Clinical trial results:
A 24-week, randomized, open-label, parallel group multinational comparison of Lantus® (insulin glargine) given in the morning as once-a-day basal insulin versus Neutral Protamine Hagedorn (NPH) insulin, in children with type 1 diabetes mellitus aged at least 1 year to less than 6 years

Summary

EudraCT number	2009-011231-12
Trial protocol	HU CZ ES DE AT Outside EU/EEA
Global end of trial date	30 March 2011

Results information

Result version number	v1
This version publication date	01 April 2016
First version publication date	21 January 2015

Trial information

Trial identification

Sponsor protocol code	EFC11202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00993473
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 Tranparency Team, sanofi-aventis recherche & développement, Contact-Us@sanofi.com
Scientific contact	Trial Tranparency Team, sanofi-aventis recherche & développement, Contact-Us@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000387-PIP01-08
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 May 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 March 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary study objective was to compare the rate of "all hypoglycemia" (composite outcome of the following hypoglycemia events: symptomatic hypoglycemia episodes, low continuous glucose monitoring system [CGMS] excursions confirmed by fingerstick blood glucose [FSBG], low FSBG readings performed at other times) between children treated with Lantus (insulin glargine) and Neutral Protamine Hagedorn (NPH) insulin.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of paediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anaesthesia may have been used to minimize distress and discomfort.

Background therapy:

Insulin lispro (Humalog®) was provided as principal bolus insulin for subcutaneous injection in the form of either pen device doseable in 0.5 units increments or vials of lispro 100 units per millilitre (U/mL). Multiple injections were given before meals and/or at bedtime at the discretion of the Investigator. Regular human insulin could be used as bolus insulin as well.

Evidence for comparator: -

Actual start date of recruitment	15 October 2009
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	Germany: 2
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Czech Republic: 7
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Brazil: 13
Country: Number of subjects enrolled	Chile: 6
Country: Number of subjects enrolled	India: 13
Country: Number of subjects enrolled	Mexico: 12
Country: Number of subjects enrolled	Peru: 5

Country: Number of subjects enrolled	Russian Federation: 18
Country: Number of subjects enrolled	South Africa: 13
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	United States: 9
Country: Number of subjects enrolled	Romania: 7
Worldwide total number of subjects	125
EEA total number of subjects	34

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)	1
Children (2-11 years)	124
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 61 centres (72 were initiated) in 16 countries between October 15, 2009 and March 30, 2011.

Pre-assignment

Screening details:

A total of 165 subjects were screened and 125 were randomized. Forty subjects (24.2%) failed the screening selection process, mainly due to noncompliance with the study required Continuous Glucose Monitoring (CGM) performance and other procedures.

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	Lantus (Insulin Glargine)

Arm description:

Lantus (insulin glargine) given as basal insulin once a day in the morning.

Arm type	Experimental
Investigational medicinal product name	Insulin Glargine
Investigational medicinal product code	HOE901
Other name	Lantus®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dose: titrated to achieve the following glycemic targets without hypoglycemia:
- Fasting blood glucose (BG) between 90 and 145 milligram per decilitre (mg/dL) (5.0 to 8.0 millimole per litre [mmol/L]), inclusive,
- Bedtime BG between 120 and 180 mg/dL (6.7 to10.0 mmol/L), inclusive,
- Nocturnal BG between 80 and 162 mg/dL (4.4 to 9.0 mmol/L), inclusive; and
- HbA1c less than (<) 7.5%.

Arm title	NPH Insulin

Arm description:

NPH human insulin given as basal insulin either once or twice per day generally in the morning and/or at bedtime.

Arm type	Active comparator
Investigational medicinal product name	Neutral Protamine Hagedorn (NPH) insulin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen, Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Titrated to achieve the following glycemic targets without hypoglycemia:

- Fasting blood glucose (BG) between 90 and 145 mg/dL (5.0 to 8.0 mmol/L), inclusive,
- Bedtime BG between 120 and 180 mg/dL (6.7 to10.0 mmol/L), inclusive,
- Nocturnal BG between 80 and 162 mg/dL (4.4 to 9.0 mmol/L), inclusive; and
- HbA1c <7.5%.

Number of subjects in period 1	Lantus (Insulin Glargine)	NPH Insulin
Started	61	64
Completed	57	54
Not completed	4	10
Consent withdrawn by subject	1	5
Family event	1	-
Adverse event	-	2
Technical problem with CGM device	-	1
Lost to follow-up	1	-
Protocol deviation	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Lantus (Insulin Glargine)
Reporting group description:	
Lantus (insulin glargine) given as basal insulin once a day in the morning.	
Reporting group title	NPH Insulin
Reporting group description:	
NPH human insulin given as basal insulin either once or twice per day generally in the morning and/or at bedtime.	

Reporting group values	Lantus (Insulin Glargine)	NPH Insulin	Total
Number of subjects	61	64	125
Age categorical Units: Subjects			
Less than or equal to 3 Years	10	17	27
Greater than 3 years	51	47	98
Age continuous Units: years			
arithmetic mean	4.3	4.1	
standard deviation	± 0.9	± 1	-
Gender categorical Units: Subjects			
Female	29	34	63
Male	32	30	62
Race Units: Subjects			
Caucasian/White	53	48	101
Black	2	2	4
Asian/Oriental	4	11	15
Other	2	3	5
Ethnicity Units: Subjects			
Hispanic	17	13	30
Non Hispanic	44	51	95
Treated by bolus insulin at baseline Units: Subjects			
Yes	54	58	112
No	7	6	13
Treated by basal insulin at baseline Units: Subjects			
Yes	58	57	115
No	3	7	10
Treated by mixed (bolus & basal) insulin at baseline Units: Subjects			
Yes	5	8	13
No	56	56	112
Number of daily basal insulin injections			

at baseline Units: Subjects			
One (1)	32	41	73
Two (2)	21	15	36
Greater than or equal to three (3)	5	1	6
Not treated with basal insulin at baseline	3	7	10
Total daily dose of basal insulin injection at baseline Units: Subjects			
Analyzed	57	57	114
Not treated by basal insulin or missing	4	7	11
Total daily dose of bolus insulin injection at baseline Units: Subjects			
Analyzed	52	57	109
Not treated by bolus insulin or missing	9	7	16
Duration of Diabetes (Median) Units: years			
median	1.63	2.05	
full range (min-max)	1 to 5.3	1 to 4.9	-
Duration of Diabetes (Mean) Units: years			
arithmetic mean	2.12	2.12	
standard deviation	± 1.16	± 1.01	-
Total daily dose of basal insulin injection at baseline (Mean) Units: International Units			
arithmetic mean	7.29	7.61	
standard deviation	± 4.11	± 4.77	-
Total daily dose of basal insulin injection at baseline (Median) Units: International Units			
median	6	6	
full range (min-max)	2 to 24	1.5 to 24	-
Total daily dose of bolus insulin injection at baseline (Mean) Units: International Units			
arithmetic mean	7.14	7.98	
standard deviation	± 3.64	± 7.2	-
Total daily dose of bolus insulin injection at baseline (Median) Units: International Units			
median	7.75	7	
full range (min-max)	1.3 to 16	0.8 to 45	-

End points

End points reporting groups

Reporting group title	Lantus (Insulin Glargine)
Reporting group description:	
Lantus (insulin glargine) given as basal insulin once a day in the morning.	
Reporting group title	NPH Insulin
Reporting group description:	
NPH human insulin given as basal insulin either once or twice per day generally in the morning and/or at bedtime.	

Primary: Event Rate of "All Hypoglycemia"

End point title	Event Rate of "All Hypoglycemia"
End point description:	
Defined as the Total Number of Episodes Divided by the Total Duration of the On-treatment Period in Years (Events Per Patient-year). The rate of "all hypoglycemia" was calculated from "all hypoglycemia" episodes which occurred during the 24-week on-treatment period and consisted of: - symptomatic hypoglycemia episodes validated by the study investigator based on entries in subjects' diaries, - low continuous glucose monitoring system (CGMS) excursions (interstitial glucose <70 mg/dL [3.9 mmol/L]) confirmed by fingerstick blood glucose (FSBG) <70 mg/dL, - low FSBG readings (values <70 mg/dL) performed at other times. The efficacy population consisted of all randomized subjects who received at least one dose of the study medication (modified intent-to-treat [mITT] population). For efficacy analyses, subjects were analyzed in the treatment group allocated by the Interactive Voice Response System (IVRS) at randomization (as randomized).	
End point type	Primary
End point timeframe:	
6 months	

End point values	Lantus (Insulin Glargine)	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	64		
Units: number of events per patient-year				
arithmetic mean (standard deviation)	192.75 (± 119.28)	168.91 (± 101.04)		

Statistical analyses

Statistical analysis title	Event Rate of "All Hypoglycemia"
Statistical analysis description:	
The sample size was calculated to ensure sufficient power so that the upper bound of the 2-sided 95% confidence interval (CI) for the Lantus/NPH ratio would not exceed 1.15 based on an expected overall rate of "all hypoglycemia" of 80 events per patient-year of exposure to NPH insulin and to Lantus. It was planned to randomize at least 45 and up to approximately 60 subjects in each of the 2 treatment groups so that at least 70 subjects would complete the 24 weeks of treatment.	
Comparison groups	NPH Insulin v Lantus (Insulin Glargine)

Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Method	Generalized Linear Model
Parameter estimate	Risk ratio (RR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.44
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[1] - Noninferiority would be demonstrated if the upper bound of the 95% CI for the ratio of the rate of "all hypoglycemia" in the Lantus group to the rate in the NPH group was <1.15. Superiority would be demonstrated if the upper bound of the 95% CI was <1. The margin for noninferiority corresponded to one-half of the 30% difference in hypoglycemia event rate considered as a clinically significant difference by American Diabetes Association 2005 Working Group on Hypoglycemia.

Secondary: Event Rate of Symptomatic Hypoglycemia (Individual Component of Primary Endpoint)

End point title	Event Rate of Symptomatic Hypoglycemia (Individual Component of Primary Endpoint)

End point description:

Event rate is defined as total number of episodes divided by the total duration of the on-treatment period in years (Events Per Patient-year). Symptomatic hypoglycemia: any event with clinical symptoms considered to result from hypoglycemia, validated by the study investigator based on data from patient diaries. Analysis was performed in mITT population.

End point type	Secondary

End point timeframe:

6 months

End point values	Lantus (Insulin Glargine)	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	64		
Units: Events per patient-year				
arithmetic mean (standard deviation)	25.54 (± 37.25)	33.02 (± 47.95)		

Statistical analyses

No statistical analyses for this end point

Secondary: Severe Symptomatic Hypoglycemia Episodes

End point title	Severe Symptomatic Hypoglycemia Episodes

End point description:

Severe symptomatic hypoglycemia: any event with clinical symptoms considered to result from a hypoglycemic episode for which the subjects required the assistance of a third party (that is, other than

the subjects, or a parent/usual caregiver; for example, from emergency personnel), because the subjects/parents could not treat the event with acute neurological impairment directly resulting from the hypoglycemic event. The occurrence of seizure, coma, unconsciousness, or the use of glucagon, were also to qualify a hypoglycemic episode as severe. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

6 months

End point values	Lantus (Insulin Glargine)	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	64		
Units: Episodes	4	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Event Rate of Severe Symptomatic Hypoglycemia

End point title	Event Rate of Severe Symptomatic Hypoglycemia

End point description:

Defined as the Total Number of Episodes Divided by the Total Duration of the On-treatment Period in Years.
Severe symptomatic hypoglycemia: any event with clinical symptoms considered to result from a hypoglycemic episode for which the subjects required the assistance of a third party (that is other than the subject, or a parent/usual caregiver; example, from emergency personnel), because the subjects/parents could not treat the event with acute neurological impairment directly resulting from the hypoglycemic event. The occurrence of seizure, coma, unconsciousness, or the use of glucagon, were also to qualify a hypoglycemic episode as severe. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

6 months

End point values	Lantus (Insulin Glargine)	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	64		
Units: Number of events per patient-year				
arithmetic mean (standard deviation)	0.14 (± 0.55)	0.07 (± 0.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Event Rate of Nocturnal Hypoglycemia

End point title	Event Rate of Nocturnal Hypoglycemia

End point description:

Defined as the Total Number of "All Hypoglycemia" Episodes Divided by the Total Duration of the On-treatment Period in Years.
Nocturnal hypoglycemia: any event from the "all hypoglycemia" total that occurred between 23:00 and 07:00 hours. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

6 months

End point values	Lantus (Insulin Glargine)	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	64		
Units: Number of events per patient-year				
arithmetic mean (standard deviation)	33.5 (± 25.62)	30.92 (± 24.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Event Rate of Nocturnal Symptomatic Hypoglycemia

End point title	Event Rate of Nocturnal Symptomatic Hypoglycemia

End point description:

Defined as the Total Number of Episodes Divided by the Total Duration of the On-treatment Period in Years.
Nocturnal symptomatic hypoglycemia: any symptomatic hypoglycemic event that occurred between 23:00 and 07:00 hours. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

6 months

End point values	Lantus (Insulin Glargine)	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	64		
Units: number of events per patient-year				
arithmetic mean (standard deviation)	2.38 (± 5.42)	3.65 (± 6.75)		

Statistical analyses

No statistical analyses for this end point

Secondary: Severe Nocturnal Hypoglycemia Episodes

End point title	Severe Nocturnal Hypoglycemia Episodes

End point description:

Severe nocturnal symptomatic hypoglycemia: any severe symptomatic hypoglycemic event that occurred between 23:00 and 07:00 hours. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

6 months

End point values	Lantus (Insulin Glargine)	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	64		
Units: Episodes	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Event Rate of Severe Nocturnal Hypoglycemia

End point title	Event Rate of Severe Nocturnal Hypoglycemia

End point description:

Defined as the Total Number of Episodes Divided by the Total Duration of the On-treatment Period in Years. Severe nocturnal symptomatic hypoglycemia: any severe symptomatic hypoglycemic event that occurred between 23:00 and 07:00 hours. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

6 months

End point values	Lantus (Insulin Glargine)	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	64		
Units: number of events per patient-year				
arithmetic mean (standard deviation)	0.04 (± 0.29)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: HbA1c: End of Treatment and Change From Baseline to End of Treatment

End point title	HbA1c: End of Treatment and Change From Baseline to End of Treatment

End point description:

Analysis was performed on mITT population. However post-baseline HbA1c values were missing for 9 subjects: 2 subjects in the Lantus group and 7 in the NPH group.

End point type	Secondary

End point timeframe:

baseline, 6 months

End point values	Lantus (Insulin Glargine)	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	64		
Units: percentage of hemoglobin				
arithmetic mean (standard deviation)				
Baseline HbA1c (n = 61, 64)	8.023 (± 1.049)	8.248 (± 1.429)		
End of treatment HbA1c (n = 59, 57)	8.071 (± 0.884)	8.344 (± 1.161)		
Absolute change from baseline (n = 59, 57)	0.036 (± 0.979)	0 (± 1.035)		

Statistical analyses

No statistical analyses for this end point

Secondary: HbA1c: End of Treatment and Change From Baseline to End of Treatment (ANCOVA Estimates)

End point title	HbA1c: End of Treatment and Change From Baseline to End of Treatment (ANCOVA Estimates)

End point description:

Assessed using an analysis of covariance (ANCOVA) model with treatment, and randomization strata (baseline number of CGM hypoglycemic excursions <0.5 events/24hours or ≥0.5 events/24 hours, and baseline HbA1c <8.5% or ≥8.5%) as fixed effects, and using the baseline value as covariate. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

baseline, 6 months

End point values	Lantus (Insulin Glargine)	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	64		
Units: percentage of hemoglobin				
arithmetic mean (standard deviation)				
End of treatment HbA1c (ANCOVA)	8.139 (± 0.1065)	8.232 (± 0.1134)		
Absolute change from baseline HbA1c (ANCOVA)	-0.048 (± 0.1065)	0.045 (± 0.1134)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reaching HbA1c Target of Less Than 7.5% at the End of Treatment Visit

End point title	Percentage of Subjects Reaching HbA1c Target of Less Than 7.5% at the End of Treatment Visit

End point description:

Percentage of subjects reaching International Society for Pediatric and Adolescent Diabetes (ISPAD)-recommended goals of Glycosylated Hemoglobin A1c <7.5% at the end of treatment visit. The population analyzed consisted of subjects from the mITT population (as defined for primary outcome measure) with post-baseline HbA1c values. 2 subjects from the Lantus group and 7 from the NPH group had no post-baseline HbA1c value.

End point type	Secondary

End point timeframe:

6 months

End point values	Lantus (Insulin Glargine)	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	57		
Units: percentage of subjects				
number (not applicable)	22	22.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Average Daily Blood Glucose (BG) Based on CGMS Values

End point title	Average Daily Blood Glucose (BG) Based on CGMS Values

End point description:

Analysis was performed on mITT population. However 1 patient in the NPH group did not have baseline CGM value and 2 other patients (1 in the Lantus group and 1 in the NPH group) did not have on-treatment CGM values.

End point type	Secondary

End point timeframe:

baseline, 6 months

End point values	Lantus (Insulin Glargine)	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	64		
Units: mmol/L				
arithmetic mean (standard deviation)				
Baseline daily BG (n= 61, 63)	11.263 (± 1.887)	11.17 (± 1.986)		
End of treatment daily BG (n= 60, 63)	11.085 (± 2.077)	11.712 (± 2.166)		
Absolute change from baseline (n= 60, 62)	-0.218 (± 2.399)	0.501 (± 1.906)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Different Types of Hypoglycemia Events

End point title	Number of Subjects With Different Types of Hypoglycemia Events

End point description:

Definitions of the different types of hypoglycemia events provided in the outcome measure description of the corresponding event rates. Analysis was performed on mITT population.

End point type	Other pre-specified

End point timeframe:

6 months

End point values	Lantus (Insulin Glargine)	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	64		
Units: subjects				
Subjects with "All hypoglycemia"	61	63		
Subjects with symptomatic hypoglycemia	40	44		
Subjects with severe symptomatic hypoglycemia	4	2		
Subjects with nocturnal hypoglycemia	59	60		
Subjects with nocturnal symptomatic hypoglycemia	17	28		
Subjects with severe noct. sympto. hypoglycemia	1	0		
Subjects with "All confirmed low CGMS excursions"	60	61		

Subjects with "All confirmed low FSBG"	61	63		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent of Blood Glucose (BG) Within the Range of 70 – 180 mg/dL (3.9-10 mmol/L)

End point title	Percent of Blood Glucose (BG) Within the Range of 70 – 180 mg/dL (3.9-10 mmol/L)

End point description:

Calculated for each subject as the percent of all on-treatment CGMS values falling within the range of 70 – 180 mg/dL (3.9 – 10 mmol/L) inclusive. The population analyzed consisted of subjects from the mITT population (as defined for primary outcome measure) with on-treatment CGM values (1 subject from the Lantus group and 1 from the NPH group did not have on-treatment CGM).

End point type	Other pre-specified

End point timeframe:

6 months

End point values	Lantus (Insulin Glargine)	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	63		
Units: percent of CGMS values within the range				
arithmetic mean (standard deviation)	41.667 (± 12.048)	38.158 (± 10.908)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Blood Glucose Variability Based on All On-treatment CGMS Values

End point title	Blood Glucose Variability Based on All On-treatment CGMS Values

End point description:

Calculated for any given subject as the standard deviation (SD) of all CGMS interstitial glucose values recorded over all CGMS placements.
The population analyzed consisted of subjects from the mITT population (as defined for primary outcome measure) with on-treatment CGM values (1 subject from the Lantus group and 1 from the NPH group did not have on-treatment CGM).

End point type	Other pre-specified

End point timeframe:

6 months

End point values	Lantus (Insulin Glargine)	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	63		
Units: mmol/L				
arithmetic mean (standard deviation)	4.954 (± 0.826)	5.089 (± 0.731)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Nocturnal Blood Glucose Variability Based on All On-treatment CGMS Values

End point title	Nocturnal Blood Glucose Variability Based on All On-treatment CGMS Values

End point description:

Calculated for any given subject as the standard deviation (SD) of all CGMS interstitial glucose values recorded during the nocturnal time period (between 23:00 and 07:00 hours). The population analyzed consisted of subjects from the mITT population (as defined for primary outcome measure) with on-treatment CGM values (1 subject from the Lantus group and 1 from the NPH group did not have on-treatment CGM).

End point type	Other pre-specified

End point timeframe:

6 months

End point values	Lantus (Insulin Glargine)	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	63		
Units: mmol/L				
arithmetic mean (standard deviation)	4.747 (± 0.973)	4.837 (± 0.825)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Event Rate of "All Confirmed Low CGMS Excursions" (Individual Component of Primary Endpoint)

End point title	Event Rate of "All Confirmed Low CGMS Excursions" (Individual Component of Primary Endpoint)

End point description:

Defined as the Total Number of Episodes Divided by the Total Duration of the On-treatment Period in Years (Events Per Patient-year)
"All confirmed low CGMS excursions" consisted of all low CGMS excursions (interstitial glucose <70 mg/dL [3.9 mmol/L]) confirmed by fingerstick blood glucose (FSBG) <70 mg/dL. Analysis was performed on mITT population.

End point type	Post-hoc

End point timeframe:

6 months

End point values	Lantus (Insulin Glargine)	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	64		
Units: events per patient year				
arithmetic mean (standard deviation)	74.61 (± 74.09)	71.6 (± 53.2)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Event Rate of "All Confirmed Low FSBG" (Individual Component of the Primary Endpoint)

End point title	Event Rate of "All Confirmed Low FSBG" (Individual Component of the Primary Endpoint)

End point description:

Defined as the Total Number of Episodes Divided by the Total Duration of the On-treatment Period in Years (Events Per Patient-year).
"All confirmed low FSBG" consisted of all low FSBG readings (values <70 mg/dL) performed at other times. Analysis was performed on mITT population.

End point type	Post-hoc

End point timeframe:

6 months

End point values	Lantus (Insulin Glargine)	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	64		
Units: events per patient year				
arithmetic mean (standard deviation)	192.69 (± 121.78)	168.24 (± 101.21)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were monitored from baseline to 7 days after last treatment visit.

Adverse event reporting additional description:

The safety analyses were conducted according to the treatment received rather than according to the randomization groups.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Lantus (insulin glargine)

Reporting group description:

Lantus (insulin glargine) given as basal insulin once a day in the morning by subcutaneous injection.

Reporting group title	NPH insulin

Reporting group description:

Neutral Protamine Hagedorn (NPH) human insulin given as basal insulin either once or twice per day generally in the morning and /or at bedtime by subcutaneous injection.

Serious adverse events	Lantus (insulin glargine)	NPH insulin	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 62 (12.90%)	2 / 63 (3.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Abdominal Pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 62 (3.23%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lower Respiratory Tract Infection			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Infection			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (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			
Dehydration			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic Ketoacidosis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 62 (1.61%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Seizure			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 62 (3.23%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 2	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 (insulin glargine)	NPH insulin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 62 (48.39%)	33 / 63 (52.38%)	
General disorders and administration site conditions			
Device Lead Damage			
alternative assessment type: Systematic			

subjects affected / exposed	5 / 62 (8.06%)	2 / 63 (3.17%)	
occurrences (all)	5	2	
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 62 (4.84%)	7 / 63 (11.11%)	
occurrences (all)	3	7	
Gastrointestinal disorders			
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 62 (8.06%)	4 / 63 (6.35%)	
occurrences (all)	5	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 62 (3.23%)	4 / 63 (6.35%)	
occurrences (all)	2	4	
Infections and infestations			
Bronchitis			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 62 (4.84%)	5 / 63 (7.94%)	
occurrences (all)	3	5	
Gastroenteritis			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 62 (9.68%)	6 / 63 (9.52%)	
occurrences (all)	6	6	
Nasopharyngitis			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 62 (9.68%)	5 / 63 (7.94%)	
occurrences (all)	6	5	
Otitis Media			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 62 (1.61%)	4 / 63 (6.35%)	
occurrences (all)	1	4	
Pharyngitis			
alternative assessment type: Systematic			

subjects affected / exposed	6 / 62 (9.68%)	2 / 63 (3.17%)	
occurrences (all)	6	2	
Tonsillitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 62 (1.61%)	4 / 63 (6.35%)	
occurrences (all)	1	4	
Upper Respiratory Tract Infection			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 62 (6.45%)	6 / 63 (9.52%)	
occurrences (all)	4	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 October 2009	Modifications of several aspects of the original protocol to in order to define procedures for screening, PK, and adverse event reporting.
28 March 2011	Modification of the PK analysis study objective, insulin glargine antibody assessment, and methodology section.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

There are numerous potential biases that could affect the timing and frequency of performance of sporadic FSBG, such as mealtime dosing and choice of bolus insulin dose, stability and familiarity with insulin regimens, and parental anxiety levels.

Notes: