



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® Both plus Mealtime Insulin in Patients with Type 2 Diabetes Mellitus with a 6-month Safety Extension Period

Summary

EudraCT number	2010-023769-23
Trial protocol	NL HU CZ LV EE SE FI DE
Global end of trial date	04 September 2013

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	EFC11628
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01499082
WHO universal trial number (UTN)	-

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	06 December 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	04 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of insulin glargine new formulation and Lantus in terms of change in HbA1c from baseline to endpoint (scheduled month 6) in adult 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	15 December 2011
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: 47
Country: Number of subjects enrolled	Czech Republic: 49
Country: Number of subjects enrolled	Estonia: 21
Country: Number of subjects enrolled	Finland: 7
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Hungary: 119
Country: Number of subjects enrolled	Latvia: 31
Country: Number of subjects enrolled	Canada: 72
Country: Number of subjects enrolled	Mexico: 16
Country: Number of subjects enrolled	Romania: 68
Country: Number of subjects enrolled	South Africa: 24
Country: Number of subjects enrolled	United States: 341
Worldwide total number of subjects	807
EEA total number of subjects	354

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)	561
From 65 to 84 years	245
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 1177 subjects were screened, of whom 370 subjects were screen failure and 807 subjects were randomized.

Pre-assignment

Screening details:

Following the main 6 month treatment period, eligible subjects previously using HOE901-U300 were randomized (1:1) in a substudy and continued with fixed-dosing (every 24 hours) or started a adaptable-dosing (at intervals of 24 +/- 3 hours) regimen for 3 Months (Month 6 to 9).

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 (evening). Dose titration seeking fasting plasma glucose 4.4-5.6 millimole per liter (mmol/L) (80 - 100 milligram per deciliter [mg/dL]). After 6 months subjects were proposed to participate to the administration substudy and to receive either HOE901-U300 once daily at intervals of 24 +/- 3 hours (adaptable dosing intervals) or to continue once daily injections of HOE901-U300 every 24 hours (fixed dosing intervals) up to Month 9.

Arm title	Lantus
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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 (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	404	403
Treated	404	402
Participated in Substudy	109 ^[1]	0 ^[2]
Modified Intent-to-Treat Population	404	400
Completed	359	355
Not completed	45	48
Adverse Event	12	16
Diverse Reasons	18	14
Randomized but not Treated	-	1
Protocol Violation	6	8
Hypoglycemia	2	3
Lost to follow-up	1	3
Site Closure for Noncompliance	5	2
Lack of efficacy	1	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 109 subjects participated in the substudy (56 subjects received adaptable dosing regimen and 53 subjects received fixed dosing regimen).

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: No subject participated in the substudy from Lantus arm as participation in substudy was allowed only to those subjects who received HOE901-U300.

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	404	403	807
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	60.1	59.8	
standard deviation	± 8.5	± 8.7	-
Gender categorical			
Units: Subjects			
Female	187	193	380
Male	217	210	427
Glycated Hemoglobin A1c (HbA1c)			
Units: Subjects			
Less Than (<) 8%	144	144	288
Greater Than or Equal to (>=) 8%	260	259	519
Body Mass Index (BMI)			
Units: kilogram per square meter (kg/m ²)			
arithmetic mean	36.6	36.6	
standard deviation	± 6.8	± 6.1	-
Duration of Diabetes			
Units: years			
arithmetic mean	15.6	16.1	
standard deviation	± 7.2	± 7.8	-
Basal Insulin Daily Dose			
Number of subjects analyzed for this baseline characteristics = 372 and 361 in HOE901-U300 and Lantus arm, respectively.			
Units: units per kilogram (U/kg)			
arithmetic mean	0.668	0.667	
standard deviation	± 0.263	± 0.241	-
Total Insulin Daily Dose			
Number of subjects analyzed for this baseline characteristics = 367 and 360 in HOE901-U300 and Lantus arm, respectively			
Units: U/kg			
arithmetic mean	1.194	1.2	
standard deviation	± 0.483	± 0.448	-

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.	
Subject analysis set title	HOE901-U300: Adaptable Dosing Intervals
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: HOE901-U300 SC injection once daily for 6 months on top of mealtime insulin. From Month 6 to Month 9 subjects received HOE901-U300 once daily at intervals of 24 +/- 3 hours.	
Subject analysis set title	HOE901-U300: Fixed Dosing Intervals
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: HOE901-U300 SC injection once daily for 6 months on top of mealtime insulin. From Month 6 up to Month 9 subjects received HOE901-U300 once daily every 24 hours.	

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 population: all randomized subjects who received at least ($\geq$)1 dose, had baseline and ≥ 1 post-baseline assessment of any efficacy variable, irrespective of compliance. Number of subjects analyzed = subjects with baseline and Week 6 HbA1c assessment. Missing data imputed using last observation carried forward.	
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	391	394		
Units: percentage of hemoglobin				
least squares mean (standard error)	-0.83 ($\pm$ 0.06)	-0.83 ($\pm$ 0.061)		

Statistical analyses

Statistical analysis title	HOE901-U300 vs. Lantus
Statistical analysis description: Analysis was performed using an analysis of covariance (ANCOVA) model with treatment, strata of screening HbA1c (<8.0 and $\geq 8.0\%$), and country as fixed effects and using the HbA1c baseline value as a covariate.	
Comparison groups	HOE901-U300 v Lantus

Number of subjects included in analysis	785
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.112
upper limit	0.107
Variability estimate	Standard error of the mean
Dispersion value	0.056

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 Endpoint

End point title	Percentage of Subjects With At Least One Severe and/or Confirmed Nocturnal Hypoglycemia From Start of Week 9 to Month 6 Endpoint
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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 ($\leq$) 3.9 millimoles per liter (mmol/L) (70 milligram per deciliter [mg/dL]). Modified intent-to-treat population.

End point type	Secondary
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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	404	400		
Units: percentage of subjects				
number (not applicable)	36.1	46		

Statistical analyses

Statistical analysis title	HOE901-U300 vs. Lantus
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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 with treatment as a factor and stratified on strata of screening HbA1c (<8.0 and $\geq 8.0\%$).

Comparison groups	HOE901-U300 v Lantus
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Number of subjects included in analysis	804
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0045
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	0.93

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

End point title	Change in Average 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. Average was assessed by the mean of at least 3 SMPG calculated over the 7 days preceding the assessment visit. mITT population. Missing data imputed using last observation carried forward. 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	365	360		
Units: mmol/L				
least squares mean (standard error)	-0.9 (± 0.182)	-0.84 (± 0.182)		

Statistical analyses

Statistical analysis title	HOE901-U300 vs. Lantus
Statistical analysis description:	Change in pre-injection SMPG was analyzed using an ANCOVA model with treatment, strata of screening HbA1c (<8.0 and ≥8.0%), and country as fixed effects and using the pre-injection SMPG baseline value as a covariate. A test for superiority of HOE901-U300 over Lantus was to be performed one-sided at level alpha = 0.025 if previous analysis for nocturnal hypoglycemia was significant.
Comparison groups	HOE901-U300 v Lantus

Number of subjects included in analysis	725
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6909
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.383
upper limit	0.254
Variability estimate	Standard error of the mean
Dispersion value	0.162

Secondary: Change in Variability of Preinjection SMPG From Baseline to Month 6 Endpoint

End point title	Change in Variability of Preinjection 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. Missing data imputed using last observation carried forward. 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	365	360		
Units: percentage of mean				
least squares mean (standard error)	-1.1 (± 1.222)	-1.08 (± 1.222)		

Statistical analyses

No statistical analyses for this end point

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. Number of subjects analyzed = subjects with baseline and Month 6 HbA1c assessment. Missing data imputed using last observation carried forward.
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	391	394		
Units: percentage of subjects				
number (not applicable)	39.6	40.9		

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
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End point description:

mITT Population. Number of subjects analyzed = subjects with baseline and Month 6 FPG assessment. Missing data imputed using last observation carried forward.

End point type	Secondary
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End point timeframe:

Baseline, Month 6

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	376	385		
Units: mmol/L				
least squares mean (standard error)	-1.29 ($\pm$ 0.191)	-1.38 ($\pm$ 0.192)		

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 Endpoint

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

mITT Population. Number of subjects analyzed = subjects with Month 6 FPG assessment. Missing data imputed using last observation carried forward.

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	389	392		
Units: percentage of subjects				
number (not applicable)	26.5	23.2		

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
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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. Missing data imputed using last observation carried forward.

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	404	400		
Units: mmol/L				
least squares mean (standard error)				
03:00 at Night Plasma Glucose (n=333,323)	-0.98 (± 0.248)	-1.16 (± 0.251)		
Pre-Breakfast Plasma Glucose (n=343,333)	-1.19 (± 0.189)	-1.49 (± 0.19)		
2 Hours After Breakfast Plasma Glucose (n=335,326)	-1.6 (± 0.241)	-1.9 (± 0.243)		
Pre-Lunch Plasma Glucose (n=337,331)	-1.05 (± 0.213)	-1.23 (± 0.216)		
2 Hours After Lunch Plasma Glucose (n=336,325)	-0.64 (± 0.28)	-0.63 (± 0.282)		
Pre-Dinner Plasma Glucose (n=338,333)	-0.47 (± 0.261)	-0.37 (± 0.26)		
2 Hours After Dinner Plasma Glucose (n=331,327)	-0.96 (± 0.298)	-1.17 (± 0.298)		

Bedtime Plasma Glucose (n=324, 325)	-0.88 (± 0.324)	-0.91 (± 0.326)		
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Statistical analyses

No statistical analyses for this end point

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

End point title	Change in Daily Basal Insulin Dose From Baseline to Month 6 Endpoint
End point description: mITT Population. Number of subjects analyzed = subjects with Baseline and Month 6 basal insulin dose assessment. Missing data imputed using last observation carried forward.	
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	403	400		
Units: U/kg				
least squares mean (standard error)	0.28 (± 0.017)	0.19 (± 0.017)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Change in 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. Missing data imputed using last observation carried forward.	
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	366	363		
Units: units on a scale				
least squares mean (standard error)	2.32 ($\pm$ 0.31)	2.24 ($\pm$ 0.313)		

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
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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 $\leq$ 3.9 mmol/L); Asymptomatic (not accompanied by typical symptoms of hypoglycaemia but with plasma glucose $\leq$ 3.9 mmol/L); Probable symptomatic (symptoms of hypoglycaemia were not accompanied by a plasma glucose determination, but was presumably caused by plasma glucose $\leq$ 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
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End point timeframe:

Up to Month 12

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	402		
Units: percentage of subjects				
number (not applicable)				
Any Hypoglycemia Event: All Hypoglycemia	87.4	92		
Severe Hypoglycemia: All Hypoglycemia	6.7	7.5		
Documented Symptomatic: All Hypoglycemia	74.8	82.8		
Asymptomatic: All Hypoglycemia	70.5	73.4		
Probable Symptomatic: All Hypoglycemia	5.7	8.5		
Relative: All Hypoglycemia	15.8	21.1		
Severe and/or Confirmed: All Hypoglycemia	85.9	91.5		

Any Hypoglycemia Event: Nocturnal Hypoglycemia	55.4	66.2		
Severe Hypoglycemia: Nocturnal	2.5	3.2		
Documented Symptomatic: Nocturnal Hypoglycemia	44.6	57.2		
Asymptomatic: Nocturnal Hypoglycemia	29.2	31.1		
Probable Symptomatic: Nocturnal Hypoglycemia	2.2	2.7		
Relative: Nocturnal Hypoglycemia	5	10		
Severe and/or Confirmed: Nocturnal Hypoglycemia	54.5	64.7		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in HbA1c From Month 6 to Month 9

End point title	Change in HbA1c From Month 6 to Month 9
End point description:	
Substudy comparing fixed dosing regimen (every 24 hours) vs. adaptive dosing regimen (every 24 +/- 3 hours) in a subset of subjects randomized to HOE901-U300 and treated for 6 months. mITT substudy population. Number of subjects analyzed = subjects with Month 6 and Month 9 HbA1c assessment. Analysis was planned to be performed for subjects enrolled in the substudy and who were receiving HOE901-U300 (Adaptable dosing intervals or Fixed dosing intervals).	
End point type	Other pre-specified
End point timeframe:	
Month 6 Up to Month 9	

End point values	HOE901-U300: Adaptable Dosing Intervals	HOE901-U300: Fixed Dosing Intervals		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	51		
Units: percentage of hemoglobin				
least squares mean (standard error)	0.21 ($\pm$ 0.111)	0.15 ($\pm$ 0.12)		

Statistical analyses

Statistical analysis title	HOE901-U300: Adaptable vs Fixed Dosing
Statistical analysis description:	
Analysis was performed using Analysis of covariance (ANCOVA) model with treatment regimen and country as fixed effects and baseline HbA1c value as a covariate.	
Comparison groups	HOE901-U300: Fixed Dosing Intervals v HOE901-U300: Adaptable Dosing Intervals

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.189
upper limit	0.298
Variability estimate	Standard error of the mean
Dispersion value	0.123

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to 12 months regardless of seriousness or relationship to investigational product.

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 the first injection of study drug up to 2 days (1 day for FPG, SMPG; 0 day for insulin glargine dose) after the last injection of study drug). Analysis was done on safety population.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	Lantus
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Reporting group description:

Lantus for 12 months on top of mealtime insulin analogue.

Reporting group title	HOE901-U300
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Reporting group description:

HOE901-U300 for 12 months on top of mealtime insulin analogue.

Serious adverse events	Lantus	HOE901-U300	
Total subjects affected by serious adverse events			
subjects affected / exposed	62 / 402 (15.42%)	53 / 404 (13.12%)	
number of deaths (all causes)	4	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-Cell Small Lymphocytic Lymphoma			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal Cell Carcinoma			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder Cancer			

subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast Angiosarcoma			
subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast Cancer			
subjects affected / exposed	0 / 402 (0.00%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Myeloid Leukaemia			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial Cancer			
subjects affected / exposed	1 / 402 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Cancer			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma Benign			
subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic Bronchial Carcinoma			
subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Prostate Cancer			

subjects affected / exposed	1 / 402 (0.25%)	3 / 404 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma Of Skin			
subjects affected / exposed	3 / 402 (0.75%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Leiomyoma			
subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Accelerated Hypertension			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic Stenosis			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extremity Necrosis			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermittent Claudication			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (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 / 402 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Immune system disorders			
Anaphylactic Reaction			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (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			
Metrorrhagia			
subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postmenopausal Haemorrhage			
subjects affected / exposed	1 / 402 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 402 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea Exertional			
subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic Pulmonary Fibrosis			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			

subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Abdominal Wound Dehiscence			
subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Airway Complication Of Anaesthesia			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle Fracture			
subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 402 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral Neck Fracture			
subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head Injury			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus Fracture			

subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus Injury			
subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural Pain			
subjects affected / exposed	0 / 402 (0.00%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural Haematoma			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (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	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity To Various Agents			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Pectoris			
subjects affected / exposed	2 / 402 (0.50%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Unstable			

subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic Valve Stenosis			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	3 / 402 (0.75%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle Branch Block Left			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			
subjects affected / exposed	1 / 402 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Chronic			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	1 / 402 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-Respiratory Arrest			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary Artery Disease			

subjects affected / exposed	1 / 402 (0.25%)	3 / 404 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			
subjects affected / exposed	1 / 402 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial Ischaemia			
subjects affected / exposed	1 / 402 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulseless Electrical Activity			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular Tachycardia			
subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered State Of Consciousness			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (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	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Accident			

subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervicobrachial Syndrome			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre Syndrome			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (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	0 / 402 (0.00%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
subjects affected / exposed	1 / 402 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Diverticulitis Intestinal Haemorrhagic			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 402 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile Duct Stone			
subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis Acute			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (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 / 402 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin Ulcer Haemorrhage			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Diabetic Nephropathy			

subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure Acute			
subjects affected / exposed	1 / 402 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure Chronic			
subjects affected / exposed	3 / 402 (0.75%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary Bladder Polyp			
subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			

subjects affected / exposed	1 / 402 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain In Extremity			
subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 402 (0.00%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylitis			
subjects affected / exposed	1 / 402 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial Cyst			
subjects affected / exposed	1 / 402 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 402 (0.00%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 402 (0.00%)	2 / 404 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cellulitis			
subjects affected / exposed	1 / 402 (0.25%)	3 / 404 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			

subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 402 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 402 (0.50%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin Abscess			
subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected Skin Ulcer			
subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lyme Disease			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	2 / 402 (0.50%)	3 / 404 (0.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	3 / 402 (0.75%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Mycoplasmal			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (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 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis Acute			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 402 (0.25%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic Embolus			
subjects affected / exposed	0 / 402 (0.00%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes Mellitus Inadequate Control			

subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (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 / 402 (0.50%)	1 / 404 (0.25%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactose Intolerance			
subjects affected / exposed	1 / 402 (0.25%)	0 / 404 (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	132 / 402 (32.84%)	131 / 404 (32.43%)	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	21 / 402 (5.22%)	22 / 404 (5.45%)	
occurrences (all)	26	25	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	21 / 402 (5.22%)	13 / 404 (3.22%)	
occurrences (all)	24	14	
Infections and infestations			
Bronchitis			
subjects affected / exposed	30 / 402 (7.46%)	23 / 404 (5.69%)	
occurrences (all)	37	24	
Influenza			

subjects affected / exposed	18 / 402 (4.48%)	22 / 404 (5.45%)	
occurrences (all)	20	23	
Nasopharyngitis			
subjects affected / exposed	36 / 402 (8.96%)	34 / 404 (8.42%)	
occurrences (all)	42	43	
Sinusitis			
subjects affected / exposed	15 / 402 (3.73%)	21 / 404 (5.20%)	
occurrences (all)	18	26	
Upper Respiratory Tract Infection			
subjects affected / exposed	34 / 402 (8.46%)	38 / 404 (9.41%)	
occurrences (all)	43	51	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2011	- Change of the definition of "nocturnal hypoglycemia" for the analysis of the first main secondary endpoint in order to exclude self-reported non-severe hypoglycemia episodes that were not confirmed by plasma glucose data. - Further clarification in dosing instructions for the mealtime insulin. - Replacement of the e-diary by a paper diary. - Clarification to "Secondary objectives" - "treatment satisfaction" was assessed and not "quality of life". - Minor corrections in study Flowchart. - Criterion of half-life of the prior investigational product added. - Harmonize the visit periods across the protocol. - Updated the definition of the safety endpoint of the local tolerability. - Explicit instruction that phone visits were to be conducted by the Investigator or qualified designee. However, the Investigator had to be consulted always when an adverse event was suspected.
11 July 2012	- Change to the definition of "nocturnal hypoglycemia" for the analysis of the first main secondary endpoint by applying a tighter time window for nocturnal hypoglycemia. - Change to visits number by addition of two phone visits during the 6-month safety extension period. - Change to the scope of data recorded into the e-CRF upon phone call visits. - Change to the reasons justifying prolongation of the screening period of one additional week. - Change to the reasons justifying re-screening. - Change to the requirements concerning return of unused investigational medicinal product (IMP) at on-site visits where IMP dispensation was scheduled, clarification on drug accountability and compliance. - Clarification of inconsistency in instructions for subject's position during blood pressure and heart rate measurements. - Explanation that for calculation of the IMP starting dose, median value of last 3 fasting self-monitored plasma glucose (SMPG) prior to the baseline visit were also be taken into account. - Clarification to safety endpoints. - Addition of symptomatic overdose with non-investigational medicinal product (NIMP) to adverse event of special interest (AESI) with immediate notification. - Clarification regarding potential change of fast-acting mealtime insulin analog. - Change to the timelines for reporting of serious adverse events (SAEs) by the Investigator.
02 August 2012	- Protocol for a substudy to compare the efficacy and safety of HOE901-U300 injected once daily every 24 hours and HOE901-U300 injected once daily at intervals of 24±3 hours in subjects randomized and treated with HOE901-U300 during the 6-month on-treatment period (starting at baseline and ending Month 6).
21 March 2013	- Addition of an independent review of all hypoglycemia events reported by the Investigator as severe and/or reported as SAEs by a Severe Hypoglycemia Review Board (SHRB) blinded to treatment arm.
25 April 2013	- Change to study periods - a 4-week follow-up period was added in order to gain data about the switch from HOE901-U300 to a marketed basal insulin.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported