Clinical trial results:
A Randomized, Open-label, 2-arm Parallel-group, Multicenter, 26-week Study Assessing the Safety and Efficacy of H0E901-U300 Versus Lantus in Older Patients with Type 2 Diabetes Inadequately Controlled on Antidiabetic Regimens Either Including no Insulin, or with Basal Insulin as Their Only Insulin

Summary

EudraCT number	2014-002399-10
Trial protocol	SE HU DE ES IT GB PL
Global end of trial date	20 May 2016

Results information

Result version number	v1 (current)
This version publication date	03 June 2017
First version publication date	03 June 2017

Trial information

Trial identification

Sponsor protocol code	EFC13799

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02320721
WHO universal trial number (UTN)	U1111-1159-3018
Other trial identifiers	Study Name: SENIOR

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 September 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority of H0E901-U300 to Lantus, in change of glycated hemoglobin A1c (HbA1c) from baseline to Week 26.

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 was 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:

Non-insulin antidiabetic drugs, except thiazolidinediones taken at a stable dose for at least 8 weeks prior to the screening visit might be continued. Doses were to be kept stable throughout the study unless there were safety concerns.

Evidence for comparator: -

Actual start date of recruitment	16 January 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 35
Country: Number of subjects enrolled	Australia: 35
Country: Number of subjects enrolled	Canada: 92
Country: Number of subjects enrolled	Colombia: 16
Country: Number of subjects enrolled	Japan: 19
Country: Number of subjects enrolled	Korea, Republic of: 25
Country: Number of subjects enrolled	Mexico: 37
Country: Number of subjects enrolled	Peru: 71
Country: Number of subjects enrolled	United States: 367
Country: Number of subjects enrolled	Poland: 51
Country: Number of subjects enrolled	Romania: 39
Country: Number of subjects enrolled	Spain: 80
Country: Number of subjects enrolled	Sweden: 33
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	France: 8

Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Hungary: 50
Country: Number of subjects enrolled	Italy: 26
Worldwide total number of subjects	1014
EEA total number of subjects	317

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)	0
From 65 to 84 years	1005
85 years and over	9

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 162 study centers across 18 countries. A total of 1515 subjects were screened between 16 January 2015 and 14 October 2015, of whom 501 were screen failures.

Pre-assignment

Screening details:

A total of 1014 subjects were randomized in 1:1 ratio to either HOE901-U300 or Lantus, stratified by screening hemoglobin A1c (HbA1c) values (<8% or ≥8%); previous use of insulin (insulin-naïve versus pre-treated); and use of sulfonylurea or meglitinides at screening (’yes’ versus ‘no’).

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 (Insulin glargine, 300 U/mL) subcutaneous (SC) injection once daily up to Week 26 on top of stable non-insulin antihyperglycemic therapy.

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

Dosage and administration details:

Self-administered by SC injection in the evening using a pre-filled pen. Dose titration to achieve fasting self-monitored plasma glucose (SMPG) from 90 to 130 mg/dL (5.0 to 7.2 mmol/L).

Arm title	Lantus

Arm description:

Lantus (Insulin glargine, 100 U/mL) SC injection once daily up to Week 26 on top of stable non-insulin antihyperglycemic therapy.

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

Dosage and administration details:

Self-administered by SC injection in the evening using a pre-filled pen. Dose titration to achieve fasting SMPG from 90 to 130 mg/dL (5.0 to 7.2 mmol/L).

Number of subjects in period 1	HOE901-U300	Lantus
Started	508	506
Treated (Safety Population)	508	505
Completed	481	472
Not completed	27	34
Randomized but not treated	-	1
Poor Compliance to protocol	3	7
Adverse event	6	6
Other than specified	15	20
Hypoglycemia	1	-
Lack of efficacy	2	-

Baseline characteristics

Reporting groups	
Reporting group title	HOE901-U300
Reporting group description:	
HOE901-U300 (Insulin glargine, 300 U/mL) subcutaneous (SC) injection once daily up to Week 26 on top of stable non-insulin antihyperglycemic therapy.	
Reporting group title	Lantus
Reporting group description:	
Lantus (Insulin glargine, 100 U/mL) SC injection once daily up to Week 26 on top of stable non-insulin antihyperglycemic therapy.	

Reporting group values	HOE901-U300	Lantus	Total
Number of subjects	508	506	1014
Age categorical			
Units: Subjects			
<75 years of age	373	400	773
≥75 years of age	135	106	241
Age continuous			
Units: years			
arithmetic mean	71.1	70.8	
standard deviation	± 4.9	± 4.8	-
Gender categorical			
Units: Subjects			
Female	258	229	487
Male	250	277	527
Randomization strata of insulin			
Units: Subjects			
Insulin-naive	166	165	331
Insulin pre-treated	342	341	683
Body Mass Index (BMI)			
Measure Analysis Population Description: Number of subjects analyzed = subjects with available data for this baseline measure.			
Units: kg/m^2			
arithmetic mean	30.9	31.2	
standard deviation	± 5.5	± 5.7	-
Duration of Type 2 Diabetes			
Units: years			
arithmetic mean	15.29	15.35	
standard deviation	± 8.17	± 7.7	-
Baseline Glycated Hemoglobin A1c (HbA1c)			
Units: percentage of HbA1c			
arithmetic mean	8.2	8.22	
standard deviation	± 0.91	± 0.92	-

End points

End points reporting groups

Reporting group title	HOE901-U300
Reporting group description:	
HOE901-U300 (Insulin glargine, 300 U/mL) subcutaneous (SC) injection once daily up to Week 26 on top of stable non-insulin antihyperglycemic therapy.	
Reporting group title	Lantus
Reporting group description:	
Lantus (Insulin glargine, 100 U/mL) SC injection once daily up to Week 26 on top of stable non-insulin antihyperglycemic therapy.	

Primary: Change in HbA1c From Baseline to Week 26

End point title	Change in HbA1c From Baseline to Week 26
End point description:	
Adjusted least square (LS) means were obtained from analysis of covariance (ANCOVA) after multiple imputation of missing data including post baseline HbA1c data during the 26-week randomized period. Intent-to-treat (ITT) population included all randomized subjects regardless of whether the treatment kit was used, and analyzed according to the treatment group allocated by randomization.	
End point type	Primary
End point timeframe:	
Baseline, Week 26	

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	508	506		
Units: percentage of hemoglobin				
least squares mean (standard error)	-0.89 (± 0.038)	-0.91 (± 0.042)		

Statistical analyses

Statistical analysis title	HOE901-U300, Lantus
Statistical analysis description:	
Analysis was performed using ANCOVA model including the fixed categorical effects of treatment group, randomization strata, as well as the continuous fixed covariates of baseline value and following multiple imputation procedure for missing data.	
Comparison groups	HOE901-U300 v Lantus

Number of subjects included in analysis	1014
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	LS Mean Difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.092
upper limit	0.129
Variability estimate	Standard error of the mean
Dispersion value	0.056

Notes:

[1] - Non-inferiority of HOE901-U300 vs Lantus was demonstrated if the upper bound of the two-sided 95% confidence interval (CI) for the difference between groups was <0.3%.

Secondary: Percentage of Subjects With At Least One Severe and/ or Confirmed (≤3.9 mmol/L [70 mg/dL]) Nocturnal Hypoglycemia (22:00 to 08:59 Hours Next Morning) During 26-Week Randomized Period

End point title	Percentage of Subjects With At Least One Severe and/ or Confirmed (≤3.9 mmol/L [70 mg/dL]) Nocturnal Hypoglycemia (22:00 to 08:59 Hours Next Morning) During 26-Week Randomized Period

End point description:

Estimated percentages from multiple imputation approach including data from the 26-week randomized period. 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 ≤3.9 mmol/L (70 mg/dL). ITT population.

End point type	Secondary

End point timeframe:

Baseline up to Week 26

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	508	506		
Units: percentage of subjects				
number (not applicable)	48.3	47.7		

Statistical analyses

Statistical analysis title	HOE901-U300, Lantus

Statistical analysis description:

Analysis was done by Cochran-Mantel-Haenszel method with randomization strata (screening HbA1c [<8.0%; ≥8.0%], previous use of insulin [naive, pre-treated], use of sulfonylurea or meglitinides at screening [yes, no]), following multiple imputation procedure for missing data.

Comparison groups	HOE901-U300 v Lantus

Number of subjects included in analysis	1014
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.8415 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative risk
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.153

Notes:

[2] - A hierarchical testing procedure was used to control type I error and handle multiple endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only if previous endpoint was statistically significant at 0.05 level.

[3] - Threshold for significance at 0.05 level.

Secondary: Percentage of Subjects With At Least One Severe and/ or Confirmed (≤3.9 mmol/L [70 mg/dL]) Nocturnal Hypoglycemia (00:00 to 05:59 Hours) During 26-Week Randomized Period

End point title	Percentage of Subjects With At Least One Severe and/ or Confirmed (≤3.9 mmol/L [70 mg/dL]) Nocturnal Hypoglycemia (00:00 to 05:59 Hours) During 26-Week Randomized Period

End point description:

Estimated percentages from multiple imputation approach including data from the 26-week randomized period. 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 ≤3.9 mmol/L (70 mg/dL). ITT population.

End point type	Secondary

End point timeframe:

Baseline up to Week 26

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	508	506		
Units: percentage of subjects				
number (not applicable)	20.2	22.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With At Least One Severe and/ or Confirmed (≤3.9 mmol/L [70 mg/dL]) Hypoglycemia Occurring at Any Time of the Day During 26-Week Randomized Period

End point title	Percentage of Subjects With At Least One Severe and/ or Confirmed (≤3.9 mmol/L [70 mg/dL]) Hypoglycemia Occurring at Any Time of the Day During 26-Week Randomized Period

End point description:

Estimated percentages from multiple imputation approach including data from the 26-week randomized period. 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 ≤3.9 mmol/L (70 mg/dL). ITT population.

End point type	Secondary

End point timeframe:

Baseline up to Week 26

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	508	506		
Units: percentage of subjects				
number (not applicable)	59.4	62.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With HbA1c <7.5% or HbA1c <7% During 26-Week Randomized Period

End point title	Percentage of Subjects With HbA1c <7.5% or HbA1c <7% During 26-Week Randomized Period

End point description:

Subjects without any available HbA1c assessment at Week 26 were considered as non-responders in the analyses. ITT population.

End point type	Secondary

End point timeframe:

Baseline up to Week 26

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	508	506		
Units: percentage of subjects				
number (not applicable)				
HbA1c <7.5%	60.6	58.9		
HbA1c <7.0%	33.3	35.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With HbA1c <7.5% or <7.0% at Week 26 and No Severe and/or Confirmed (≤3.9 mmol/L [70 mg/dL]) Hypoglycemia During 26-Week Randomized Period

End point title	Percentage of Subjects With HbA1c <7.5% or <7.0% at Week 26 and No Severe and/or Confirmed (≤3.9 mmol/L [70 mg/dL]) Hypoglycemia During 26-Week Randomized Period

End point description:

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 ≤3.9 mmol/L (70 mg/dL). ITT population.

End point type	Secondary

End point timeframe:

Baseline up to Week 26

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	508	506		
Units: percentage of subjects				
number (not applicable)				
HbA1c <7.5%	26.4	21.5		
HbA1c <7.0%	14	12.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Fasting Plasma Glucose (FPG) From Baseline to Week 26

End point title	Change in Fasting Plasma Glucose (FPG) From Baseline to Week 26

End point description:

Adjusted LS means from multiple imputation approach including post baseline values during the 26-week randomized period. ITT population. Here 'number of subjects analysed' signifies subjects with available data for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	484	482		
Units: mmol/L				
least squares mean (standard error)	-1.68 (± 0.122)	-1.77 (± 0.135)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in World Health Organization-5 (WHO-5) Well-Being Questionnaire Percentage Score From Baseline to Week 26

End point title	Change in World Health Organization-5 (WHO-5) Well-Being Questionnaire Percentage Score From Baseline to Week 26

End point description:

WHO-5 well-being index evaluates positive psychological well-being during the past 2 weeks and consists of 5 questions, each rated on a 6-point Likert scale from 0 (not present) to 5 (constantly present). Total raw score was transformed into a percentage score ranging from 0 (worst possible quality of life) to 100 (best possible quality of life). ITT population. Here 'number of subjects analysed' signifies subjects with available data for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	484	476		
Units: scores on a scale				
least squares mean (standard error)	-1.16 (± 0.751)	0.22 (± 0.758)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Requiring Rescue Therapy Over the 26 Weeks of Treatment

End point title	Percentage of Subjects Requiring Rescue Therapy Over the 26 Weeks of Treatment

End point description:

Routine fasting self-monitored plasma glucose (SMPG) and central laboratory FPG (and HbA1c after Week 14) values were used to determine the requirement of rescue medication. Threshold values at Week 14: FPG >200 mg/dL (11 mmol/L), or HbA1c >8.5%. ITT population.

End point type	Secondary

End point timeframe:

Baseline up to Week 26

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	508	506		
Units: percentage of subjects				
number (not applicable)	3.7	2.6		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects With Hypoglycemia (Any Hypoglycemia, Documented Symptomatic Hypoglycemia, Severe and/or Confirmed Hypoglycemia) During the 26 Weeks of Treatment

End point title	Percentage of Subjects With Hypoglycemia (Any Hypoglycemia, Documented Symptomatic Hypoglycemia, Severe and/or Confirmed Hypoglycemia) During the 26 Weeks of Treatment

End point description:

Hypoglycemia events were hypoglycemia of any category, severe hypoglycemia (an event that required assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions); documented symptomatic hypoglycemia (symptoms of hypoglycemia with plasma glucose ≤3.9 mmol/L [70 mg/dL]); confirmed hypoglycemia (with or without symptoms of hypoglycemia and plasma glucose ≤3.9 mmol/L). Safety population included all randomized subjects who actually received at least 1 dose or part of a dose of investigational medicinal product (IMP) and analyzed according to the treatment actually received. Here 'n' signifies number of subjects evaluable for this end point in the specified categories.

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 26

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	508	505		
Units: percentage of subjects				
number (not applicable)				
Any hypoglycemia (n= 508, 505)	62.6	66.5		
Documented symptomatic hypoglycemia (n=508, 505)	32.9	34.7		
Severe and/or confirmed hypoglycemia (n= 508, 505)	58.1	60.6		
Severe and/or confirmed:<75years (n=373, 399)	59.2	60.9		
Severe and/or confirmed:≥75 years age (n=135, 106)	54.8	59.4		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Hypoglycemia (Any Hypoglycemia, Documented Symptomatic Hypoglycemia, Severe and/or Confirmed Hypoglycemia) Event Rate Per Subject Year During the 26 Weeks of Treatment

End point title	Hypoglycemia (Any Hypoglycemia, Documented Symptomatic Hypoglycemia, Severe and/or Confirmed Hypoglycemia) Event Rate Per Subject Year During the 26 Weeks of Treatment

End point description:

Hypoglycemia events were hypoglycemia of any category, severe hypoglycemia (an event that required assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions); documented symptomatic hypoglycemia (symptoms of hypoglycemia with plasma glucose ≤3.9 mmol/L [70 mg/dL]); confirmed hypoglycemia (with or without symptoms of hypoglycemia and plasma glucose ≤3.9 mmol/L). Safety population.

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 26

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	508	505		
Units: rate per subject year				
number (not applicable)				
Any hypoglycemia	6.06	7.74		
Documented symptomatic hypoglycemia	1.85	2.56		
Severe and/or confirmed hypoglycemia	5.17	6.36		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Hypoglycemia (Any Hypoglycemia, Documented Symptomatic Hypoglycemia, Severe and/or Confirmed Hypoglycemia) Event Rate Per Subject Year: By Age Categorical Data During the 26 Weeks of Treatment

End point title	Hypoglycemia (Any Hypoglycemia, Documented Symptomatic Hypoglycemia, Severe and/or Confirmed Hypoglycemia) Event Rate Per Subject Year: By Age Categorical Data During the 26 Weeks of Treatment

End point description:

Hypoglycemia events were hypoglycemia of any category, severe hypoglycemia (an event that required assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative

actions); documented symptomatic hypoglycemia (symptoms of hypoglycemia with plasma glucose ≤3.9 mmol/L [70 mg/dL]); confirmed hypoglycemia (with or without symptoms of hypoglycemia and plasma glucose ≤3.9 mmol/L). Safety population. Here 'n' signifies number of subjects evaluable for this end point in the specified categories.

End point type	Post-hoc

End point timeframe:

Baseline up to Week 26

End point values	HOE901-U300	Lantus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	508	505		
Units: event rate per subject year				
number (not applicable)				
Any hypoglycemia:<75 years age (n= 373, 399)	6.44	7.85		
Any hypoglycemia:≥75 years age (n= 135,106)	5.01	7.32		
Documented symptomatic:<75 years (n=373, 399)	2.11	2.52		
Documented symptomatic:≥75 years (n=135, 106)	1.12	2.71		
Severe and/or confirmed:<75 years (n= 373, 399)	5.43	6.37		
Severe and/or confirmed:≥75 years(n= 135, 106)	4.46	6.28		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Day 184) regardless of seriousness or relationship to IMP.

Adverse event reporting additional description:

Reported AEs and deaths were treatment emergent that is AEs that developed/worsened and deaths that occurred during 'on treatment period' (from first dose of IMP injection up to 2 days after the last injection of IMP, regardless of introduction of rescue therapy). Analysis was performed using safety population which included all treated subjects.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	HOE901-U300

Reporting group description:

HOE901-U300 (Insulin glargine, 300 U/mL) SC injection once daily up to Week 26 on top of stable non-insulin antihyperglycemic therapy.

Reporting group title	Lantus

Reporting group description:

Lantus (Insulin glargine, 100 U/mL) SC injection once daily up to Week 26 on top of stable non-insulin antihyperglycemic therapy.

Serious adverse events	HOE901-U300	Lantus	
Total subjects affected by serious adverse events			
subjects affected / exposed	41 / 508 (8.07%)	34 / 505 (6.73%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma Of Colon			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (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 / 508 (0.20%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder Cancer			

subjects affected / exposed	0 / 508 (0.00%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's Disease			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast Cancer			
subjects affected / exposed	0 / 508 (0.00%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Lymphocytic Leukaemia			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial Cancer Metastatic			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Glioblastoma			
subjects affected / exposed	0 / 508 (0.00%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Neoplasm			
subjects affected / exposed	0 / 508 (0.00%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung Adenocarcinoma			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Neoplasm			

subjects affected / exposed	0 / 508 (0.00%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal Adenocarcinoma			
subjects affected / exposed	0 / 508 (0.00%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic Carcinoma			
subjects affected / exposed	2 / 508 (0.39%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate Cancer			
subjects affected / exposed	3 / 508 (0.59%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Cancer			
subjects affected / exposed	0 / 508 (0.00%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma Of Skin			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional Cell Carcinoma			
subjects affected / exposed	0 / 508 (0.00%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive Crisis			
subjects affected / exposed	1 / 508 (0.20%)	2 / 505 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Venous Disease			

subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (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			
Death			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast Mass			
subjects affected / exposed	0 / 508 (0.00%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural Effusion			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hepatic Enzyme Increased			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle Fracture			
subjects affected / exposed	0 / 508 (0.00%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			

subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur Fracture			
subjects affected / exposed	0 / 508 (0.00%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart Injury			
subjects affected / exposed	0 / 508 (0.00%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Left Ventricular Failure			
subjects affected / exposed	0 / 508 (0.00%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Myocardial Infarction			
subjects affected / exposed	2 / 508 (0.39%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Unstable			
subjects affected / exposed	2 / 508 (0.39%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	0 / 508 (0.00%)	2 / 505 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular Block			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Chronic			

subjects affected / exposed	0 / 508 (0.00%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac Failure Congestive			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (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	2 / 508 (0.39%)	2 / 505 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Ischaemia			
subjects affected / exposed	0 / 508 (0.00%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus Node Dysfunction			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Embolic Stroke			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Coma			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Unconsciousness			

subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iiird Nerve Paresis			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Stroke			
subjects affected / exposed	2 / 508 (0.39%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Loss Of Consciousness			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuromyopathy			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 508 (0.20%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
subjects affected / exposed	0 / 508 (0.00%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 508 (0.00%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Gastric Ulcer Haemorrhage			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (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	0 / 508 (0.00%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Haemorrhage			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile Duct Stone			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis Acute			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (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			
Angioedema			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (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			
Acute Kidney Injury			

subjects affected / exposed	1 / 508 (0.20%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Kidney Disease			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Colic			
subjects affected / exposed	0 / 508 (0.00%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal Mass			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis Pyrophosphate			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (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 / 508 (0.00%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Arthritis Infective			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bacterial Pyelonephritis			
subjects affected / exposed	0 / 508 (0.00%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 508 (0.00%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 508 (0.00%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis Bacterial			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infection			
subjects affected / exposed	0 / 508 (0.00%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal Abscess			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 508 (0.20%)	3 / 505 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	0 / 508 (0.00%)	2 / 505 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (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			
Hyperkalaemia			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (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	1 / 508 (0.20%)	1 / 505 (0.20%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 508 (0.20%)	0 / 505 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	HOE901-U300	Lantus	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 508 (12.20%)	64 / 505 (12.67%)	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	37 / 508 (7.28%)	38 / 505 (7.52%)	
occurrences (all)	45	44	
Upper Respiratory Tract Infection			
subjects affected / exposed	27 / 508 (5.31%)	28 / 505 (5.54%)	
occurrences (all)	30	30	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 March 2016	Following amendments were made: Modified Statistical approach to efficacy analyses based on health authority recommendations. Specifically, an ITT approach was used for the primary analysis of primary and secondary efficacy endpoints. A sensitivity analysis using only on-treatment data was performed on the primary and main secondary efficacy endpoints. The definition of the efficacy analysis population was updated accordingly.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported