Clinical trial results:
A Randomized, 30-Week, Active-controlled, Open-Label, 2-Treatment Arm, Parallel-group, Multicenter Study Comparing the Efficacy and Safety of the Insulin Glargine/Lixisenatide Fixed Ratio Combination to Insulin Glargine With or Without Metformin in Patients with Type 2 Diabetes Mellitus (T2DM)

Summary

EudraCT number	2013-003132-79
Trial protocol	EE SE LT CZ NL ES HU SK DK
Global end of trial date	09 July 2015

Results information

Result version number	v1 (current)
This version publication date	24 July 2016
First version publication date	24 July 2016

Trial information

Trial identification

Sponsor protocol code	EFC12405

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02058160
WHO universal trial number (UTN)	U1111-1148-4351
Other trial identifiers	Study Name: LixiLan-L

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 August 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of the insulin glargine/lixisenatide fixed ratio combination (FRC) to insulin glargine in glycated hemoglobin (HbA1c) change from baseline to Week 30.

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:

If previously taken at a stable dose of at least 1500 mg/day or maximal tolerated dose for at least 3 months prior to screening, metformin as a background treatment was to be continued at a stable dose throughout the study unless prevented by a specific issue related to this treatment. Other oral antidiabetic treatment (OAD) if previously taken, were to be discontinued at start of run-in (6 weeks prior randomization).

Evidence for comparator: -

Actual start date of recruitment	27 January 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Canada: 22
Country: Number of subjects enrolled	Chile: 29
Country: Number of subjects enrolled	Mexico: 58
Country: Number of subjects enrolled	Romania: 42
Country: Number of subjects enrolled	Russian Federation: 101
Country: Number of subjects enrolled	Ukraine: 62
Country: Number of subjects enrolled	United States: 175
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Poland: 37
Country: Number of subjects enrolled	Slovakia: 40
Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	Sweden: 16

Country: Number of subjects enrolled	Czech Republic: 41
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	Estonia: 8
Country: Number of subjects enrolled	Hungary: 42
Country: Number of subjects enrolled	Lithuania: 19
Worldwide total number of subjects	736
EEA total number of subjects	283

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)	506
From 65 to 84 years	228
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 187 centers in 18 countries. A total of 1930 subjects were screened between January 27, 2014 and October 15, 2014. 912 subjects were not eligible for run-in phase mainly due to HbA1c value being out of the protocol-defined range.

Pre-assignment

Screening details:

After screening phase, 1018 subjects entered 6 week run–in phase, during which subjects were switched (if necessary) to insulin glargine; and dose was titrated/stabilized. Any OAD other than metformin were stopped. 282 subjects were run-in failures and 736 were randomized in 1:1 to FRC & insulin glargine arms in open-label treatment period.

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	Insulin Glargine/Lixisenatide Fixed Ratio Combination

Arm description:

Fixed Ratio Combination (FRC) of insulin glargine/lixisenatide once daily (QD) dose individually adjusted up to 30 weeks.

Arm type	Experimental
Investigational medicinal product name	Insulin glargine (100 U/mL)/Lixisenatide
Investigational medicinal product code	HOE901/AVE0010
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

FRC was self-administered QD in the morning within 1 hour before breakfast using one of the 2 available prefilled disposable SoloStar® pen-injectors: pen A or B, depending upon dose.
Pen A contained 100 U/mL insulin glargine (Lantus, 100 U/mL) and 50 mcg/mL lixisenatide in a ratio of 2 U:1 mcg and was used for administration doses from 10 U/5 mcg up to 40 U/20 mcg. Pen B contained 100 U/mL insulin glargine (Lantus, 100 U/mL) and 33 mcg/mL lixisenatide in a ratio of 3 U:1 mcg and was used for administration doses from 30 U/10 mcg up to the maximal daily dose of 60 U/20 mcg. In order not to exceed the highest recommended initiation dose of 10 mcg for lixisenatide, the FRC was initiated at a dose of either 20 U/10mcg with Pen A or 30 U/10 mcg with Pen B, depending on subject's dose on the day before randomization.
The dose was kept stable for 2 weeks and then adjusted to reach and maintain fasting self-monitored plasma glucose (SMPG) of 80 mg/dL to 100 mg/dL (4.4 mmol/L to 5 mmol/L).

Arm title	Insulin Glargine

Arm description:

Insulin glargine QD dose individually adjusted up to 30 weeks.

Arm type	Active comparator
Investigational medicinal product name	Insulin glargine
Investigational medicinal product code	HOE901
Other name	Lantus
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin glargine 100 U/mL was self-administered QD at approximately the same time every day. The

time of the injection was decided at the discretion of the subject and Investigator, at run-in start, and was to remain roughly the same throughout the study.
The first dose after randomization was the same as the one administered on the day before randomization, and then dose was adjusted to reach and maintain fasting SMPG of 80 mg/dL to 100 mg/dL (4.4 mmol/L to 5.6 mmol/L).

Number of subjects in period 1	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine
Started	367	369
Treated	365	365
Completed	336	355
Not completed	31	14
Other than specified above	12	6
Adverse events	12	3
Randomized but not treated	2	4
Poor compliance to protocol	4	1
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Insulin Glargine/Lixisenatide Fixed Ratio Combination
Reporting group description:	
Fixed Ratio Combination (FRC) of insulin glargine/lixisenatide once daily (QD) dose individually adjusted up to 30 weeks.	
Reporting group title	Insulin Glargine
Reporting group description:	
Insulin glargine QD dose individually adjusted up to 30 weeks.	

Reporting group values	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine	Total
Number of subjects	367	369	736
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	59.6	60.3	
standard deviation	± 9.4	± 8.7	-
Gender categorical Units: Subjects			
Female	202	190	392
Male	165	179	344
Race Units: Subjects			
Caucasian	337	338	675
Black	17	21	38
Asian/Oriental	12	8	20
Other	1	2	3
Ethnicity Units: Subjects			
Hispanic	66	66	132
Not Hispanic	301	303	604
Oral Antidiabetic Drug (OAD) Use Units: Subjects			
Yes	349	350	699
No	18	19	37
OAD Use at Screening By Class Units: Subjects			
Metformin	170	190	360
Sulfonylurea	16	14	30
Sodiumglucose cotransporter-2 (SGLT-2) inhibitor	0	1	1
Dipeptidyl peptidase-4 (DPP-4) inhibitor	2	4	6
Glinide	1	1	2
Metformin + Sulfonylurea	137	118	255

Metformin + DPP-4 inhibitor	20	18	38
Metformin + Glinide	2	3	5
Sulfonylurea + DPP-4 inhibitor	1	1	2
None	18	19	37
Body Mass Index (BMI)			
Units: kg/m^2			
arithmetic mean	31.33	30.96	
standard deviation	± 4.25	± 4.15	-
Duration of Diabetes			
(N = 367, 368)			
Units: years			
arithmetic mean	12.02	12.13	
standard deviation	± 6.64	± 6.85	-
Daily Dose of Metformin			
(N = 329, 329)			
Units: mg			
arithmetic mean	2082.8	2042	
standard deviation	± 499.2	± 455.9	-
HbA1c			
Units: Percentage of HbA1c			
arithmetic mean	8.07	8.08	
standard deviation	± 0.68	± 0.73	-
Fasting Plasma Glucose (FPG)			
Units: mmol/L			
arithmetic mean	7.34	7.36	
standard deviation	± 1.95	± 2.12	-

End points

End points reporting groups

Reporting group title	Insulin Glargine/Lixisenatide Fixed Ratio Combination
Reporting group description:	
Fixed Ratio Combination (FRC) of insulin glargine/lixisenatide once daily (QD) dose individually adjusted up to 30 weeks.	
Reporting group title	Insulin Glargine
Reporting group description:	
Insulin glargine QD dose individually adjusted up to 30 weeks.	

Primary: Change in HbA1c From Baseline to Week 30

End point title	Change in HbA1c From Baseline to Week 30
End point description:	
Change in HbA1c was calculated by subtracting baseline value from Week 30 value. Modified intent-to-treat (mITT) population: all randomized subjects who had both baseline and at least one post-baseline efficacy assessment. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline HbA1c assessment during study period.	
End point type	Primary
End point timeframe:	
Baseline, Week 30	

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	364	364		
Units: Percentage of hemoglobin				
least squares mean (standard error)	-1.13 (± 0.057)	-0.62 (± 0.055)		

Statistical analyses

Statistical analysis title	Insulin Glargine/Lixisenatide vs Insulin Glargine
Statistical analysis description:	
Analysis was performed using Mixed-effect model with repeated measures (MMRM) with treatment groups, randomization strata of Week -1 HbA1c (<8.0, ≥8.0%), randomization strata of metformin use at screening, visits, treatment-by-visit interaction and country as fixed effects and baseline HbA1c value-by-visit interaction as covariates. A hierarchical testing procedure was used to control type I error and handle multiple endpoint analyses.	
Comparison groups	Insulin Glargine/Lixisenatide Fixed Ratio Combination v Insulin Glargine

Number of subjects included in analysis	728
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001 [2]
Method	Mixed models analysis
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	-0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.633
upper limit	-0.397
Variability estimate	Standard error of the mean
Dispersion value	0.06

Notes:

[1] - Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.05 level.
[2] - Threshold for significance at 0.05 level.

Secondary: Percentage of Subjects with HbA1c <7.0% or ≤6.5% at Week 30

End point title	Percentage of Subjects with HbA1c <7.0% or ≤6.5% at Week 30

End point description:

mITT population. Subjects with no value for HbA1c at Week 30 were counted as non-responders.

End point type	Secondary

End point timeframe:

Week 30

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	366	365		
Units: Percentage of subjects				
number (not applicable)				
HbA1c <7.0%	54.9	29.6		
HbA1c ≤ 6.5%	33.9	14.2		

Statistical analyses

Statistical analysis title	HbA1c <7.0%: FRC vs Insulin Glargine

Statistical analysis description:

Analysis was performed using Cochran-Mantel-Haenszel method stratified on randomization strata of Week -1 HbA1c (<8.0%, ≥8.0%) and randomization strata of metformin use at screening. This analysis was out of testing order.

Comparison groups	Insulin Glargine/Lixisenatide Fixed Ratio Combination v Insulin Glargine

Number of subjects included in analysis	731
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	25.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.94
upper limit	32.1

Notes:

[3] - Threshold for significance at 0.05 level.

Statistical analysis title	HbA1c ≤6.5%: FRC vs Insulin Glargine

Statistical analysis description:

Analysis was performed using Cochran-Mantel-Haenszel method stratified on randomization strata of Week -1 HbA1c (<8.0%, ≥8.0%) and randomization strata of metformin use at screening. This analysis was out of testing order.

Comparison groups	Insulin Glargine/Lixisenatide Fixed Ratio Combination v Insulin Glargine
Number of subjects included in analysis	731
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	19.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.9
upper limit	25.62

Notes:

[4] - Threshold for significance at 0.05 level.

Secondary: Change in 2-hour Plasma Blood Glucose Excursion from Baseline to Week 30

End point title	Change in 2-hour Plasma Blood Glucose Excursion from Baseline to Week 30

End point description:

Plasma glucose excursion = 2-hour postprandial glucose (PPG) minus plasma glucose value obtained 30 minutes prior to the start of the meal and before investigational medicinal product (IMP) administration, if IMP was injected before breakfast. Change in plasma glucose excursions were calculated by subtracting baseline value from Week 30 value. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline plasma glucose excursion assessment during study period. Missing data was imputed using last observation carried forward (LOCF).

End point type	Secondary

End point timeframe:

Baseline, Week 30

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	329	336		
Units: mmol/L				
least squares mean (standard error)	-3.9 (± 0.285)	-0.47 (± 0.274)		

Statistical analyses

Statistical analysis title	FRC vs Insulin Glargine

Statistical analysis description:

Testing according to the hierarchical testing procedure (continued only if previous endpoints were statistically significant). Analysis was performed using analysis of covariance (ANCOVA) model with treatment groups, randomization strata of Week -1 HbA1c [<8.0, ≥8.0%], randomization strata of metformin use at screening and country as fixed effects and baseline 2-hour plasma glucose excursion value as a covariate.

Comparison groups	Insulin Glargine/Lixisenatide Fixed Ratio Combination v Insulin Glargine
Number of subjects included in analysis	665
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-3.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.925
upper limit	-2.939
Variability estimate	Standard error of the mean
Dispersion value	0.251

Notes:

[5] - Threshold for significance at 0.05 level.

Secondary: Change in Body Weight From Baseline to Week 30

End point title	Change in Body Weight From Baseline to Week 30

End point description:

Change in body weight was calculated by subtracting baseline value from Week 30 value. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline body weight assessment during study period.

End point type	Secondary

End point timeframe:

Baseline, Week 30

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	365		
Units: kg				
least squares mean (standard error)	-0.67 (± 0.181)	0.7 (± 0.178)		

Statistical analyses

Statistical analysis title	FRC vs Insulin Glargine

Statistical analysis description:

Testing according to the hierarchical testing procedure (continued only if previous endpoints were statistically significant). Analysis was performed using MMRM model with treatment groups, randomization strata of Week -1 HbA1c (<8.0, ≥8.0%), randomization strata of metformin use at screening, scheduled visits, treatment-by-visit interaction and country as fixed effects and baseline body weight value-by-visit interaction as covariates.

Comparison groups	Insulin Glargine/Lixisenatide Fixed Ratio Combination v Insulin Glargine
Number of subjects included in analysis	730
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.808
upper limit	-0.93
Variability estimate	Standard error of the mean
Dispersion value	0.224

Notes:

[6] - Threshold for significance at 0.05 level.

Secondary: Mean Change in 7-point SMPG Profile From Baseline to Week 30

End point title	Mean Change in 7-point SMPG Profile From Baseline to Week 30

End point description:

Subjects recorded a 7-point plasma glucose profile measured before and 2-hours after each meal and at bedtime, two times in a week before baseline, before visit Week 12 and before visit Week 30 and the average value across the profiles performed in the week before a visit for the 7 time points was calculated. Change in average 7 point SMPG was calculated by subtracting baseline value from Week 30 value. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post baseline 7-point SMPG assessment during study period.

End point type	Secondary

End point timeframe:

Baseline, Week 30

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323	320		
Units: mmol/L				
least squares mean (standard error)	-1.5 (± 0.137)	-0.6 (± 0.13)		

Statistical analyses

Statistical analysis title	FRC vs Insulin Glargine

Statistical analysis description:

Testing according to the hierarchical testing procedure (continued only if previous endpoints were statistically significant). Analysis was performed using MMRM model with treatment groups, randomization strata of Week -1 HbA1c (<8.0, ≥8.0%), randomization strata of metformin use at screening, scheduled visits, treatment-by-visit interaction and country as fixed effects and baseline average SMPG value-by-visit interaction as covariates.

Comparison groups	Insulin Glargine/Lixisenatide Fixed Ratio Combination v Insulin Glargine
Number of subjects included in analysis	643
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.154
upper limit	-0.64
Variability estimate	Standard error of the mean
Dispersion value	0.131

Notes:

[7] - Threshold for significance at 0.05 level.

Secondary: Percentage of Subjects Reaching HbA1c <7.0% With No Body Weight Gain at Week 30

End point title	Percentage of Subjects Reaching HbA1c <7.0% With No Body Weight Gain at Week 30

End point description:

mITT population. Subjects without HbA1c and/or body weight value at Week 30 were counted as non-responders.

End point type	Secondary

End point timeframe:

Week 30

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	366	365		
Units: Percentage of subjects				
number (not applicable)	34.2	13.4		

Statistical analyses

Statistical analysis title	FRC vs Insulin Glargine

Statistical analysis description:

Testing according to the hierarchical testing procedure (continued only if previous endpoints were statistically significant). Analysis was performed using Cochran-Mantel-Haenszel method stratified on randomization strata of Week-1 HbA1c (<8.0%, ≥8.0%) and randomization strata of metformin use at screening.

Comparison groups	Insulin Glargine/Lixisenatide Fixed Ratio Combination v Insulin Glargine
Number of subjects included in analysis	731
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	20.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.98
upper limit	26.66

Notes:

[8] - Threshold for significance at 0.05 level.

Secondary: Change in Daily Insulin Glargine Dose From Baseline to Week 30

End point title	Change in Daily Insulin Glargine Dose From Baseline to Week 30

End point description:

mITT population. The analysis included scheduled measurements obtained up to the date of last injection of IMP. Here, number of subjects analyzed=subjects with insulin glargine dose assessment during study period.

End point type	Secondary

End point timeframe:

Baseline, Week 30

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	364	365		
Units: Units (U)				
least squares mean (standard error)	10.64 (± 0.601)	10.89 (± 0.587)		

Statistical analyses

Statistical analysis title	FRC vs Insulin Glargine

Statistical analysis description:

Testing according to the hierarchical testing procedure (continued only if previous endpoints were statistically significant). Analysis was performed using MMRM model with treatment groups, randomization strata of Week -1 HbA1c (<8.0, ≥8.0%), randomization strata of metformin use at screening, scheduled visits, treatment-by-visit interaction, and country as fixed effects, and baseline daily insulin glargine dose-by-visit interaction as a covariate.

Comparison groups	Insulin Glargine/Lixisenatide Fixed Ratio Combination v Insulin Glargine
Number of subjects included in analysis	729
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7362 [9]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.762
upper limit	1.246
Variability estimate	Standard error of the mean
Dispersion value	0.766

Notes:

[9] - Threshold for significance at 0.05 level.

Secondary: Percentage of Subjects Reaching HbA1c <7.0% with No Body Weight Gain at Week 30 and No Documented (Plasma Glucose [PG] ≤ 70 mg/dL [3.9 mmol/L]) Symptomatic Hypoglycemia During 30-Week Treatment Period

End point title	Percentage of Subjects Reaching HbA1c <7.0% with No Body Weight Gain at Week 30 and No Documented (Plasma Glucose [PG] ≤ 70 mg/dL [3.9 mmol/L]) Symptomatic Hypoglycemia During 30-Week Treatment Period

End point description:

Documented symptomatic hypoglycemia was an event during which typical symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of ≤70 mg/dL (3.9 mmol/L). mITT population. Subjects without HbA1c and/or body weight value at Week 30 were counted as non-

responders.

End point type	Secondary

End point timeframe:

Baseline up to Week 30

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	366	365		
Units: Percentage of subjects				
number (not applicable)	19.9	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Fasting Plasma Glucose (FPG) From Baseline to Week 30

End point title	Change in Fasting Plasma Glucose (FPG) From Baseline to Week 30

End point description:

Change in FPG was calculated by subtracting baseline value from Week 30 value. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline FPG assessment during study period.

End point type	Secondary

End point timeframe:

Baseline, Week 30

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	364	364		
Units: mmol/L				
least squares mean (standard error)	-0.35 (± 0.142)	-0.46 (± 0.138)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in 2-Hour PPG From Baseline to Week 30

End point title	Change in 2-Hour PPG From Baseline to Week 30

End point description:

Change in PPG was calculated by subtracting baseline value from Week 30 value. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline PPG assessment during study period. Missing data was imputed using LOCF.

End point type	Secondary

End point timeframe:

Baseline, Week 30

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	332	340		
Units: mmol/L				
least squares mean (standard error)	-4.72 (± 0.322)	-1.39 (± 0.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reaching HbA1c <7.0% with No Documented Symptomatic Hypoglycemia (PG ≤ 70 mg/dL [3.9 mmol/L]) During 30-Week Treatment Period

End point title	Percentage of Subjects Reaching HbA1c <7.0% with No Documented Symptomatic Hypoglycemia (PG ≤ 70 mg/dL [3.9 mmol/L]) During 30-Week Treatment Period

End point description:

Documented symptomatic hypoglycemia was an event during which typical symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of ≤70 mg/dL (3.9 mmol/L). mITT population. Subjects with no value for HbA1c at Week 30 were counted as non-responders.

End point type	Secondary

End point timeframe:

Baseline up to Week 30

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	366	365		
Units: Percentage of subjects				
number (not applicable)	31.7	18.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Requiring Rescue Therapy During 30-Week Treatment Period

End point title	Percentage of Subjects Requiring Rescue Therapy During 30-Week Treatment Period

End point description:

Routine fasting SMPG and central laboratory FPG (and HbA1c after Week 12) values were used to determine the requirement of rescue medication. If fasting SMPG value exceeded the specified limit for 3 consecutive days, the central laboratory FPG (and HbA1c after week 12) were performed. mITT population.

End point type	Secondary

End point timeframe:

Baseline up to Week 30

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	366	365		
Units: Percentage of subjects				
number (not applicable)	2.7	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Documented Symptomatic Hypoglycemia Events Per Subject-Year

End point title	Number of Documented Symptomatic Hypoglycemia Events Per Subject-Year

End point description:

Documented symptomatic hypoglycemia was an event during which symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of ≤ 70 mg/dL (3.9 mmol/L). Analysis was performed on safety population defined as all randomized subjects who received at least one dose of IMP regardless of the amount of treatment administered.

End point type	Secondary

End point timeframe:

First dose of study drug up to 1 day after the last dose administration (median treatment exposure 211 days [FRC], 210 days [Insulin glargine])

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	365		
Units: Events per subject-year				
number (not applicable)	3.03	4.22		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Documented Symptomatic Hypoglycemia

End point title	Percentage of Subjects with Documented Symptomatic Hypoglycemia

End point description:

Documented symptomatic hypoglycemia was an event during which symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of ≤ 70 mg/dL (3.9 mmol/L). Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

First dose of study drug up to 1 day after the last dose administration (median treatment exposure 211 days [FRC], 210 days [Insulin glargine])

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	365		
Units: Percentage of subjects				
number (not applicable)	40	42.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Severe Symptomatic Hypoglycemia

End point title	Percentage of Subjects with Severe Symptomatic Hypoglycemia

End point description:

Severe symptomatic hypoglycemia was an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Plasma glucose measurements might not have been available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal was considered sufficient evidence that the event had been induced by a low plasma glucose concentration. Severe symptomatic hypoglycemia included all episodes in which neurological impairment was severe enough to prevent self-treatment, and which were thus thought to place subjects at risk for injury to themselves or others. Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

First dose of study drug up to 1 day after the last dose administration (median treatment exposure 211 days [FRC], 210 days [Insulin glargine])

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	365		
Units: Percentage of subjects				
number (not applicable)	1.1	0.3		

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 (Week 30) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs and deaths are treatment-emergent that is AEs that developed/worsened and deaths that occurred during on-emergent period' (time from first injection of open-label IMP up to 3 days after the last injection of IMP. Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Insulin Glargine/Lixisenatide Fixed Ratio Combination

Reporting group description:

Fixed Ratio Combination (FRC) of Insulin glargine /lixisenatide QD dose individually adjusted up to 30 weeks (median exposure: 211 days).

Reporting group title	Insulin Glargine

Reporting group description:

Insulin glargine QD dose individually adjusted up to 30 weeks (median exposure: 210 days).

Serious adverse events	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 365 (5.48%)	18 / 365 (4.93%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign Breast Neoplasm			
subjects affected / exposed	1 / 365 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign Gastric Neoplasm			
subjects affected / exposed	1 / 365 (0.27%)	0 / 365 (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	1 / 365 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder Cancer			
subjects affected / exposed	0 / 365 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Kaposi's Sarcoma			
subjects affected / exposed	0 / 365 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma Of The Tongue			
subjects affected / exposed	1 / 365 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 365 (0.00%)	1 / 365 (0.27%)	
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 Discomfort			
subjects affected / exposed	0 / 365 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 365 (0.00%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			

subjects affected / exposed	0 / 365 (0.00%)	1 / 365 (0.27%)	
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			
Meniscus Injury			
subjects affected / exposed	0 / 365 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scar			
subjects affected / exposed	1 / 365 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural Haematoma			
subjects affected / exposed	1 / 365 (0.27%)	0 / 365 (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 / 365 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Unstable			
subjects affected / exposed	2 / 365 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis Coronary Artery			
subjects affected / exposed	1 / 365 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	0 / 365 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiopulmonary Failure			
subjects affected / exposed	0 / 365 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial Infarction			
subjects affected / exposed	1 / 365 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular Tachycardia			
subjects affected / exposed	1 / 365 (0.27%)	0 / 365 (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			
Hypoglycaemic Seizure			
subjects affected / exposed	1 / 365 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Unconsciousness			
subjects affected / exposed	2 / 365 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 365 (0.00%)	1 / 365 (0.27%)	
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 / 365 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis Chronic			

subjects affected / exposed	1 / 365 (0.27%)	0 / 365 (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			
Renal Impairment			
subjects affected / exposed	0 / 365 (0.00%)	1 / 365 (0.27%)	
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			
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 365 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 365 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendonitis			
subjects affected / exposed	1 / 365 (0.27%)	0 / 365 (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			
Osteomyelitis			
subjects affected / exposed	0 / 365 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 365 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Wound Infection			
subjects affected / exposed	0 / 365 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	2 / 365 (0.55%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	81 / 365 (22.19%)	42 / 365 (11.51%)	
Nervous system disorders			
Headache			
subjects affected / exposed	21 / 365 (5.75%)	10 / 365 (2.74%)	
occurrences (all)	32	11	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	38 / 365 (10.41%)	2 / 365 (0.55%)	
occurrences (all)	44	3	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	32 / 365 (8.77%)	32 / 365 (8.77%)	
occurrences (all)	35	36	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 July 2014	- Exclusion criterion was modified to limit exclusion to subjects who used insulin products other than basal insulin within 1 year prior to screening and to clarify the duration of short-term treatment. - Monitoring and evaluating of device/pen-related events was added. - Changes to collection of pharmacokinetic (PK) and antibody sampling were made. - The calculated creatinine clearance categories at screening used for the description of demographic and baseline characteristics were changed. - Contraceptive methods allowed for women of childbearing potential were clarified. - The statistical method used for the efficacy analyses was changed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported