Clinical trial results:
A 6-Month, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus® Injected in the Morning or Evening in Patients with Type 1 Diabetes Mellitus with a 6-month Safety Extension Period

Summary

EudraCT number	2012-001524-35
Trial protocol	DK SE FI CZ LV HU NL EE
Global end of trial date	14 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	EFC12456

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01683266
WHO universal trial number (UTN)	U1111-1128-5517

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	02 July 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 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 (HOE901-U300) and Lantus (overall, regardless the injection time) in terms of change of HbA1c from baseline to endpoint (scheduled Month 6) in subjects 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: -
Evidence for comparator: -

Actual start date of recruitment	12 September 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: 17
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Denmark: 26
Country: Number of subjects enrolled	Estonia: 24
Country: Number of subjects enrolled	Finland: 17
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Latvia: 16
Country: Number of subjects enrolled	Canada: 22
Country: Number of subjects enrolled	Japan: 46
Country: Number of subjects enrolled	Romania: 29
Country: Number of subjects enrolled	United States: 330
Worldwide total number of subjects	549
EEA total number of subjects	151

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)	494
From 65 to 84 years	54
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 846 subjects were screened, of whom 297 subjects were screen failure and 549 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 on top of mealtime insulin analogue.

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 in morning or 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 on top of mealtime insulin analogue.

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 in morning or 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	274	275
Modified Intent-to-Treat Population	273	273
Completed	219	225
Not completed	55	50
Adverse Event	5	4
Perceived Lack of Efficacy	1	1
Selection Criterion/Protocol Violation	7	5
Serious Adverse Event of Hypoglycemia	-	1
Protocol Violation	13	6
Nonserious Hypoglycemia	-	3
Personal Reason	17	25
Lost to follow-up	5	-
Possibly Hypoglycemia	1	-
Site Closure/Site Withdrawal	1	3
Lack of efficacy	5	2

Baseline characteristics

Reporting groups	
Reporting group title	HOE901-U300
Reporting group description:	
HOE901-U300 for 12 months on top of mealtime insulin analogue.	
Reporting group title	Lantus
Reporting group description:	
Lantus for 12 months on top of mealtime insulin analogue.	

Reporting group values	HOE901-U300	Lantus	Total
Number of subjects	274	275	549
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	46.4	48.2	
standard deviation	± 13.9	± 13.4	-
Gender categorical Units: Subjects			
Female	125	111	236
Male	149	164	313
Glycated Hemoglobin (HbA1c) Units: Subjects			
Less Than (<) 8%	105	105	210
Greater Than or Equal to (>=) 8%	169	170	339
Body Mass Index (BMI) Units: kilogram per square meter (kg/m^2)			
arithmetic mean	27.6	27.6	
standard deviation	± 5.5	± 4.7	-
Duration of Diabetes			
Number of subjects analyzed for this baseline characteristics = 274 and 272 for each reporting group, respectively.			
Units: years			
arithmetic mean	20.5	21.4	
standard deviation	± 12.7	± 13.1	-
Basal Insulin Daily Dose			
Number of subjects analyzed for this baseline characteristics = 201 and 210 for each reporting group, respectively.			
Units: units per kilogram (U/kg)			
arithmetic mean	0.381	0.372	
standard deviation	± 0.173	± 0.152	-
Total Insulin Daily Dose			
Number of subjects analyzed for this baseline characteristics = 195 and 198 for each reporting group, respectively.			
Units: U/kg			
arithmetic mean	0.714	0.724	
standard deviation	± 0.278	± 0.245	-

End points

End points reporting groups

Reporting group title	HOE901-U300
Reporting group description: HOE901-U300 for 12 months on top of mealtime insulin analogue.	
Reporting group title	Lantus
Reporting group description: Lantus for 12 months on top of mealtime insulin analogue.	

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: Modified Intent-to-Treat (mITT) population: all randomized subjects who received at least (>=)1 dose, had baseline and >=1 post-baseline assessment of any efficacy variable, irrespective of compliance. Number of subjects analyzed = subjects with baseline and Month 6 HbA1c assessment.	
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	225	229		
Units: percentage of hemoglobin				
least squares mean (standard error)	-0.4 (± 0.051)	-0.44 (± 0.051)		

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	454
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	-0.098
upper limit	0.185
Variability estimate	Standard error of the mean
Dispersion value	0.072

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 HbA1c <7% at Month 6 Endpoint

End point title	Percentage of Subjects With HbA1c <7% at Month 6 Endpoint
End point description: mITT 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	273	273		
Units: percentage of subjects				
number (not applicable)	16.8	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With HbA1c Less Than or Equal to 6.5% at Month 6 Endpoint

End point title	Percentage of Subjects With HbA1c Less Than or Equal to 6.5% at Month 6 Endpoint
End point description: mITT 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	273	273		
Units: percentage of subjects				
number (not applicable)	8.1	5.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Change In Average Pre-Injection Self-Monitored Plasma Glucose (SMPG) From Baseline Month 6 Endpoint

End point title	Change In Average Pre-Injection Self-Monitored Plasma Glucose (SMPG) From Baseline Month 6 Endpoint

End point description:

Pre-injection SMPG was measured within 30 minutes prior to the injection of the study drug. Average was assessed by the mean of at least 3 SMPG calculated over the 7 days preceding the assessment visit. mITT population. Number of subjects analyzed = subjects with baseline and Month 6 pre-injection SMPG 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	117	105		
Units: millimole per liter (mmol/L)				
least squares mean (standard error)	-1.16 (± 0.223)	-0.82 (± 0.233)		

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; pre-injection SMPG value and pre-injection SMPG value-by-visit interaction as continuous fixed covariates.

Comparison groups	HOE901-U300 v Lantus
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean difference
Point estimate	-0.35

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.982
upper limit	0.287
Variability estimate	Standard error of the mean
Dispersion value	0.322

Secondary: Change in Variability of Pre-injection SMPG From Baseline to Month 6 Endpoint

End point title	Change in Variability of Pre-injection 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. 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. mITT population. Number of subjects analyzed = subjects with baseline and Month 6 pre-injection SMPG 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	117	105		
Units: percentage of mean				
least squares mean (standard error)	-3.03 (± 1.573)	-1.76 (± 1.651)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

mITT Population. Number of subjects analyzed = subjects with baseline and Month 6 FPG 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	213	216		
Units: mmol/L				
least squares mean (standard error)	-0.95 (± 0.263)	-1.14 (± 0.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Fasting Plasma Glucose (FPG) <5.6 mmol/L (100 mg/dL) At Month 6

End point title	Percentage of Subjects With Fasting Plasma Glucose (FPG) <5.6 mmol/L (100 mg/dL) At Month 6
End point description: mITT 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	273	273		
Units: percentage of subjects				
number (not applicable)	9.9	12.8		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Subjects With FPG <7.2 mmol/L (130 mg/dL) at Month 6 Endpoint
End point description: mITT Population. Number of subjects analyzed = subjects with baseline and Month 6 FPG assessment.	
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	273	273		
Units: percentage of subjects				
number (not applicable)	25.3	25.6		

Statistical analyses

No statistical analyses for this end point

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

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

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. mITT Population. Here, n = subjects with Baseline and Month 6 8-point SMPG assessment separately for each analysed time point.

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	273	273		
Units: mmol/L				
arithmetic mean (standard deviation)				
03:00 at Night (n= 156, 159)	-0.47 (± 4.56)	-0.67 (± 4.98)		
Pre-Breakfast (n= 166, 167)	-0.86 (± 5.3)	-0.07 (± 5.2)		
2 Hours After Breakfast (n= 152, 156)	-0.62 (± 4.75)	-1.18 (± 5.66)		
Pre-Lunch (n= 166, 166)	-0.95 (± 4.53)	-0.93 (± 4.76)		
2 Hours After Lunch (n= 163,163)	-0.13 (± 5.2)	-1.43 (± 5.37)		
Pre-Dinner (n= 165,166)	-0.56 (± 6)	-1.74 (± 5.28)		
2 Hours After Dinner (n= 154,152)	-0.93 (± 5.27)	-1.19 (± 5.51)		
Bedtime (n= 141,146)	-0.8 (± 5.39)	-1.91 (± 5.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Daily Average Total Insulin Dose From Baseline to Month 6 Endpoint

End point title	Change in Daily Average Total Insulin Dose From Baseline to Month 6 Endpoint

End point description:

mITT Population. Number of subjects analyzed = subjects with Baseline and Month 6 daily average total 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	173	158		
Units: U/kg				
arithmetic mean (standard deviation)	0.19 (± 0.22)	0.1 (± 0.16)		

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. mITT Population. Number of subjects analyzed = subjects with Baseline and Month 6 DTSQ 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	212	206		
Units: units on a scale				
least squares mean (standard error)	1 (± 0.331)	1.41 (± 0.334)		

Statistical analyses

No statistical analyses for this end point

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

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

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	275		
Units: percentage of subjects				
number (not applicable)				
Any Hypoglycemia Event: All Hypoglycemia	95.3	94.9		
Severe Hypoglycemia: All Hypoglycemia	9.1	11.3		
Documented Symptomatic: All Hypoglycemia	87.6	86.5		
Asymptomatic: All Hypoglycemia	76.6	81.5		
Probable Symptomatic: All Hypoglycemia	11.3	15.3		
Relative: All Hypoglycemia	14.6	9.5		
Severe and/or Confirmed: All Hypoglycemia	94.9	94.5		
Any Hypoglycemia Event: Nocturnal Hypoglycemia	73.4	74.9		
Severe Hypoglycemia: Nocturnal Hypoglycemia	3.3	3.3		
Documented Symptomatic: Nocturnal Hypoglycemia	64.2	63.3		
Asymptomatic: Nocturnal Hypoglycemia	35	38.9		
Probable Symptomatic: Nocturnal Hypoglycemia	5.1	6.5		
Relative: Nocturnal Hypoglycemia	4	5.5		
Severe and/or Confirmed: Nocturnal Hypoglycemia	72.6	74.5		

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 (as the time from first injection of IMP up to 2 days after the last injection of IMP). 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 in morning or evening for 12 months on top of mealtime insulin.

Reporting group title	HOE901-U300

Reporting group description:

HOE901-U300 SC injection once daily in morning or evening for 12 months on top of mealtime insulin.

Serious adverse events	Lantus	HOE901-U300	
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 275 (9.45%)	27 / 274 (9.85%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant Melanoma			
subjects affected / exposed	1 / 275 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Femoral Artery Occlusion			
subjects affected / exposed	0 / 275 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	1 / 275 (0.36%)	0 / 274 (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	1 / 275 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 275 (0.00%)	1 / 274 (0.36%)	
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			
Accidental Overdose			
subjects affected / exposed	0 / 275 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain Contusion			
subjects affected / exposed	1 / 275 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Comminuted Fracture			
subjects affected / exposed	0 / 275 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 275 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint Dislocation			

subjects affected / exposed	1 / 275 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Open Fracture			
subjects affected / exposed	0 / 275 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 275 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella Fracture			
subjects affected / exposed	0 / 275 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic Fracture			
subjects affected / exposed	1 / 275 (0.36%)	0 / 274 (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 / 275 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road Traffic Accident			
subjects affected / exposed	2 / 275 (0.73%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Compression Fracture			
subjects affected / exposed	0 / 275 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural Haematoma			

subjects affected / exposed	1 / 275 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon Rupture			
subjects affected / exposed	0 / 275 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic Vertebral Fracture			
subjects affected / exposed	1 / 275 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	1 / 275 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular Block Complete			
subjects affected / exposed	0 / 275 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Disease			
subjects affected / exposed	0 / 275 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 275 (0.36%)	0 / 274 (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	0 / 275 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic Neuropathy			

subjects affected / exposed	1 / 275 (0.36%)	0 / 274 (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	1 / 275 (0.36%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Unconsciousness			
subjects affected / exposed	1 / 275 (0.36%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss Of Consciousness			
subjects affected / exposed	1 / 275 (0.36%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 275 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 275 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic Foot			
subjects affected / exposed	1 / 275 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 275 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Renal Failure Acute			
subjects affected / exposed	1 / 275 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Retention			
subjects affected / exposed	1 / 275 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Dupuytren's Contracture			
subjects affected / exposed	1 / 275 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 275 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 275 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Tonsillitis			
subjects affected / exposed	1 / 275 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 275 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1n1 Influenza			
subjects affected / exposed	0 / 275 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pyelonephritis			
subjects affected / exposed	0 / 275 (0.00%)	1 / 274 (0.36%)	
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 / 275 (0.36%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Infection			
subjects affected / exposed	0 / 275 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic Ketoacidosis			
subjects affected / exposed	1 / 275 (0.36%)	2 / 274 (0.73%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	13 / 275 (4.73%)	16 / 274 (5.84%)	
occurrences causally related to treatment / all	10 / 16	13 / 17	
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	86 / 275 (31.27%)	113 / 274 (41.24%)	
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 275 (4.73%)	17 / 274 (6.20%)	
occurrences (all)	14	29	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	7 / 275 (2.55%)	14 / 274 (5.11%)	
occurrences (all)	9	15	

Infections and infestations			
Influenza			
subjects affected / exposed	14 / 275 (5.09%)	16 / 274 (5.84%)	
occurrences (all)	15	16	
Nasopharyngitis			
subjects affected / exposed	35 / 275 (12.73%)	43 / 274 (15.69%)	
occurrences (all)	37	56	
Sinusitis			
subjects affected / exposed	11 / 275 (4.00%)	14 / 274 (5.11%)	
occurrences (all)	11	20	
Upper Respiratory Tract Infection			
subjects affected / exposed	26 / 275 (9.45%)	38 / 274 (13.87%)	
occurrences (all)	39	49	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 August 2013	- Route and method of investigational medicinal product (IMP) administration – clarification of the definition of injection area and injection site within that area. - Timing of IMP injection – clarification of the window for timing of IMP injections. - Adjustment of IMP – clarification of titration beyond 6 to 8 weeks. - Non-investigational medicinal product (NIMP) – emphasis of the need to avoid daytime hypoglycemia, specific guidance on when to begin optimization of the mealtime insulin dose, recording of all doses of mealtime insulin analog. - Review of severe hypoglycemia classification by external Review Board – all hypoglycemia events reported by Investigator as severe and/or reported as serious adverse events (SAEs) were to be independently reviewed by a Severe Hypoglycemia Review Board (SHRB) blinded to treatment arm. This was to ensure consistent use of the severe hypoglycemia classification according to American Diabetes Association definition across the study. Both the Investigators' classification and the Review Board's assessment were to be reported. - Screening period – clarification that screening period could be extended from 2 to 3 weeks. - SMPG and change to the scope of data recorded into the electronic case report form upon phone call visits – clarification of documentation of SMPG. Furthermore, in order to reduce burden to subjects and minimize potential for transcription errors, the amount of SMPG data to be collected during phone call visits was reduced to the minimum required for the IMP dose adjustment. However, the remaining SMPG as well as IMP and mealtime insulin dose data of the week prior to the phone call visits recorded by the subject in the diary, were collected at the subsequent on-site visits. - Reporting of SAE and adverse events of special interest (AESI) – clarification of the process of SAE and AESI reporting.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported