Clinical trial results:
A Randomized, 30 Week, Active-controlled, Open-label, 3-Treatment Arm, Parallel-group Multicenter Study Comparing the Efficacy and Safety of Insulin Glargine/Lixisenatide Fixed Ratio Combination to Insulin Glargine Alone and to Lixisenatide Alone on Top of Metformin in Patients with Type 2 Diabetes Mellitus (T2DM)

Summary

EudraCT number	2013-003131-30
Trial protocol	GB DE BE IT EE SE LT LV CZ ES HU DK FR
Global end of trial date	17 June 2015

Results information

Result version number	v1 (current)
This version publication date	30 June 2016
First version publication date	30 June 2016

Trial information

Trial identification

Sponsor protocol code	EFC12404

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02058147
WHO universal trial number (UTN)	U1111-1148-4334
Other trial identifiers	Study Name: LixiLan-O

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

Global end of trial reached?	Yes
Global end of trial date	17 June 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 lixisenatide in glycosylated hemoglobin (HbA1c) change from baseline to Week 30, and to demonstrate the non-inferiority of the FRC to insulin glargine in HbA1c change from baseline to Week 30. If noninferiority was shown, statistical superiority of the FRC compared to insulin glargine on HbA1c change from baseline to Week 30 was to be tested according to the prespecified testing hierarchy.

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:

Subjects were treated for at least 3 months prior to screening with metformin with or without a second oral anti-diabetic treatment (OAD). Subjects receiving metformin plus another OAD at screening had to stop the second OAD at the start of run-in (4 weeks prior randomization). For all subjects, the dose of metformin was optimized during run-in and had to be ≥1500 mg/day to allow randomization.

Evidence for comparator: -

Actual start date of recruitment	12 February 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: 11
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Chile: 45
Country: Number of subjects enrolled	United States: 362
Country: Number of subjects enrolled	Mexico: 72
Country: Number of subjects enrolled	Romania: 58
Country: Number of subjects enrolled	Russian Federation: 106
Country: Number of subjects enrolled	South Africa: 49
Country: Number of subjects enrolled	Ukraine: 59
Country: Number of subjects enrolled	Poland: 47
Country: Number of subjects enrolled	Spain: 47

Country: Number of subjects enrolled	Sweden: 19
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Czech Republic: 73
Country: Number of subjects enrolled	Denmark: 16
Country: Number of subjects enrolled	Estonia: 19
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Hungary: 56
Country: Number of subjects enrolled	Italy: 26
Country: Number of subjects enrolled	Latvia: 27
Country: Number of subjects enrolled	Lithuania: 35
Worldwide total number of subjects	1170
EEA total number of subjects	455

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)	864
From 65 to 84 years	306
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 240 centers in 23 countries. A total of 2457 subjects were screened between February 12, 2014 and September 16, 2014. 978 subjects were not eligible for run-in mainly due to glycosylated hemoglobin (HbA1c) value at screening visit being out of the protocol defined range.

Pre-assignment

Screening details:

After 2 weeks screening period, 1479 subjects underwent 4--week run–in period. 309 subjects were run-in failures. A total of 1170 subjects were randomized in 2:2:1 to insulin glargine/lixisenatide, insulin glargine and lixisenatide 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:

Insulin glargine 10 U/ Lixisenatide 5 mcg fixed-ratio combination (FRC) once daily (QD) for first week post-randomization, followed by dose adjustment (avoiding hypoglycemia) to reach and maintain fasting self-monitored plasma glucose (SMPG) of 80 mg/dL to 100 mg/dL (4.4 mmol/L to 5.6 mmol/L) up to 30 weeks.

Arm type	Experimental
Investigational medicinal product name	Insulin glargine/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:

Insulin glargine/Lixisenatide fixed ratio combination was self-administered QD in the morning within one hour before breakfast using one of the 2 available prefilled disposable SoloStar® pen-injectors: Pen A or B, depending upon the 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 of doses from 10U/5mcg to 40U/20mcg.
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 to administer doses above 30U/10 mcg up to the maximal daily dose of 60U/20 mcg.

Arm title	Insulin Glargine

Arm description:

Insulin glargine 10 U QD for first week post-randomization, followed by dose adjustment (avoiding hypoglycemia) to reach and maintain fasting SMPG of 80 mg/dL to 100 mg/dL (4.4 mmol/L to 5.6 mmol/L) 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.

Arm title	Lixisenatide

Arm description:

Lixisenatide 10 mcg QD for 2 weeks post-randomization, then at a maintenance dose of 20 mcg QD up to 30 weeks.

Arm type	Active comparator
Investigational medicinal product name	Lixisenatide
Investigational medicinal product code	AVE0010
Other name	Lyxumia
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Lixisenatide was self-administered QD within 0 to 60 minutes before breakfast or evening meal. If the maintenance dose of 20 mcg was not tolerated, dose could be reduced to 10 mcg.

Number of subjects in period 1	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine	Lixisenatide
Started	469	467	234
Treated	469	467	233
Completed	440	440	205
Not completed	29	27	29
Randomized but not treated	-	-	1
Adverse event	12	9	21
Other than specified	8	9	-
Poor compliance to protocol	8	9	4
Lack of efficacy	1	-	3

Baseline characteristics

Reporting groups	
Reporting group title	Insulin Glargine/Lixisenatide Fixed Ratio Combination
Reporting group description:	
Insulin glargine 10 U/ Lixisenatide 5 mcg fixed-ratio combination (FRC) once daily (QD) for first week post-randomization, followed by dose adjustment (avoiding hypoglycemia) to reach and maintain fasting self-monitored plasma glucose (SMPG) of 80 mg/dL to 100 mg/dL (4.4 mmol/L to 5.6 mmol/L) up to 30 weeks.	
Reporting group title	Insulin Glargine
Reporting group description:	
Insulin glargine 10 U QD for first week post-randomization, followed by dose adjustment (avoiding hypoglycemia) to reach and maintain fasting SMPG of 80 mg/dL to 100 mg/dL (4.4 mmol/L to 5.6 mmol/L) up to 30 weeks.	
Reporting group title	Lixisenatide
Reporting group description:	
Lixisenatide 10 mcg QD for 2 weeks post-randomization, then at a maintenance dose of 20 mcg QD up to 30 weeks.	

Reporting group values	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine	Lixisenatide
Number of subjects	469	467	234
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	58.2	58.3	58.7
standard deviation	± 9.5	± 9.4	± 8.7
Gender categorical Units: Subjects			
Female	247	230	101
Male	222	237	133
Race Units: Subjects			
Caucasian	417	421	216
Black	33	33	12
Asian/Oriental	8	7	3
Other	11	6	3
Ethnicity Units: Subjects			
Hispanic	85	87	51
Not Hispanic	384	380	183
Second OAD use Units: Subjects			
Yes	274	270	133
No	195	197	101
Second OAD use at screening by class Units: Subjects			

Sulfonylurea	259	249	123
Glinide	3	10	5
Sodium-glucose cotransporter-2 inhibitor	2	2	0
Dipeptidyl peptidase-4 inhibitor	12	11	5
None	193	195	101
Body Mass Index (BMI)			
Units: kg/m^2			
arithmetic mean	31.64	31.66	31.99
standard deviation	± 4.4	± 4.51	± 4.39
Duration of Diabetes			
Units: years			
arithmetic mean	8.89	8.66	8.89
standard deviation	± 5.51	± 5.59	± 6.26
Daily dose of metformin			
Units: mg			
arithmetic mean	2246.1	2244.7	2267.3
standard deviation	± 456.8	± 444.7	± 427.4
HbA1c			
Units: percentage of HbA1c			
arithmetic mean	8.08	8.08	8.13
standard deviation	± 0.71	± 0.69	± 0.72
Fasting plasma glucose (FPG)			
Units: mmol/L			
arithmetic mean	9.87	9.75	9.75
standard deviation	± 2.35	± 2.32	± 2.19

Reporting group values	Total		
Number of subjects	1170		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	578		
Male	592		
Race			
Units: Subjects			
Caucasian	1054		
Black	78		
Asian/Oriental	18		
Other	20		
Ethnicity			
Units: Subjects			
Hispanic	223		
Not Hispanic	947		
Second OAD use			

Units: Subjects			
Yes	677		
No	493		
Second OAD use at screening by class Units: Subjects			
Sulfonylurea	631		
Glinide	18		
Sodium-glucose cotransporter-2 inhibitor	4		
Dipeptidyl peptidase-4 inhibitor	28		
None	489		
Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean			
standard deviation	-		
Duration of Diabetes Units: years			
arithmetic mean			
standard deviation	-		
Daily dose of metformin Units: mg			
arithmetic mean			
standard deviation	-		
HbA1c Units: percentage of HbA1c			
arithmetic mean			
standard deviation	-		
Fasting plasma glucose (FPG) Units: mmol/L			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Insulin Glargine/Lixisenatide Fixed Ratio Combination
Reporting group description:	
Insulin glargine 10 U/ Lixisenatide 5 mcg fixed-ratio combination (FRC) once daily (QD) for first week post-randomization, followed by dose adjustment (avoiding hypoglycemia) to reach and maintain fasting self-monitored plasma glucose (SMPG) of 80 mg/dL to 100 mg/dL (4.4 mmol/L to 5.6 mmol/L) up to 30 weeks.	
Reporting group title	Insulin Glargine
Reporting group description:	
Insulin glargine 10 U QD for first week post-randomization, followed by dose adjustment (avoiding hypoglycemia) to reach and maintain fasting SMPG of 80 mg/dL to 100 mg/dL (4.4 mmol/L to 5.6 mmol/L) up to 30 weeks.	
Reporting group title	Lixisenatide
Reporting group description:	
Lixisenatide 10 mcg QD for 2 weeks post-randomization, then at a maintenance dose of 20 mcg QD 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	Lixisenatide	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	467	464	233	
Units: percentage of hemoglobin				
least squares mean (standard error)	-1.63 (± 0.038)	-1.34 (± 0.039)	-0.85 (± 0.052)	

Statistical analyses

Statistical analysis title	Insulin Glargine/Lixisenatide vs Lixisenatide
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 second OAD use at screening, visit, treatment-by-visit interaction, and country as fixed effects and baseline HbA1c	

value-by-visit interaction as a covariate.

Comparison groups	Insulin Glargine/Lixisenatide Fixed Ratio Combination v Lixisenatide
Number of subjects included in analysis	700
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Mixed models analysis
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	-0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.898
upper limit	-0.665
Variability estimate	Standard error of the mean
Dispersion value	0.059

Notes:

[1] - Threshold for significance ≤ 0.05.

Statistical analysis title	Insulin Glargine/Lixisenatide vs Insulin glargine

Statistical analysis description:

Analysis was performed using MMRM model with treatment groups, randomization strata of Week --1 HbA1c (<8.0, ≥8.0%), randomization strata of second OAD use at screening, visit, treatment-by-visit interaction, and country as fixed effects and baseline HbA1c value-by-visit interaction as a covariate.

Comparison groups	Insulin Glargine/Lixisenatide Fixed Ratio Combination v Insulin Glargine
Number of subjects included in analysis	931
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.384
upper limit	-0.194
Variability estimate	Standard error of the mean
Dispersion value	0.048

Notes:

[2] - Predefined non-inferiority margin of 0.3%.
Test of superiority of Insulin glargine/Lixisenatide FRC over Insulin glargine was also performed according to hierarchical testing procedure no. 6.

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 without Week 30 value for HbA1c 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	Lixisenatide	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	468	466	233	
Units: percentage of subjects				
number (not applicable)				
HbA1c <7.0%	73.7	59.4	33	
HbA1c ≤6.5%	55.8	39.5	19.3	

Statistical analyses

Statistical analysis title	HbA1c <7.0%: FRC vs Lixisenatide

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 second OAD use at screening. This analysis was out of testing order.

Comparison groups	Insulin Glargine/Lixisenatide Fixed Ratio Combination v Lixisenatide
Number of subjects included in analysis	701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	40.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	33.63
upper limit	47.59

Notes:

[3] - Threshold for significance ≤ 0.05.

Statistical analysis title	HbA1c ≤6.5%: FRC vs Lixisenatide

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 second OAD use at screening. This analysis was out of testing order.

Comparison groups	Insulin Glargine/Lixisenatide Fixed Ratio Combination v Lixisenatide

Number of subjects included in analysis	701
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	36.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	29.81
upper limit	42.95

Notes:

[4] - Threshold for significance ≤ 0.05.

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 second OAD 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	934
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	14.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.37
upper limit	20.25

Notes:

[5] - Threshold for significance ≤ 0.05.

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 second OAD 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	934
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	16.35

Confidence interval	
level	95 %
sides	2-sided
lower limit	10.13
upper limit	22.58

Notes:

[6] - Threshold for significance ≤ 0.05.

Secondary: Change in Plasma Glucose Excursion from Baseline to Week 30

End point title	Change in Plasma Glucose Excursion from Baseline to Week 30

End point description:

Plasma glucose excursion = 2-hour postprandial plasma glucose (PPG) value minus plasma glucose value obtained 30 minutes prior to the start of 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. Missing data was imputed using last observation carried forward (LOCF). Here, number of subjects analyzed=subjects with baseline and at least one post-baseline plasma glucose excursion 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	Lixisenatide	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	428	425	192	
Units: mmol/L				
least squares mean (standard error)	-2.31 (± 0.154)	-0.18 (± 0.157)	-3.23 (± 0.216)	

Statistical analyses

Statistical analysis title	Insulin Glargine/Lixisenatide vs Insulin glargine

Statistical analysis description:

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 second OAD use at screening, & country as fixed effects & baseline plasma glucose excursion value as a covariate. A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Here, it is test no. 1 of testing order.

Comparison groups	Insulin Glargine/Lixisenatide Fixed Ratio Combination v Insulin Glargine
Number of subjects included in analysis	853
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.0001 [8]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.498
upper limit	-1.77
Variability estimate	Standard error of the mean
Dispersion value	0.185

Notes:

[7] - Testing was performed in following order: 1. & 2. FRC v insulin glargine for both test of 2h-Glucose excursion; & body weight; 3. & 4. FRC vs lixisenatide for both FPG; & 7-point SMPG; 5. to 10. FRC vs insulin glargine for endpoints: subjects reached HbA1c<7% with no body weight gain; HbA1c (superiority); 7-point SMPG; subjects reached HbA1c<7% with no body weight gain & symptomatic hypoglycemia; insulin glargine dose; & FPG.
[8] - Hierarchical testing sequence continued only when co-primary hypotheses (superiority of FRC to lixisenatide & non-inferiority of FRC to insulin glargine for HbA1c change from baseline) was statistically significant. Threshold for significance ≤ 0.05.

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	Lixisenatide	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	467	465	233	
Units: kg				
least squares mean (standard error)	-0.29 (± 0.182)	1.11 (± 0.183)	-2.3 (± 0.256)	

Statistical analyses

Statistical analysis title	Insulin Glargine/Lixisenatide vs Insulin glargine

Statistical analysis description:

Testing according to the hierarchical testing procedure (continued only if previous endpoints were statistically significant). Here, it is test no. 2 of testing order. Analysis was performed using MMRM model with treatment groups, randomization strata of Week --1 HbA1c (<8.0, ≥8.0%), randomization strata of second OAD use at screening, visit, treatment-by-visit interaction, and country as fixed effects and baseline body weight value-by-visit interaction as a covariate.

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

Number of subjects included in analysis	932
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.891
upper limit	-0.91
Variability estimate	Standard error of the mean
Dispersion value	0.25

Notes:

[9] - Threshold for significance ≤ 0.05.

Secondary: Change in FPG From Baseline to Week 30

End point title	Change in 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	Lixisenatide	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	465	465	232	
Units: mmol/L				
least squares mean (standard error)	-3.46 (± 0.09)	-3.27 (± 0.091)	-1.5 (± 0.124)	

Statistical analyses

Statistical analysis title	Insulin Glargine/Lixisenatide vs Lixisenatide

Statistical analysis description:

Testing according to the hierarchical testing procedure (continued only if previous endpoints were statistically significant). Here, it is test no. 3 of testing order. Analysis was performed using MMRM model with treatment groups, randomization strata of Week -1 HbA1c (<8.0, ≥8.0%), randomization strata of second OAD use at screening, visit, treatment-by-visit interaction, and country as fixed effects and baseline FPG value-by-visit interaction as a covariate.

Comparison groups	Insulin Glargine/Lixisenatide Fixed Ratio Combination v Lixisenatide

Number of subjects included in analysis	697
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-1.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.246
upper limit	-1.682
Variability estimate	Standard error of the mean
Dispersion value	0.144

Notes:

[10] - Threshold for significance ≤ 0.05

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	Lixisenatide	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	421	411	204	
Units: mmol/L				
least squares mean (standard error)	-3.35 (± 0.081)	-2.66 (± 0.084)	-1.95 (± 0.111)	

Statistical analyses

Statistical analysis title	Insulin Glargine/Lixisenatide vs Lixisenatide

Statistical analysis description:

Testing according to the hierarchical testing procedure (continued only if previous endpoints were statistically significant). Here, it is test no. 4 of testing order. Analysis was performed using MMRM model with treatment groups, randomization strata of Week -1 HbA1c (<8.0, ≥8.0%), randomization strata of second OAD use at screening, visit, treatment-by-visit interaction, and country as fixed effects

and baseline 7-point SMPG value-by-visit interaction as a covariate.

Comparison groups	Insulin Glargine/Lixisenatide Fixed Ratio Combination v Lixisenatide
Number of subjects included in analysis	625
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [11]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.645
upper limit	-1.158
Variability estimate	Standard error of the mean
Dispersion value	0.124

Notes:

[11] - Threshold for significance ≤ 0.05.

Statistical analysis title	Insulin Glargine/Lixisenatide vs Insulin Glargine

Statistical analysis description:

Testing according to the hierarchical testing procedure (continued only if previous endpoints were statistically significant). Here, it is test no. 7 of testing order. Analysis was performed using MMRM model with treatment groups, randomization strata of Week -1 HbA1c (<8.0, ≥8.0%), randomization strata of second OAD use at screening, visit, treatment-by-visit interaction, and country as fixed effects and baseline 7-point SMPG value-by-visit interaction, as a covariate.

Comparison groups	Insulin Glargine/Lixisenatide Fixed Ratio Combination v Insulin Glargine
Number of subjects included in analysis	832
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.892
upper limit	-0.495
Variability estimate	Standard error of the mean
Dispersion value	0.101

Notes:

[12] - Threshold for significance ≤ 0.05.

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 any 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	Lixisenatide	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	468	466	233	
Units: Percentage of subjects				
number (not applicable)	43.2	25.1	27.9	

Statistical analyses

Statistical analysis title	Insulin Glargine/Lixisenatide vs Insulin glargine

Statistical analysis description:

Testing according to the hierarchical testing procedure (continued only if previous endpoints were statistically significant). Here, it is test no. 5 of testing order. Analysis was performed using Cochran-Mantel-Haenszel method stratified on randomization strata of Week-1 HbA1c (<8%, ≥8%) and randomization strata of second OAD use at screening.

Comparison groups	Insulin Glargine/Lixisenatide Fixed Ratio Combination v Insulin Glargine
Number of subjects included in analysis	934
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	18.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.15
upper limit	24.01

Notes:

[13] - Threshold for significance ≤ 0.05.

Secondary: Change in HbA1c From Baseline to Week 30 (Superiority of Insulin Glargine/Lixisenatide vs Insulin Glargine)

End point title	Change in HbA1c From Baseline to Week 30 (Superiority of Insulin Glargine/Lixisenatide vs Insulin Glargine)

End point description:

Change in HbA1c 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 HbA1c 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	Lixisenatide	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	467	464	233	
Units: percentage of hemoglobin				
least squares mean (standard error)	-1.63 (± 0.038)	-1.34 (± 0.039)	-0.85 (± 0.052)	

Statistical analyses

Statistical analysis title	Insulin Glargine/Lixisenatide vs Insulin Glargine

Statistical analysis description:

Testing according to the hierarchical testing procedure (continued only if previous endpoints were statistically significant). Here, it is test no. 6 of testing order. Analysis was performed using MMRM model with treatment groups, randomization strata of Week -1 HbA1c (<8.0, ≥8.0%), randomization strata of second OAD use at screening, visit, treatment-by-visit interaction, and country as fixed effects and baseline HbA1c value-by-visit interaction as a covariate.

Comparison groups	Insulin Glargine/Lixisenatide Fixed Ratio Combination v Insulin Glargine
Number of subjects included in analysis	931
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.384
upper limit	-0.194
Variability estimate	Standard error of the mean
Dispersion value	0.048

Notes:

[14] - Threshold for significance ≤ 0.05.

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 any 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	Lixisenatide	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	468	466	233	
Units: Percentage of subjects				
number (not applicable)	31.8	18.9	26.2	

Statistical analyses

Statistical analysis title	Insulin Glargine/Lixisenatide vs Insulin Glargine

Statistical analysis description:

Testing according to the hierarchical testing procedure (continued only if previous endpoints were statistically significant). Here, it is test no. 8 of testing order. Analysis was performed using Cochran-Mantel-Haenszel method stratified on randomization strata of Week-1 HbA1c (<8.0%, ≥8.0%) and randomization strata of second OAD use at screening.

Comparison groups	Insulin Glargine v Insulin Glargine/Lixisenatide Fixed Ratio Combination
Number of subjects included in analysis	934
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [15]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	12.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.5
upper limit	18.45

Notes:

[15] - Threshold for significance ≤ 0.05.

Secondary: Average Daily Insulin Glargine Dose at Week 30

End point title	Average Daily Insulin Glargine Dose at Week 30[16]

End point description:

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

End point type	Secondary

End point timeframe:

Week 30

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point is reporting results only for the arms in which Insulin glargine was administered.

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	467	463		
Units: Units (U)				
least squares mean (standard error)	39.77 (± 0.699)	40.46 (± 0.701)		

Statistical analyses

Statistical analysis title	Insulin Glargine/Lixisenatide vs Insulin Glargine

Statistical analysis description:

Testing according to the hierarchical testing procedure (continued only if previous endpoints were statistically significant). Here, it is test no. 9 of testing order. Analysis was performed using MMRM model with treatment groups, randomization strata of Week-1 HbA1c (<8.0, ≥8.0%), randomization strata of second OAD use at screening, visit, treatment-by-visit interaction, and country as fixed effects.

Comparison groups	Insulin Glargine/Lixisenatide Fixed Ratio Combination v Insulin Glargine
Number of subjects included in analysis	930
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4857 [17]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.632
upper limit	1.252
Variability estimate	Standard error of the mean
Dispersion value	0.99

Notes:

[17] - Threshold for significance ≤ 0.05.

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:

The 2-hour PPG test measured blood glucose 2 hours after eating a liquid standardized breakfast meal. Change in PPG was calculated by subtracting baseline value from Week 30 value. Missing data was

imputed using LOCF. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline 2¬hour PPG 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	Lixisenatide	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	430	430	196	
Units: mmol/L				
least squares mean (standard error)	-5.68 (± 0.176)	-3.31 (± 0.178)	-4.58 (± 0.245)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reaching HbA1c <7.0% at Week 30 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% at Week 30 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). The analysis included all HbA1c measurements at week 30, including those obtained after the IMP discontinuation or the introduction of rescue medication. mITT population. Subjects without Week 30 value for HbA1c 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	Lixisenatide	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	468	466	233	
Units: Percentage of subjects				
number (not applicable)	53.6	44.4	30.5	

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) was 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	Lixisenatide	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	468	466	233	
Units: Percentage of subjects				
number (not applicable)	3.6	3.4	12.4	

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)

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine	Lixisenatide	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	469	467	233	
Units: Events per subject-year				
number (not applicable)	1.44	1.22	0.34	

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)

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine	Lixisenatide	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	469	467	233	
Units: Percentage of Subjects				
number (not applicable)	25.6	23.6	6.4	

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 of 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)

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Insulin Glargine	Lixisenatide	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	469	467	233	
Units: Percentage of subjects				
number (not applicable)	0	0.2	0	

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-treatment period' (time from first injection of open-label IMP up to 3 days [1 day for symptomatic hypoglycemia] after the last injection of IMP regardless of the introduction of rescue therapy).

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:

Insulin glargine 10 U/ Lixisenatide 5 mcg fixed-ratio combination (FRC) once daily (QD) for first week post-randomization, followed by dose adjustment (avoiding hypoglycemia) to reach and maintain fasting SMPG of 80 mg/dL to 100 mg/dL (4.4 mmol/L to 5.6 mmol/L) up to 30 weeks (median exposure: 211 days).

Reporting group title	Lixisenatide

Reporting group description:

Lixisenatide 10 mcg QD for 2 weeks post-randomization, then at a maintenance dose of 20 mcg QD up to Week 30 (median exposure: 211 days).

Reporting group title	Insulin Glargine

Reporting group description:

Insulin glargine 10 U QD for first week post-randomization, followed by dose adjustment (avoiding hypoglycemia) to reach and maintain fasting SMPG of 80 mg/dL to 100 mg/dL (4.4 mmol/L to 5.6 mmol/L) up to 30 weeks (median exposure: 211 days).

Serious adverse events	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Lixisenatide	Insulin Glargine
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 469 (3.84%)	9 / 233 (3.86%)	19 / 467 (4.07%)
number of deaths (all causes)	1	1	2
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung Cancer Metastatic			
subjects affected / exposed	1 / 469 (0.21%)	0 / 233 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lung Neoplasm Malignant			

subjects affected / exposed	0 / 469 (0.00%)	1 / 233 (0.43%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases To Liver			
subjects affected / exposed	0 / 469 (0.00%)	1 / 233 (0.43%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic Carcinoma			
subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate Cancer Recurrent			
subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous Cell Carcinoma Of Skin			
subjects affected / exposed	1 / 469 (0.21%)	0 / 233 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous Cell Carcinoma Of The Oral Cavity			
subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Thyroid Adenoma			
subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 469 (0.21%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Death			
subjects affected / exposed	0 / 469 (0.00%)	1 / 233 (0.43%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic Reaction			
subjects affected / exposed	0 / 469 (0.00%)	1 / 233 (0.43%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Acquired Phimosis			
subjects affected / exposed	1 / 469 (0.21%)	0 / 233 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical Dysplasia			
subjects affected / exposed	1 / 469 (0.21%)	0 / 233 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metrorrhagia			
subjects affected / exposed	1 / 469 (0.21%)	0 / 233 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute Pulmonary Oedema			
subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Chronic Obstructive Pulmonary Disease			

subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Failure			
subjects affected / exposed	0 / 469 (0.00%)	1 / 233 (0.43%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Electrocardiogram St-T Segment Abnormal			
subjects affected / exposed	1 / 469 (0.21%)	0 / 233 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase Increased			
subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Comminuted Fracture			
subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon Rupture			
subjects affected / exposed	1 / 469 (0.21%)	0 / 233 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity To Various Agents			
subjects affected / exposed	0 / 469 (0.00%)	1 / 233 (0.43%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac Failure Acute			
subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac Failure Chronic			
subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Failure Congestive			
subjects affected / exposed	1 / 469 (0.21%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Coronary Artery Disease			
subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Infarction			
subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	1 / 469 (0.21%)	0 / 233 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Lacunar Infarction			
subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Radiculopathy			
subjects affected / exposed	0 / 469 (0.00%)	1 / 233 (0.43%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient Ischaemic Attack			
subjects affected / exposed	1 / 469 (0.21%)	1 / 233 (0.43%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Oesophagitis			
subjects affected / exposed	1 / 469 (0.21%)	0 / 233 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis Chronic			
subjects affected / exposed	1 / 469 (0.21%)	0 / 233 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 469 (0.21%)	0 / 233 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	1 / 469 (0.21%)	0 / 233 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute Kidney Injury			

subjects affected / exposed	0 / 469 (0.00%)	1 / 233 (0.43%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder Prolapse			
subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus Urinary			
subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Colic			
subjects affected / exposed	1 / 469 (0.21%)	0 / 233 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Costochondritis			
subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Osteoarthritis			
subjects affected / exposed	0 / 469 (0.00%)	1 / 233 (0.43%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Erysipelas			
subjects affected / exposed	1 / 469 (0.21%)	1 / 233 (0.43%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile Infection			
subjects affected / exposed	1 / 469 (0.21%)	0 / 233 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis Staphylococcal			
subjects affected / exposed	0 / 469 (0.00%)	1 / 233 (0.43%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis Acute			
subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	2 / 469 (0.43%)	0 / 233 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 469 (0.00%)	0 / 233 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes Mellitus Inadequate Control			
subjects affected / exposed	0 / 469 (0.00%)	1 / 233 (0.43%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic Acidosis			

subjects affected / exposed	0 / 469 (0.00%)	1 / 233 (0.43%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Insulin Glargine/Lixisenatide Fixed Ratio Combination	Lixisenatide	Insulin Glargine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	138 / 469 (29.42%)	98 / 233 (42.06%)	85 / 467 (18.20%)
Nervous system disorders			
Headache			
subjects affected / exposed	24 / 469 (5.12%)	18 / 233 (7.73%)	15 / 467 (3.21%)
occurrences (all)	28	22	16
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	42 / 469 (8.96%)	21 / 233 (9.01%)	20 / 467 (4.28%)
occurrences (all)	54	26	26
Nausea			
subjects affected / exposed	45 / 469 (9.59%)	56 / 233 (24.03%)	17 / 467 (3.64%)
occurrences (all)	63	76	17
Vomiting			
subjects affected / exposed	15 / 469 (3.20%)	15 / 233 (6.44%)	7 / 467 (1.50%)
occurrences (all)	18	19	9
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	26 / 469 (5.54%)	15 / 233 (6.44%)	25 / 467 (5.35%)
occurrences (all)	33	18	27
Upper Respiratory Tract Infection			
subjects affected / exposed	33 / 469 (7.04%)	12 / 233 (5.15%)	23 / 467 (4.93%)
occurrences (all)	38	13	25

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 July 2014	Following changes were made: •Inclusion criterion was modified to allow enrollment of subjects with prior metformin and Dipeptidyl peptidase-4 (DPP-4) inhibitor treatment. •Monitoring and evaluating of device/pen-related events was added. •Changes to collection of pharmacokinetic (PK) and antibody sampling were made. PK assessments in the lixisenatide group were only to be done in subjects who injected IMP in the morning. Blood samples for PK and antibody analyses were to be analyzed before initiating rescue therapy. Blood samples for antibody analyses had to be collected and assessed at Week 30 for subjects who permanently discontinued IMP and stayed in the study. •Calculated creatinine clearance categories at screening used for the description of demographic and baseline characteristics were changed to be consistent with the draft Food and Drugs Administration (FDA) guideline for Industry. •Contraceptive methods allowed for women of childbearing potential were clarified following a request from the Danish Health Authority for subjects from Denmark. •Primary efficacy analyses were to be performed using assessment collected during the study instead of during the on-treatment period •The step-down testing procedure for efficacy endpoints was updated •Analyses of pancreatitis and pancreatic neoplasm positively adjudicated by pancreatic safety assessment committee (PSAC) were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported