.8 (± 0.105)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With FPG <5.6 mmol/L (100 mg/dL) at Month 6

End point title	Percentage of Subjects With FPG <5.6 mmol/L (100 mg/dL) at Month 6

End point description:

Only FPG measurements performed before initiation of rescue therapy were considered in the analysis. Month 6 value corresponds to the observed value at Month 6 visit. mITT Population. Subjects without

any available FPG assessment at Month 6 were considered as failures (non-responders).

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	432	430		
Units: percentage of subjects				
number (not applicable)	26.2	29.5		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Change in each time-point of 8-point SMPG profile: 03:00 hours (clock time) at night; before and 2 hours after breakfast; before and 2 hours after lunch; before and 2 hours after dinner; and at bedtime. Only 8-point SMPG profiles measurements performed before initiation of rescue therapy were considered in the analysis. Month 6 value corresponds to the observed value at Month 6 visit. mITT Population. Only subjects from the mITT population with a value at baseline and at specified timepoint were analyzed (represented by n=X, X in the category titles).

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	432	430		
Units: mmol/L				
arithmetic mean (standard deviation)				
03:00 at Night Plasma Glucose (n=281,277)	-2.63 (± 3.24)	-3.01 (± 3.75)		
Pre-Breakfast Plasma Glucose (n=292,286)	-3.28 (± 2.72)	-3.72 (± 2.96)		
2 Hours After Breakfast Plasma Glucose (n=278,278)	-3.69 (± 3.65)	-4.08 (± 4.03)		
Pre-Lunch Plasma Glucose (n=289,281)	-2.58 (± 3.39)	-3.39 (± 3.76)		
2 Hours After Lunch Plasma Glucose (n=280,269)	-2.19 (± 3.88)	-3.13 (± 3.77)		
Pre-Dinner Plasma Glucose (n=291,285)	-2.57 (± 3.49)	-2.43 (± 3.79)		

2 Hours After Dinner Plasma Glucose (n=282,269)	-2.36 (± 3.89)	-2.33 (± 4.03)		
Bedtime Plasma Glucose (n=249,249)	-2.19 (± 3.75)	-2.26 (± 3.66)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in 24-hour Average 8-point SMPG Profile From Baseline to Month 6 Endpoint

End point title	Change in 24-hour Average 8-point SMPG Profile From Baseline to Month 6 Endpoint

End point description:

Change in 24-hour average of 8-point SMPG profile. 8-point SMPG was assessed at: 03:00 hours (clock time) at night; before and 2 hours after breakfast; before and 2 hours after lunch; before and 2 hours after dinner; and at bedtime. Only 24-hour average 8-point SMPG measurements performed before initiation of rescue therapy were considered in the analysis. Month 6 Endpoint is either the observed value at Month 6 visit or value retrieved according to time windows. mITT Population. Number of subjects analyzed = subjects included in the mITT population with baseline and at least one post-baseline 24-hour average 8-point SMPG assessment (Week 2, Week 4, Week 8, Week 12, Month 4 and/or Month 6).

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	381	393		
Units: mmol/L				
least squares mean (standard error)	-2.72 (± 0.088)	-2.9 (± 0.089)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Variability of 24 Hour Average 8-point SMPG Profiles From Baseline to Month 6 Endpoint

End point title	Change in Variability of 24 Hour Average 8-point SMPG Profiles From Baseline to Month 6 Endpoint

End point description:

Variability is assessed by the mean of coefficient of variation calculated as 100 multiplied by (standard deviation/mean) over at least 5 measurements of the 8-point profiles. Only variability of 24-hour 8-point SMPG measurements performed before initiation of rescue therapy were considered in the analysis. Month 6 Endpoint is either the observed value at Month 6 visit or value retrieved according to time windows. mITT Population. Number of subjects analyzed = subjects included in the mITT population with baseline and at least one post-baseline variability of 24-hour average 8-point SMPG assessment (Week 2, Week 4, Week 8, Week 12, Month 4 and/or Month 6).

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	381	393		
Units: percentage of mean				
least squares mean (standard error)	1.53 (± 0.643)	1.41 (± 0.647)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Daily Basal Insulin Dose From Baseline to Month 6

End point title	Change in Daily Basal Insulin Dose From Baseline to Month 6

End point description:

Only insulin dose measurements performed before initiation of rescue therapy were considered in the analysis. Month 6 value corresponds to the observed value at Month 6 visit. mITT Population. Number of subjects analyzed = subjects included in the mITT population with Baseline and Month 6 basal insulin dose assessment.

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	362	340		
Units: U/kg				
arithmetic mean (standard deviation)	0.43 (± 0.29)	0.34 (± 0.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Total Treatment Satisfaction Score Using The Diabetes Treatment Satisfaction Questionnaire (DTSQs) From Baseline to Month 6 Endpoint

End point title	Change in Total Treatment Satisfaction Score Using The Diabetes Treatment Satisfaction Questionnaire (DTSQs) From Baseline to Month 6 Endpoint

End point description:

DTSQ is a validated measure to assess how satisfied subjects with diabetes are with their treatment and

how they perceive hyper- and hypoglycemia. It consists of 8 questions which are answered on a Likert scale from 0 to 6. DTSQ treatment satisfaction score is the sum of question 1 and 4-8 scores and ranges between 0 and 36, where higher scores indicate more treatment satisfaction. Only DTSQ total score measurements performed before initiation of rescue therapy were considered in the analysis. Month 6 Endpoint is either the observed value at Month 6 visit or value retrieved according to time windows. mITT Population. Number of subjects analyzed = subjects included in the mITT population with Baseline and at least one post-baseline DTSQ assessment (Week 12 and/or Month 6).

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	371	367		
Units: units on a scale				
least squares mean (standard error)	4.89 (± 0.246)	5.12 (± 0.251)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Hypoglycemia (All and Nocturnal) Events From Baseline up to Month 12

End point title	Percentage of Subjects With Hypoglycemia (All and Nocturnal) Events From Baseline up to Month 12

End point description:

Hypoglycaemia included: Severe (required assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions); Documented symptomatic (typical symptoms of hypoglycaemia were accompanied by plasma glucose =<3.9 mmol/L); Asymptomatic (not accompanied by typical symptoms of hypoglycaemia but with plasma glucose =<3.9 mmol/L); Probable symptomatic (symptoms of hypoglycaemia were not accompanied by a plasma glucose determination, but was presumably caused by plasma glucose =<3.9 mmol/L); and Relative (subject reported any of the typical symptoms of hypoglycaemia, and interpreted the symptoms as indicative of hypoglycaemia, but with plasma glucose >3.9 mmol/L). Safety population: all subjects randomized and treated, regardless of amount of treatment administered. In event of subjects having received treatments different from those assigned according to the randomization schedule, safety analyses were conducted according to treatment received.

End point type	Secondary

End point timeframe:

Up to 12 months

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	435	438		
Units: percentage of subjects				
number (not applicable)				
Any Hypoglycemia Event: All Hypoglycemia	58.9	63.2		

Severe Hypoglycemia: All Hypoglycemia	1.4	2.1		
Documented Symptomatic: All Hypoglycemia	39.1	44.1		
Asymptomatic: All Hypoglycemia	41.6	46.8		
Probable Symptomatic: All Hypoglycemia	3.2	3		
Relative: All Hypoglycemia	10.6	11.6		
Severe and/or Confirmed: All Hypoglycemia	56.3	61.2		
Any Hypoglycemia Event: Nocturnal Hypoglycemia	27.6	30.1		
Severe Hypoglycemia: Nocturnal Hypoglycemia	0	0.7		
Documented Symptomatic: Nocturnal Hypoglycemia	18.6	20.8		
Asymptomatic: Nocturnal Hypoglycemia	13.3	16		
Probable Symptomatic: Nocturnal Hypoglycemia	0.7	0		
Relative: Nocturnal Hypoglycemia	4.4	3.2		
Severe and/or Confirmed: Nocturnal Hypoglycemia	25.3	29.5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of informed consent form up to study completion regardless of seriousness or relationship to study drug.

Adverse event reporting additional description:

Reported adverse events and deaths are treatment-emergent that is AEs that developed/worsened and death that occurred during on-treatment period (time from first injection of study drug up to 2 day after the last injection of study drug). Analysis was done on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Lantus

Reporting group description:

Lantus SC injection once daily for 12 months in combination with non-insulin antihyperglycemic drug(s).

Reporting group title	HOE901-U300

Reporting group description:

HOE901-U300 SC injection once daily for 12 months in combination with non-insulin antihyperglycemic drug(s).

Serious adverse events	Lantus	HOE901-U300	
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 438 (8.90%)	35 / 435 (8.05%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal Cell Carcinoma			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast Cancer			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate Cancer			

subjects affected / exposed	1 / 438 (0.23%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral Arterial Occlusive Disease			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose Vein			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Medical Device Removal			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 438 (0.00%)	2 / 435 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menorrhagia			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute Pulmonary Oedema			

subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Respiratory Failure			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	2 / 438 (0.46%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial Lung Disease			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep Apnoea Syndrome			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Bilirubin Increased			

subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb Injury			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Injuries			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib Fracture			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road Traffic Accident			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Limb Fracture			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	2 / 438 (0.46%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Angina Pectoris			
subjects affected / exposed	2 / 438 (0.46%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Unstable			
subjects affected / exposed	1 / 438 (0.23%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis Coronary Artery			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial Fibrillation			
subjects affected / exposed	1 / 438 (0.23%)	2 / 435 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	1 / 438 (0.23%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Disease			
subjects affected / exposed	0 / 438 (0.00%)	2 / 435 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			
subjects affected / exposed	1 / 438 (0.23%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular Tachycardia			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Carotid Artery Aneurysm			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Artery Embolism			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Infarction			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Accident			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Unconsciousness			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Stroke			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (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 / 438 (0.23%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Cataract			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal Detachment			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Hernia			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain			
subjects affected / exposed	3 / 438 (0.68%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis Ischaemic			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum Intestinal			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal Ulcer			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric Ulcer Haemorrhage			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Haemorrhage			

subjects affected / exposed	2 / 438 (0.46%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic Ulcer			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestinal Obstruction			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical Hernia			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			

subjects affected / exposed	0 / 438 (0.00%)	2 / 435 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 438 (0.23%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis Pyrophosphate			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank Pain			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 438 (0.46%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain In Extremity			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spinal Osteoarthritis			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic Foot Infection			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 438 (0.00%)	2 / 435 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver Abscess			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar Pneumonia			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infection			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative Wound Infection			

subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Mycosis			
subjects affected / exposed	0 / 438 (0.00%)	1 / 435 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 438 (0.23%)	0 / 435 (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	Lantus	HOE901-U300	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	107 / 438 (24.43%)	115 / 435 (26.44%)	
Nervous system disorders			
Headache			
subjects affected / exposed	22 / 438 (5.02%)	36 / 435 (8.28%)	
occurrences (all)	28	48	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	47 / 438 (10.73%)	41 / 435 (9.43%)	
occurrences (all)	59	48	
Sinusitis			
subjects affected / exposed	23 / 438 (5.25%)	11 / 435 (2.53%)	
occurrences (all)	30	13	
Upper Respiratory Tract Infection			
subjects affected / exposed	34 / 438 (7.76%)	45 / 435 (10.34%)	
occurrences (all)	44	60	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 August 2013	- Review of severe hypoglycemia classification by an external Review Board. - Procedures when the titration extends beyond the originally planned 8 to 12 weeks post-randomization. - Clarification of definition of an injection area and an injection site within that area. - Clarification of timing of investigational medicinal product (IMP) injection. - Clarification of the screening period. - Clarification of serious adverse event (SAE) and adverse event of special interest (AESI) reporting. - Clarification of uses and documentation of SMPG. - Change to the scope of data recorded into the electronic case report form (e-CRF) upon phone call visits.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported