



## 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 in Combination With Oral Antihyperglycemic Drug(s) in Subjects With Type 2 Diabetes Mellitus With a 6 Month Safety Extension Period

#### Summary

EudraCT number	2010-023770-39
Trial protocol	DE PT ES HU FI
Global end of trial date	22 November 2013

#### Results information

Result version number	v1 (current)
This version publication date	05 April 2016
First version publication date	14 June 2015

#### Trial information

##### Trial identification

Sponsor protocol code	EFC11629
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01499095
WHO universal trial number (UTN)	U1111-1118-6943

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	10 January 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	22 November 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 Glycated Hemoglobin A1c (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	14 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	Spain: 30
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 28
Country: Number of subjects enrolled	Germany: 24
Country: Number of subjects enrolled	Hungary: 34
Country: Number of subjects enrolled	Mexico: 61
Country: Number of subjects enrolled	Russian Federation: 91
Country: Number of subjects enrolled	South Africa: 12
Country: Number of subjects enrolled	Chile: 61
Country: Number of subjects enrolled	Canada: 47
Country: Number of subjects enrolled	Romania: 100
Country: Number of subjects enrolled	United States: 322
Worldwide total number of subjects	811
EEA total number of subjects	217

Notes:

<b>Subjects enrolled per age group</b>	
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)	621
From 65 to 84 years	190
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

A total of 1250 subjects were screened, of whom 439 subjects were screen failure and 811 subject were randomized.

### Pre-assignment

Screening details:

Following the main 6 month treatment period, eligible subject 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
<b>Arm title</b>	HOE901-U300

Arm description:

HOE901-U300 for 12 months in combination with oral antidiabetic 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]). 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.

<b>Arm title</b>	Lantus
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Arm description:

Lantus (HOE901-U100) for 12 months in combination with oral antidiabetic drug(s).

Arm type	Active comparator
Investigational medicinal product name	Insulin glargine
Investigational medicinal product code	HOE901-U100
Other name	
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).

<b>Number of subjects in period 1</b>	HOE901-U300	Lantus
Started	404	407
Treated	403	406
Participated in Substudy	89 <sup>[1]</sup>	0 <sup>[2]</sup>
Modified Intent-to-Treat Population	403	405
Completed	315	314
Not completed	89	93
Lack of Efficacy	2	1
Received Rescue Therapy	32	40
Adverse Event	12	7
Perceived Lack of Efficacy	1	1
Lost to Follow-up	6	4
Diverse Reasons	22	25
Insulin Dropped Below Authorized Dose	-	5
Protocol Violation	6	7
Randomized But Not Treated	1	1
Hypoglycemia	3	1
Change in Injection Schedule	2	-
Diagnosed With Type 1 Diabetes Mellitus	2	1

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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: 89 subjects participated in the substudy (45 subjects received adaptable dosing regimen and 44 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 in combination with oral antidiabetic drug(s).	
Reporting group title	Lantus
Reporting group description: Lantus (HOE901-U100) for 12 months in combination with oral antidiabetic drug(s).	

Reporting group values	HOE901-U300	Lantus	Total
Number of subjects	404	407	811
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	57.9 ± 9.1	58.5 ± 9.2	-
Gender categorical Units: Subjects			
Female	217	222	439
Male	187	185	372
Glycated Hemoglobin A1c (HbA1c) Units: Subjects			
Less Than (<) 8%	144	146	290
Greater Than or Equal to (>=) 8%	260	261	521
Body Mass Index (BMI) Units: kilogram per square meter arithmetic mean standard deviation	34.8 ± 6.6	34.8 ± 6.1	-
Duration of Diabetes			
Number of subjects analyzed for this baseline characteristics = 403 and 407 in HOE901--U300 and Lantus arm, respectively.			
Units: years median full range (min-max)	11.6 1 to 54	11.7 1 to 51	-
Basal Insulin Daily Dose			
Number of subjects analyzed for this baseline characteristics = 378 and 382 in HOE901-U300 and Lantus arm, respectively.			
Units: units per kilogram arithmetic mean standard deviation	0.66 ± 0.221	0.681 ± 0.253	-

## End points

### End points reporting groups

Reporting group title	HOE901-U300
Reporting group description: HOE901-U300 for 12 months in combination with oral antidiabetic drug(s).	
Reporting group title	Lantus
Reporting group description: Lantus (HOE901-U100) for 12 months in combination with oral antidiabetic drug(s).	
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 in combination with oral antidiabetic drug(s). 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 12 months in combination with of oral antidiabetic drug(s). 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: Only measurements performed before initiation of rescue therapy were considered in the analysis. Modified Intent-to-Treat population: all randomized subjects who received at least ( $\geq$ ) 1 dose, had baseline and $\geq 1$ 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	386	392		
Units: percentage of hemoglobin				
least squares mean (standard error)	-0.57 ( $\pm$ 0.094)	-0.56 ( $\pm$ 0.093)		

### 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	778
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[1]</sup>
Parameter estimate	Least Squares (LS) Mean difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.139
upper limit	0.119
Variability estimate	Standard error of the mean
Dispersion value	0.066

Notes:

[1] - Stepwise closed testing approach was 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 subjects 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 mmol/L (70 milligram per deciliter [mg/dL]). Only measurements performed before initiation of rescue therapy were considered in the analysis. 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	403	405		
Units: percentage of subjects				
number (not applicable)	21.6	27.9		

### 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
Number of subjects included in analysis	808
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.038
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	0.99

### 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:	Preinjection 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. Only measurements performed before initiation of rescue therapy were considered in the analysis. mITT population. Missing data imputed using last observation carried forward. Number of subjects analyzed = subjects with baseline and Month 6 preinjection 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	353	350		
Units: mmol/L				
least squares mean (standard error)	-0.56 (± 0.278)	-0.51 (± 0.275)		

### Statistical analyses

Statistical analysis title	HOE901-U300 vs Lantus
Statistical analysis description:	Change in pre-injection SMPG was analysed 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 hypoglycaemia was significant.
Comparison groups	Lantus v HOE901-U300

Number of subjects included in analysis	703
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8279
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.438
upper limit	0.35
Variability estimate	Standard error of the mean
Dispersion value	0.201

### 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:	Preinjection SMPG was measured within 30 minutes prior to the injection of the study drug. Variability was assessed by the mean of co-efficient 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 measurements performed before initiation of rescue therapy were considered in the analysis. mITT population. Missing data imputed using last observation carried forward. Number of subjects analyzed = subjects with baseline and Month 6 preinjection 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	353	350		
Units: percentage of mean				
least squares mean (standard error)	-2.34 (± 1.425)	-0.53 (± 1.408)		

### 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:	Only measurements performed before initiation of rescue therapy were considered in the analysis. mITT Population. Number of subjects analyzed = subjects with Month 6 HbA1c assessment. Missing data

imputed using last observation carried forward.

End point type	Secondary
End point timeframe:	
Month 6	

<b>End point values</b>	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	386	392		
Units: percentage of subjects				
number (not applicable)	30.6	30.4		

### 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:

Only measurements performed before initiation of rescue therapy were considered in the analysis. mITT Population. Number of subjects analyzed = subject 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

<b>End point values</b>	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	375	379		
Units: mmol/L				
least squares mean (standard error)	-1.03 (± 0.242)	-1.21 (± 0.241)		

### 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:

Only measurements performed before initiation of rescue therapy were considered in the analysis. mITT Population. Number of subjects analyzed = subjects with Month 6 FPG assessment. Missing data imputed using last observation carried forward.

End point type	Secondary
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End point timeframe:

Month 6

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	384	390		
Units: percentage of subjects				
number (not applicable)	29.4	33.6		

## 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
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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. Only measurements performed before initiation of rescue therapy were considered in the analysis. mITT population. Only subjects from the mITT population with a value at baseline and at the specified timepoint were analyzed (represented by n=X, X in the category titles). 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	403	405		
Units: mmol/L				
least squares mean (standard error)				
03:00 at Night (n= 338, 328)	-0.56 (± 0.323)	-0.9 (± 0.321)		
Pre-breakfast (n= 347, 338)	-1.31 (± 0.221)	-1.81 (± 0.219)		
2 hours after breakfast (n= 341, 328)	-1.41 (± 0.331)	-1.82 (± 0.329)		
Pre-lunch (n= 344, 332)	-0.64 (± 0.3)	-1.12 (± 0.298)		

2 hours after lunch (n= 339, 328)	-1.02 (± 0.342)	-1.04 (± 0.34)		
Pre-dinner (n=347, 336)	-0.94 (± 0.327)	-0.69 (± 0.324)		
2 hours after dinner (n= 338, 327)	-0.69 (± 0.359)	-1 (± 0.357)		
Bedtime (n= 325, 303)	-0.99 (± 0.345)	-1 (± 0.343)		

## 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:	Only measurements performed before initiation of rescue therapy were considered in the analysis. 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	402	403		
Units: U/kg				
least squares mean (standard error)	0.28 (± 0.021)	0.17 (± 0.021)		

## 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. Only measurements performed before initiation of rescue therapy were considered in the analysis. 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	346	359		
Units: units on a scale				
least squares mean (standard error)	3.05 ( $\pm$ 0.448)	3.61 ( $\pm$ 0.44)		

## 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
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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	403	406		
Units: percentage of subjects				
number (not applicable)				
Any Hypoglycemia Event: All Hypoglycemia	79.9	83		
Severe Hypoglycemia: All Hypoglycemia	1.7	1.5		
Documented Symptomatic: All Hypoglycemia	58.8	63.3		
Asymptomatic: All Hypoglycemia	58.6	64		
Probable Symptomatic: All Hypoglycemia	2.7	3.4		
Relative: All Hypoglycemia	7.9	12.8		

Severe and/or Confirmed: All Hypoglycemia	78.4	82		
Any Hypoglycemia Event: Nocturnal Hypoglycemia	39.7	46.1		
Severe Hypoglycemia: Nocturnal Hypoglycemia	0.2	0.5		
Documented Symptomatic: Nocturnal Hypoglycemia	29.5	34.2		
Asymptomatic: Nocturnal Hypoglycemia	14.4	22.2		
Probable Symptomatic: Nocturnal Hypoglycemia	1.2	1		
Relative: Nocturnal Hypoglycemia	2.2	6.4		
Severe and/or Confirmed: Nocturnal Hypoglycemia	37.5	44.6		

## 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. Only measurements performed before initiation of rescue therapy were considered in the analysis. mITT substudy population. Number of subjects analyzed = subjects with Month 6 and Month 9 HbA1c assessment. Analysis was planned to be performed for subjects who were receiving HOE901-U300 (Adaptable dosing intervals or Fixed dosing intervals). Missing data imputed using last observation carried forward.	
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	40	37		
Units: percentage of hemoglobin				
least squares mean (standard error)	-0.12 (± 0.151)	-0.25 (± 0.162)		

## 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 (Month 6) HbA1c value as a covariate.	

Comparison groups	HOE901-U300: Adaptable Dosing Intervals v HOE901-U300: Fixed Dosing Intervals
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Least squares mean difference
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.152
upper limit	0.415
Variability estimate	Standard error of the mean
Dispersion value	0.142



## 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
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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	HOE901-U300
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Reporting group description:

HOE901-U300 for 12 months in combination with oral antidiabetic drug(s).

Reporting group title	Lantus
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Reporting group description:

Lantus (HOE901-U100) for 12 months in combination with oral antidiabetic drug(s).

Serious adverse events	HOE901-U300	Lantus	
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 403 (7.44%)	30 / 406 (7.39%)	
number of deaths (all causes)	3	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive Lobular Breast Carcinoma			
subjects affected / exposed	2 / 403 (0.50%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant Melanoma			
subjects affected / exposed	0 / 403 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic Syndrome			
subjects affected / exposed	1 / 403 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Oesophageal Adenocarcinoma Stage Iv			
subjects affected / exposed	1 / 403 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Papillary Thyroid Cancer			
subjects affected / exposed	1 / 403 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue Neoplasm Malignant Stage Unspecified			
subjects affected / exposed	0 / 403 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Angiopathy			
subjects affected / exposed	1 / 403 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 403 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	1 / 403 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 403 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	1 / 403 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 403 (0.00%)	1 / 406 (0.25%)	
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			
Contusion			
subjects affected / exposed	1 / 403 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroparesis Postoperative			
subjects affected / exposed	1 / 403 (0.25%)	0 / 406 (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 / 403 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament Rupture			
subjects affected / exposed	0 / 403 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post Procedural Haematoma			
subjects affected / exposed	1 / 403 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative Wound Complication			
subjects affected / exposed	1 / 403 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Acute Myocardial Infarction			
subjects affected / exposed	2 / 403 (0.50%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Angina Pectoris			
subjects affected / exposed	0 / 403 (0.00%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Unstable			
subjects affected / exposed	1 / 403 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Disorder			
subjects affected / exposed	1 / 403 (0.25%)	0 / 406 (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 / 403 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	1 / 403 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular Disorder			
subjects affected / exposed	1 / 403 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Disease			
subjects affected / exposed	1 / 403 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial Infarction			

subjects affected / exposed	2 / 403 (0.50%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nodal Rhythm			
subjects affected / exposed	0 / 403 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular Tachycardia			
subjects affected / exposed	0 / 403 (0.00%)	1 / 406 (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			
Cerebrospinal Fluid Leakage			
subjects affected / exposed	1 / 403 (0.25%)	0 / 406 (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 / 403 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 403 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Stroke			
subjects affected / exposed	0 / 403 (0.00%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Lower Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 403 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Acute			

subjects affected / exposed	0 / 403 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis Acute			
subjects affected / exposed	0 / 403 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder Polyp			
subjects affected / exposed	0 / 403 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin Ulcer			
subjects affected / exposed	0 / 403 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	1 / 403 (0.25%)	0 / 406 (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			
Calculus Urinary			
subjects affected / exposed	0 / 403 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure Acute			
subjects affected / exposed	0 / 403 (0.00%)	1 / 406 (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			
Back Pain			

subjects affected / exposed	1 / 403 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral Disc Degeneration			
subjects affected / exposed	1 / 403 (0.25%)	0 / 406 (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	0 / 403 (0.00%)	1 / 406 (0.25%)	
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	1 / 403 (0.25%)	0 / 406 (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			
Bronchitis			
subjects affected / exposed	0 / 403 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 403 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Sinusitis			
subjects affected / exposed	1 / 403 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Echinococcosis			
subjects affected / exposed	0 / 403 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected Bites			

subjects affected / exposed	0 / 403 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised Infection			
subjects affected / exposed	0 / 403 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 403 (0.00%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis Chronic			
subjects affected / exposed	0 / 403 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Superinfection			
subjects affected / exposed	1 / 403 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculous Pleurisy			
subjects affected / exposed	0 / 403 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 403 (0.00%)	1 / 406 (0.25%)	
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	2 / 403 (0.50%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound Infection			



subjects affected / exposed	1 / 403 (0.25%)	0 / 406 (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			
Hypoglycaemia			
subjects affected / exposed	1 / 403 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obesity			
subjects affected / exposed	0 / 403 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	HOE901-U300	Lantus	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	106 / 403 (26.30%)	96 / 406 (23.65%)	
Nervous system disorders			
Headache			
subjects affected / exposed	27 / 403 (6.70%)	20 / 406 (4.93%)	
occurrences (all)	45	26	
Infections and infestations			
Bronchitis			
subjects affected / exposed	25 / 403 (6.20%)	23 / 406 (5.67%)	
occurrences (all)	31	26	
Nasopharyngitis			
subjects affected / exposed	49 / 403 (12.16%)	31 / 406 (7.64%)	
occurrences (all)	63	37	
Upper Respiratory Tract Infection			
subjects affected / exposed	23 / 403 (5.71%)	35 / 406 (8.62%)	
occurrences (all)	25	45	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2011	<ul style="list-style-type: none"><li>- 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.</li><li>- Replacement of the e-diary by a paper diary.</li><li>- Clarification to "Secondary objectives" - "treatment satisfaction" was assessed and not "quality of life".</li><li>- Minor corrections in study Flowchart.</li><li>- Update in the exclusion criterion - criterion of half-live of the prior investigational product added.</li><li>- Harmonize the visit periods across the protocol.</li><li>- Update of 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.</li></ul> <p>However, the Investigator had to be consulted always when an adverse event was suspected.</p>
11 July 2012	<ul style="list-style-type: none"><li>- 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.</li><li>- Change to visits number by addition of 2 phone visits during the 6-month safety extension period.</li><li>- Reduction of the number of mandatory 4-point profiles required to be done by the subjects.</li><li>- Change to the scope of data recorded into the electronic case report form upon phone call visits.</li><li>- Change to the reasons justifying prolongation of the screening period of one additional week.</li><li>- Change to the reasons justifying re-screening.</li><li>- Change to the requirements concerning return of unused study drug at on-site visits where study drug dispensation was scheduled, clarification on drug accountability and compliance.</li><li>- Clarification of inconsistency in instructions for subject's position during blood pressure and heart rate measurements.</li><li>- Explanation that for calculation of the study drug starting dose, median value of last 3 fasting SMPG prior to the baseline visit were also be taken into account.</li><li>- Clarification to safety endpoints.</li><li>- Addition of symptomatic overdose with non-study drug to adverse event of special interest with immediate notification.</li><li>- Change to the timelines for reporting of serious adverse events by the Investigator.</li></ul>
02 August 2012	Protocol for a 3-month administration sub study to compare the efficacy and safety of HOE901-U300 injected once daily every 24 hours and HOE901-U300 injected once daily at intervals of $24\pm 3$ 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 serious adverse events by a Severe Hypoglycemia Review Board 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:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported