Clinical trial results:
A 26-Week Randomized, Open-label, Active Controlled, Parallel-group, Study Assessing the Efficacy and Safety of the Insulin Glargine/Lixisenatide Fixed Ratio Combination in Adults With Type 2 Diabetes Inadequately Controlled on GLP-1 Receptor Agonist and Metformin (Alone or With Pioglitazone and/or SGLT2 Inhibitors), Followed by a Fixed Ratio Combination Single-arm 26-Week Extension Period

Summary

EudraCT number	2014-004850-32
Trial protocol	SK EE ES DE IT
Global end of trial date	17 November 2018

Results information

Result version number	v1 (current)
This version publication date	02 December 2019
First version publication date	02 December 2019

Trial information

Trial identification

Sponsor protocol code	EFC13794

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02787551
WHO universal trial number (UTN)	U1111-1168-4639
Other trial identifiers	STUDY NAME: LixiLan-G

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	13 December 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 November 2018
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) versus GLP-1 receptor agonist (GLP-1 RA) in hemoglobin A1c (HbA1c) change from Baseline to Week 26.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject was participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy:

Oral anti-diabetic (OAD) treatment metformin, pioglitazone, and sodium-glucose co-transporter 2 (SGLT2) inhibitors (canagliflozin, dapagliflozin, empagliflozin) was used as background therapy.

Evidence for comparator: -

Actual start date of recruitment	06 July 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 62
Country: Number of subjects enrolled	Slovakia: 75
Country: Number of subjects enrolled	Spain: 48
Country: Number of subjects enrolled	Estonia: 13
Country: Number of subjects enrolled	Germany: 20
Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	Israel: 17
Country: Number of subjects enrolled	Italy: 33
Country: Number of subjects enrolled	United States: 223
Worldwide total number of subjects	514
EEA total number of subjects	251

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)	334
From 65 to 84 years	180
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 112 sites in 9 countries. A total of 840 subjects were screened between 06 July 2016 and 01 November 2017, of which 326 were screen failures. Screen failures were mainly due to glycated hemoglobin (HbA1c) level lesser than (<) 7% or more than (>) 9% at screening visit.

Pre-assignment

Screening details:

A total of 514 subjects were randomized in 1:1 (Insulin Glargine/Lixisenatide FRC or GLP-1 RA) ratio. Randomization was stratified by values of HbA1c at screening (=8%) & GLP-1 RA subtype at screening (once/twice daily [QD/BID], once weekly [QW] formulations).

Period 1

Period 1 title	Core Period: 26 Weeks
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 (FRC)

Arm description:

FRC injected subcutaneously QD for 26 weeks on top of oral anti-diabetic drug (OAD) therapy. Dose individually adjusted.

Arm type	Experimental
Investigational medicinal product name	Insulin glargine/lixisenatide fixed-ratio combination
Investigational medicinal product code	HOE901/AVE0010
Other name	Soliqua
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

FRC was self-administered with a pre-filled disposable SoloStar® pen-injector. Dose of the combination was titrated according to the subject's need for insulin. FRC was given QD in the morning in the hour (0 to 60 minutes) before breakfast. Dose was individually titrated throughout the study to reach and maintain fasting SMPG: 80-100 milligrams per deciliter (mg/dL) (4.4 - 5.6 millimoles per litre [mmol/L]) avoiding hypoglycemia.

Arm title	GLP-1 Receptor Agonist

Arm description:

GLP-1 RA receptor agonist (liraglutide QD, exenatide BID, exenatide extended-release QW, albiglutide QW, or dulaglutide QW) injected subcutaneously for 26 weeks on top of OAD therapy. GLP-1 RAs were administered as per local labeling at the same dose schedule as prior to randomisation.

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

Dosage and administration details:

QD at any time of day, independently of meals. Victoza is a marketed product and the dose used was in accordance with labeling document.

Investigational medicinal product name	Exenatide
Investigational medicinal product code	
Other name	Byetta®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

BID at any time within the 60 minute period before the morning and evening meal. Byetta is a marketed product and the dose used was in accordance with labeling document.

Investigational medicinal product name	Exenatide extended-release
Investigational medicinal product code	
Other name	Bydureon®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

QW at any time of day, independently of meals. Bydureon is a marketed product and the dose used was in accordance with labeling document.

Investigational medicinal product name	Albiglutide
Investigational medicinal product code	
Other name	Tanzeum®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

QW at any time of day, independently of meals. Tanzeum is a marketed product and the dose used was in accordance with labeling document.

Investigational medicinal product name	Dulaglutide
Investigational medicinal product code	
Other name	Trulicity®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

QW at any time of day, independently of meals. Trulicity is a marketed product and the dose used was in accordance with labeling document.

Number of subjects in period 1	Insulin Glargine/Lixisenatide Fixed Ratio Combination (FRC)	GLP-1 Receptor Agonist
Started	257	257
Treated	255	256
Completed	230	246
Not completed	27	11
Randomized but not treated	2	1
Adverse event	10	-
Withdrawal by Subject	9	9
Other than specified	3	1
Poor compliance to protocol	2	-
Lack of efficacy	1	-

Period 2

Period 2 title	Extension Period:26 Weeks(Upto 52 Weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Insulin Glargine/Lixisenatide FRC- Single Arm Extension Period

Arm description:

Subjects who completed core treatment period and met eligibility criteria entered in extension treatment period and received same treatment (FRC injected subcutaneously QD on top of OAD therapy) for 26 weeks (up to Week 52). Dose individually adjusted.

Arm type	Experimental
Investigational medicinal product name	Insulin glargine/lixisenatide fixed-ratio combination
Investigational medicinal product code	HOE901/AVE0010
Other name	Soliqua
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

FRC was self-administered with a pre-filled disposable SoloStar® pen-injector. Dose of the combination was titrated according to the subject's need for insulin. FRC was given QD in the morning in the hour (0 to 60 minutes) before breakfast. Dose was individually titrated throughout the study to reach and maintain fasting SMPG: 80-100 mg/dL (4.4 - 5.6 mmol/L) avoiding hypoglycemia.

Number of subjects in period 2[1]	Insulin Glargine/Lixisenatide FRC- Single Arm Extension Period
Started	206
Completed	197
Not completed	9
Adverse event	1
Other than specified	5
Poor compliance to protocol	3

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Out of 230 subjects, 206 subjects completed core period and met eligibility criteria for extension period.

Baseline characteristics

Reporting groups	
Reporting group title	Insulin Glargine/Lixisenatide Fixed Ratio Combination (FRC)
Reporting group description:	
FRC injected subcutaneously QD for 26 weeks on top of oral anti-diabetic drug (OAD) therapy. Dose individually adjusted.	

Reporting group title	GLP-1 Receptor Agonist
Reporting group description:	
GLP-1 RA receptor agonist (liraglutide QD, exenatide BID, exenatide extended-release QW, albiglutide QW, or dulaglutide QW) injected subcutaneously for 26 weeks on top of OAD therapy. GLP-1 RAs were administered as per local labeling at the same dose schedule as prior to randomisation.	

Reporting group values	Insulin Glargine/Lixisenatide Fixed Ratio Combination (FRC)	GLP-1 Receptor Agonist	Total
Number of subjects	257	257	514
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	59.2	60.0	
standard deviation	± 9.6	± 10.3	-
Gender categorical Units: Subjects			
Female	131	113	244
Male	126	144	270
Race/Ethnicity Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian/Oriental	3	4	7
Native Hawaiian or Other Pacific Islander	1	0	1
White	241	244	485
Black	12	7	19
Unknown or Not Reported	0	2	2
Body Mass Index (BMI) Units: Subjects			
<30	71	69	140
>=30	186	188	374
GLP-1 receptor agonist use by type at screening Units: Subjects			
Once/twice daily formulation	153	154	307
Once weekly formulation	104	103	207
Duration of diabetes Units: years			
arithmetic mean	11.23	10.95	
standard deviation	± 7.42	± 6.08	-

Hemoglobin A1C (HbA1C) Units: percentage of HbA1c arithmetic mean standard deviation	 7.78 ± 0.62	 7.80 ± 0.56	 -
Daily dose of metformin at baseline Units: milligrams (mg) arithmetic mean standard deviation	 1966.93 ± 434.56	 2030.74 ± 497.15	 -
Daily dose of pioglitazone at baseline			
Data for Daily dose of pioglitazone at baseline is reported for 34 subjects.			
Units: mg arithmetic mean standard deviation	 31.25 ± 10.03	 32.73 ± 8.83	 -
Daily dose of SGLT2 inhibitor (Canagliflozin) at baseline			
Data for daily dose of Canagliflozin at baseline is reported for 19 subjects.			
Units: mg arithmetic mean standard deviation	 214.29 ± 106.90	 283.33 ± 57.74	 -
Daily dose of SGLT2 inhibitor (Empagliflozin) at baseline			
Data for daily dose of Empagliflozin at baseline is reported for 15 subjects.			
Units: mg arithmetic mean standard deviation	 15.42 ± 7.49	 16.67 ± 8.20	 -
Daily dose of SGLT2 inhibitor (Dapagliflozin) at baseline			
Data for daily dose of Dapagliflozin at baseline is reported for 18 subjects.			
Units: mg arithmetic mean standard deviation	 9.62 ± 3.80	 9.00 ± 2.24	 -
Duration of GLP-1 receptor agonist treatment Units: years arithmetic mean standard deviation	 1.89 ± 1.76	 1.92 ± 1.85	 -

End points

End points reporting groups

Reporting group title	Insulin Glargine/Lixisenatide Fixed Ratio Combination (FRC)

Reporting group description:

FRC injected subcutaneously QD for 26 weeks on top of oral anti-diabetic drug (OAD) therapy. Dose individually adjusted.

Reporting group title	GLP-1 Receptor Agonist

Reporting group description:

GLP-1 RA receptor agonist (liraglutide QD, exenatide BID, exenatide extended-release QW, albiglutide QW, or dulaglutide QW) injected subcutaneously for 26 weeks on top of OAD therapy. GLP-1 RAs were administered as per local labeling at the same dose schedule as prior to randomisation.

Reporting group title	Insulin Glargine/Lixisenatide FRC- Single Arm Extension Period

Reporting group description:

Subjects who completed core treatment period and met eligibility criteria entered in extension treatment period and received same treatment (FRC injected subcutaneously QD on top of OAD therapy) for 26 weeks (up to Week 52). Dose individually adjusted.

Primary: Change From Baseline in Glycated Hemoglobin (HbA1c) to Week 26: Core Period

End point title	Change From Baseline in Glycated Hemoglobin (HbA1c) to Week 26: Core Period

End point description:

Change in HbA1c was calculated by subtracting baseline value from Week 26 value. Adjusted least squares (LS) mean and standard error (SE) were obtained from Mixed-effect model with repeated measures (MMRM) to account for missing data using all available post baseline data during the 26 week treatment period. Modified Intent-To-Treat (mITT) population:all randomised subjects who had a baseline and at least 1 post-baseline assessment of any primary/secondary endpoints, irrespective of compliance with study protocol and procedures. Here, "number of subjects analysed" = subjects with baseline and at least 1 post-baseline HbA1c assessment.

End point type	Primary

End point timeframe:

Baseline, Week 26

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination (FRC)	GLP-1 Receptor Agonist		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	253		
Units: percentage of HbA1c				
least squares mean (standard error)	-1.02 (± 0.048)	-0.38 (± 0.048)		

Statistical analyses

Statistical analysis title	FRC vs. GLP-1 RA

Statistical analysis description:

Analysis was performed using MMRM with treatment groups, randomisation strata of Week -2 HbA1c (<8.0%, >=8.0%), GLP-1 RA subtype at screening, visits, treatment-by-visit interaction, world region as fixed effects, baseline HbA1c value-by-visit interaction as a covariate. Analysis included all scheduled measurements obtained during 26-week randomised treatment period, including those obtained after IMP discontinuation/introduction of rescue medication.

Comparison groups	Insulin Glargine/Lixisenatide Fixed Ratio Combination (FRC) v GLP-1 Receptor Agonist
Number of subjects included in analysis	503
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	-0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.77
upper limit	-0.508
Variability estimate	Standard error of the mean
Dispersion value	0.067

Notes:

[1] - Threshold for significance at 0.05 level.

Primary: Change From Baseline in Glycated Hemoglobin (HbA1c) to Week 52: Single Arm Extension Period

End point title	Change From Baseline in Glycated Hemoglobin (HbA1c) to Week 52: Single Arm Extension Period[2]

End point description:

Change in HbA1c was calculated by subtracting baseline value from Week 52 value. Analysis was performed on mITT population who entered the extension period. Here, "number of subjects analysed"= subjects with baseline and at least 1 post-baseline HbA1c assessment.

End point type	Primary

End point timeframe:

Baseline, Week 52

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Insulin Glargine/Lixisenatide FRC-Single Arm Extension Period			
Subject group type	Reporting group			
Number of subjects analysed	202			
Units: percentage of HbA1c				
arithmetic mean (standard error)	-1.01 (± 0.063)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reaching HbA1c <7% or <=6.5% at Week 26: Core Period

End point title	Percentage of Subjects Reaching HbA1c <7% or <=6.5% at Week 26: Core Period

End point description:

Subjects without any available HbA1c assessment at Week 26 were considered as non-responders. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Week 26

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination (FRC)	GLP-1 Receptor Agonist		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	252	253		
Units: percentage of subjects				
number (not applicable)				
HbA1c <7%	61.9	25.7		
HbA1c <=6.5%	40.5	9.9		

Statistical analyses

Statistical analysis title	FRC vs. GLP-1 RA

Statistical analysis description:

HbA1c <7.0%: Insulin Glargine/Lixisenatide FRC vs GLP-1 Receptor Agonist. Analysis was performed using Cochran-Mantel-Haenszel method stratified on randomisation strata of Week -2 HbA1c (<8.0%, >=8.0%), and randomisation strata of GLP-1 receptor agonist subtype at screening. Hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially per pre-specified order (only HbA1c < 7% was part of testing).

Comparison groups	Insulin Glargine/Lixisenatide Fixed Ratio Combination (FRC) v GLP-1 Receptor Agonist

Number of subjects included in analysis	505
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percentage
Point estimate	36.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.11
upper limit	43.99

Notes:

[3] - Threshold for significance <=0.05

Secondary: Percentage of Subjects Reaching HbA1c <7 % or <=6.5% at Week 52: Single Arm Extension Period

End point title	Percentage of Subjects Reaching HbA1c <7 % or <=6.5% at Week 52: Single Arm Extension Period

End point description:

Subjects without any available HbA1c assessment at Week 52 were considered as non-responders. Analysis was performed on mITT population who entered the extension period.

End point type	Secondary

End point timeframe:

Week 52

End point values	Insulin Glargine/Lixisenatide FRC-Single Arm Extension Period			
Subject group type	Reporting group			
Number of subjects analysed	206			
Units: percentage of subjects				
number (not applicable)				
HbA1c <7%	64.1			
HbA1c <=6.5%	42.7			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Change in FPG was calculated by subtracting baseline value from Week 26 value. Adjusted LS means and SE were obtained from MMRM to account for missing data using all available post baseline data during the 26 week treatment period. Analysis was performed using mITT population. Here, "number of subjects analysed"= subjects with baseline and at least one post-baseline FPG assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination (FRC)	GLP-1 Receptor Agonist		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	251	253		
Units: millimoles per litre (mmol/L)				
least squares mean (standard error)	-2.28 (± 0.120)	-0.60 (± 0.119)		

Statistical analyses

Statistical analysis title	FRC vs. GLP-1 RA

Statistical analysis description:

Analysis was performed using MMRM with treatment groups, randomisation strata of Week -2 HbA1c (<8.0%, >=8.0%), randomisation strata of GLP-1 RA subtype at screening, scheduled visit, treatment-by-visit interaction, and world region as fixed effects, and and baseline FPG value-by visit interaction as a covariate. Testing according to the hierarchical testing procedure (continued only if previous end points were statistically significant).

Comparison groups	GLP-1 Receptor Agonist v Insulin Glargine/Lixisenatide Fixed Ratio Combination (FRC)
Number of subjects included in analysis	504
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-1.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.001
upper limit	-1.341
Variability estimate	Standard error of the mean
Dispersion value	0.168

Notes:

[4] - Threshold for significance at 0.05 level.

Secondary: Change From Baseline in Fasting Plasma Glucose (FPG) to Week 52:

Single Arm Extension Period

End point title	Change From Baseline in Fasting Plasma Glucose (FPG) to Week 52: Single Arm Extension Period

End point description:

Change in FPG was calculated by subtracting baseline value from Week 52 value. Analysis was performed on mITT population who entered the extension period. Here, "number of subjects analysed"= subjects with baseline and at least one post-baseline FPG assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Insulin Glargine/Lixisenatide FRC-Single Arm Extension Period			
Subject group type	Reporting group			
Number of subjects analysed	196			
Units: mmol/L				
arithmetic mean (standard error)	-2.27 (± 0.173)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Daily Average of the 7-point Self-monitored Plasma Glucose (SMPG) to Week 26: Core Period

End point title	Change From Baseline in the Daily Average of the 7-point Self-monitored Plasma Glucose (SMPG) to Week 26: Core Period

End point description:

The 7-point SMPG profile was measured at the following 7 points: pre-prandial and 2 hours postprandial for breakfast, lunch, dinner and at bedtime. Two hours postprandial (breakfast, lunch and dinner) was defined as 2 hours after the start of the meal. Adjusted LS means and SE were obtained from MMRM to account for missing data using all available post baseline data during the 26 week treatment period. Analysis was performed using mITT population. Here, "number of subjects analysed"= subjects with baseline and at least one post-baseline 7-point SMPG assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination (FRC)	GLP-1 Receptor Agonist		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	220		
Units: mmol/L				
least squares mean (standard error)	-1.69 (± 0.114)	-0.67 (± 0.112)		

Statistical analyses

Statistical analysis title	FRC vs. GLP-1 RA

Statistical analysis description:

Analysis was performed using MMRM with treatment groups, randomisation strata of Week -2 HbA1c (<8.0%, >=8.0%), randomisation strata of GLP-1 RA subtype at screening, scheduled visit, treatment-by-visit interaction, and world region as fixed effects, and baseline average SMPG value-by-visit interaction as a covariate. Testing according to the hierarchical testing procedure (continued only if previous end points were statistically significant).

Comparison groups	Insulin Glargine/Lixisenatide Fixed Ratio Combination (FRC) v GLP-1 Receptor Agonist
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.325
upper limit	-0.708
Variability estimate	Standard error of the mean
Dispersion value	0.157

Notes:

[5] - Threshold for significance at 0.05 level.

Secondary: Change From Baseline in the Daily Average of the 7-point Self-monitored Plasma Glucose (SMPG) to Week 52: Single Arm Extension Period

End point title	Change From Baseline in the Daily Average of the 7-point Self-monitored Plasma Glucose (SMPG) to Week 52: Single Arm Extension Period

End point description:

The 7-point SMPG profile was measured at the following 7 points: pre-prandial and 2 hours postprandial for breakfast, lunch, dinner and at bedtime. Two hours postprandial (breakfast, lunch and dinner) was defined as 2 hours after the start of the meal. Analysis was performed on mITT population who entered the extension period. Here, "number of subjects analysed"= subjects with baseline and at least one post-baseline 7-point SMPG assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Insulin Glargine/Lixisenatide FRC-Single Arm Extension Period			
Subject group type	Reporting group			
Number of subjects analysed	142			
Units: mmol/L				
arithmetic mean (standard error)	-1.68 (± 0.176)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in 2-Hour Postprandial Plasma Glucose (PPG) During Standardized Meal Test to Week 26: Core Period

End point title	Change From Baseline in 2-Hour Postprandial Plasma Glucose (PPG) During Standardized Meal Test to Week 26: Core Period

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 26 value. Missing data was imputed using LOCF. Analysis was performed on mITT population. Here, "number of subjects analysed"= subjects with baseline and at least one post-baseline plasma glucose assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination (FRC)	GLP-1 Receptor Agonist		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	215	222		
Units: mmol/L				
least squares mean (standard error)	-3.96 (± 0.211)	-1.11 (± 0.205)		

Statistical analyses

Statistical analysis title	FRC vs. GLP-1 RA

Statistical analysis description:

Analysis was performed using analysis of covariance (ANCOVA) model with treatment groups, randomisation strata of Week -2 HbA1c (<8.0%, >=8.0%), randomisation strata of GLP-1 RA subtype (once/twice daily formulations, once weekly formulations) at screening, and world region as fixed effects and baseline 2-hour PPG value as a covariate. Testing according to the hierarchical testing procedure (continued only if previous endpoints were statistically significant).

Comparison groups	Insulin Glargine/Lixisenatide Fixed Ratio Combination (FRC) v GLP-1 Receptor Agonist
Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	ANCOVA
Parameter estimate	LS Mean Difference]
Point estimate	-2.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.42
upper limit	-2.279
Variability estimate	Standard error of the mean
Dispersion value	0.29

Notes:

[6] - Threshold for significance at 0.05 level.

Secondary: Change From Baseline in 2-Hour Postprandial Plasma Glucose (PPG) During Standardized Meal Test to Week 52: Single Arm Extension Period

End point title	Change From Baseline in 2-Hour Postprandial Plasma Glucose (PPG) During Standardized Meal Test to Week 52: Single Arm Extension Period

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 52 value. Missing data was imputed using LOCF. Analysis was performed on mITT population who entered the extension period. Here, "number of subjects analysed"=subjects with baseline and at least one post-baseline plasma glucose assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Insulin Glargine/Lixisenatide FRC-Single Arm Extension Period			
Subject group type	Reporting group			
Number of subjects analysed	192			
Units: mmol/L				
arithmetic mean (standard error)	-4.30 (± 0.284)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in 2-Hour Blood Glucose Excursion During Standardized Meal Test to Week 26: Core Period

End point title	Change From Baseline in 2-Hour Blood Glucose Excursion During Standardized Meal Test to Week 26: Core Period

End point description:

2-hour plasma glucose excursion = 2-hour 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 26 value. Missing data was imputed using LOCF. Analysis was performed using mITT population. Here, "number of subjects analysed"= subjects with baseline and Week 26 assessments.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination (FRC)	GLP-1 Receptor Agonist		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	215	220		
Units: mmol/L				
least squares mean (standard error)	-1.51 (± 0.177)	-0.52 (± 0.173)		

Statistical analyses

Statistical analysis title	FRC vs. GLP-1 RA

Statistical analysis description:

Analysis was performed using ANCOVA model with treatment groups, randomisation strata of Week -2 HbA1c (<8.0%, >=8.0%), randomisation strata of GLP-1 receptor agonist subtype (once/twice daily formulations, once weekly formulations) at screening, and world region as fixed effects and baseline 2-hour plasma glucose excursion value as a covariate. Testing according to the hierarchical testing procedure (continued only if previous endpoints were statistically significant).

Comparison groups	Insulin Glargine/Lixisenatide Fixed Ratio Combination (FRC) v GLP-1 Receptor Agonist

Number of subjects included in analysis	435
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.468
upper limit	-0.508
Variability estimate	Standard error of the mean
Dispersion value	0.244

Notes:

[7] - Threshold for significance at 0.05 level.

Secondary: Change From Baseline in 2-Hour Blood Glucose Excursion During Standardized Meal Test to Week 52: Single Arm Extension Period

End point title	Change From Baseline in 2-Hour Blood Glucose Excursion During Standardized Meal Test to Week 52: Single Arm Extension Period

End point description:

2-hour plasma glucose excursion = 2-hour PPG value minus plasma glucose value obtained 30 minutes prior to the start of meal and before IMP administration if IMP was injected before breakfast. Change in plasma glucose excursions were calculated by subtracting baseline value from Week 52 value. Missing data was imputed using LOCF. Analysis was performed on mITT population who entered the extension period. Here, "number of subjects analysed"= subjects with baseline and Week 52 assessments.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Insulin Glargine/Lixisenatide FRC-Single Arm Extension Period			
Subject group type	Reporting group			
Number of subjects analysed	192			
Units: mmol/L				
arithmetic mean (standard error)	-1.85 (± 0.209)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Requiring Rescue Therapy During the 26 Week

Treatment Period: Core Period

End point title	Percentage of Subjects Requiring Rescue Therapy During the 26 Week Treatment Period: Core Period

End point description:

Routine HbA1c value was used to determine the requirement of rescue medication. Threshold values at Week 12 or later on Week 12: HbA1c >8%. Analysis was performed using mITT population.

End point type	Secondary

End point timeframe:

From Baseline to Week 26

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination (FRC)	GLP-1 Receptor Agonist		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	252	253		
Units: percentage of subjects				
number (not applicable)	4.8	15.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Requiring Rescue Therapy During the 52 Week Treatment Period: Single Arm Extension Period

End point title	Percentage of Subjects Requiring Rescue Therapy During the 52 Week Treatment Period: Single Arm Extension Period

End point description:

Routine HbA1c value was used to determine the requirement of rescue medication. Threshold values at Week 12 or later on Week 12: HbA1c >8%. Analysis was performed on mITT population who entered the extension period.

End point type	Secondary

End point timeframe:

From Week 26 to Week 52

End point values	Insulin Glargine/Lixisenatide FRC-Single Arm Extension Period			
Subject group type	Reporting group			
Number of subjects analysed	206			
Units: percentage of subjects				
number (not applicable)	1.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Body Weight at Week 26: Core Period

End point title	Change From Baseline in Body Weight at Week 26: Core Period

End point description:

Change in body weight was calculated by subtracting baseline value from Week 26 value. Analysis was performed using mITT population. Here, "number of subjects analysed" = subjects with baseline and at least one post-baseline body weight assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination (FRC)	GLP-1 Receptor Agonist		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	251	253		
Units: kilogram (kg)				
least squares mean (standard error)	1.89 (± 0.222)	-1.14 (± 0.220)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Body Weight to Week 52: Single Arm Extension Period

End point title	Change From Baseline in Body Weight to Week 52: Single Arm Extension Period

End point description:

Change in body weight was calculated by subtracting baseline value from Week 52 value. Analysis was performed using mITT population who entered the extension period. Here, "number of subjects analysed"=subjects with baseline and at least one post-baseline body weight assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Insulin Glargine/Lixisenatide FRC-Single Arm Extension Period			
Subject group type	Reporting group			
Number of subjects analysed	202			
Units: kg				
arithmetic mean (standard error)	2.78 (± 0.294)			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Documented symptomatic hypoglycemia was an event during which symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of <=3.9 mmol/L (70 mg/dL). Hypoglycemic episodes with plasma glucose of <3.0 mmol/L (54 mg/dL) were also analysed. Analysis was performed on safety population which included all randomised subjects who received at least one dose of open-label IMP, regardless of the amount of treatment administered. Subjects were analysed according to the treatment actually received (as treated).

End point type	Secondary

End point timeframe:

From Baseline to Week 26

End point values	Insulin Glargine/Lixisenatide Fixed Ratio Combination (FRC)	GLP-1 Receptor Agonist		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	255	256		
Units: events per subject-year				
number (not applicable)				
Documented symptomatic hypoglycemia(<=3.9 mmol/ L)	1.54	0.08		
Documented symptomatic hypoglycemia (<3.0 mmol/ L)	0.25	0.01		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Documented Symptomatic Hypoglycemia Events Per Subject-Year: Single Arm Extension Period

End point title	Number of Documented Symptomatic Hypoglycemia Events Per Subject-Year: Single Arm Extension Period

End point description:

Documented symptomatic hypoglycemia was an event during which symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of <=3.9 mmol/L (70 mg/dL). Hypoglycemic episodes with plasma glucose of <3.0 mmol/L (54 mg/dL) were also analysed. Analysis was performed on safety population who entered the extension period and their data for whole study duration was analysed and reported.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Insulin Glargine/Lixisenatide FRC-Single Arm Extension Period			
Subject group type	Reporting group			
Number of subjects analysed	206			
Units: events per subject-year				
number (not applicable)				
Documented symptomatic hypoglycemia(<=3.9 mmol/ L)	1.59			
Documented symptomatic hypoglycemia (<3.0 mmol/ L)	0.24			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of informed consent until the end of the study (up to 52 weeks).

Adverse event reporting additional description:

Reported AEs are treatment-emergent that is AEs that developed/worsened during during the period from the administration of first dose of the study treatments up to 3 days (9 days for the weekly GLP1) after the last administration. Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Fixed Ratio Combination

Reporting group description:

FRC injected subcutaneously QD for 26 weeks on top of OAD therapy. Dose individually adjusted (median exposure: 183 days).

Reporting group title	GLP-1 Receptor Agonist

Reporting group description:

GLP-1 Receptor Agonist GLP-1 RA receptor agonist (liraglutide QD, exenatide BID, exenatide extendedrelease QW, albiglutide QW, or dulaglutide QW) injected subcutaneously for 26 weeks on top of OAD therapy. GLP-1 RAs were administered as per local labeling at the same dose schedule as prior to randomization (median exposure: 183 days).

Reporting group title	Fixed Ratio Combination Whole Study period

Reporting group description:

Participants who completed core treatment period and met eligibility criteria entered in extension treatment period and received same treatment (FRC injected subcutaneously QD on top of OAD therapy) for 26 weeks (up to Week 52). Dose individually adjusted (median exposure: 365 days).

Serious adverse events	Fixed Ratio Combination	GLP-1 Receptor Agonist	Fixed Ratio Combination Whole Study period
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 255 (3.92%)	9 / 256 (3.52%)	21 / 206 (10.19%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenosquamous Cell Lung Cancer			
subjects affected / exposed	0 / 255 (0.00%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal Cell Carcinoma			

subjects affected / exposed	0 / 255 (0.00%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder Papilloma			
subjects affected / exposed	0 / 255 (0.00%)	1 / 256 (0.39%)	0 / 206 (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
Endometrial Adenocarcinoma			
subjects affected / exposed	1 / 255 (0.39%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glioblastoma			
subjects affected / exposed	0 / 255 (0.00%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatic Neoplasm			
subjects affected / exposed	0 / 255 (0.00%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive Ductal Breast Carcinoma			
subjects affected / exposed	0 / 255 (0.00%)	1 / 256 (0.39%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary Thyroid Cancer			
subjects affected / exposed	1 / 255 (0.39%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Cell Carcinoma			
subjects affected / exposed	0 / 255 (0.00%)	1 / 256 (0.39%)	0 / 206 (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
Vascular disorders			
Vasculitis Necrotising			

subjects affected / exposed	0 / 255 (0.00%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 255 (0.00%)	1 / 256 (0.39%)	0 / 206 (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
Oedema Peripheral			
subjects affected / exposed	0 / 255 (0.00%)	0 / 256 (0.00%)	1 / 206 (0.49%)
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, thoracic and mediastinal disorders			
Acute Pulmonary Oedema			
subjects affected / exposed	1 / 255 (0.39%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Aspiration			
subjects affected / exposed	0 / 255 (0.00%)	0 / 256 (0.00%)	1 / 206 (0.49%)
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			
Ankle Fracture			
subjects affected / exposed	1 / 255 (0.39%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	2 / 255 (0.78%)	0 / 256 (0.00%)	2 / 206 (0.97%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot Fracture			

subjects affected / exposed	1 / 255 (0.39%)	0 / 256 (0.00%)	0 / 206 (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
Hip Fracture			
subjects affected / exposed	0 / 255 (0.00%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	1 / 255 (0.39%)	0 / 256 (0.00%)	0 / 206 (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
Rib Fracture			
subjects affected / exposed	0 / 255 (0.00%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin Laceration			
subjects affected / exposed	0 / 255 (0.00%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid Haemorrhage			
subjects affected / exposed	1 / 255 (0.39%)	0 / 256 (0.00%)	0 / 206 (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
Subcutaneous Haematoma			
subjects affected / exposed	1 / 255 (0.39%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Arteriosclerosis Coronary Artery			
subjects affected / exposed	0 / 255 (0.00%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Fibrillation			

subjects affected / exposed	1 / 255 (0.39%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Failure			
subjects affected / exposed	0 / 255 (0.00%)	0 / 256 (0.00%)	1 / 206 (0.49%)
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	0 / 255 (0.00%)	0 / 256 (0.00%)	2 / 206 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary Artery Disease			
subjects affected / exposed	0 / 255 (0.00%)	0 / 256 (0.00%)	2 / 206 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic Cardiomyopathy			
subjects affected / exposed	1 / 255 (0.39%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral Infarction			
subjects affected / exposed	0 / 255 (0.00%)	1 / 256 (0.39%)	0 / 206 (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
Diabetic Neuropathy			
subjects affected / exposed	0 / 255 (0.00%)	1 / 256 (0.39%)	0 / 206 (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
Hypoglycaemic Unconsciousness			
subjects affected / exposed	1 / 255 (0.39%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraventricular Haemorrhage			

subjects affected / exposed	1 / 255 (0.39%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid Haemorrhage			
subjects affected / exposed	0 / 255 (0.00%)	0 / 256 (0.00%)	2 / 206 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenal Ulcer			
subjects affected / exposed	0 / 255 (0.00%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large Intestine Polyp			
subjects affected / exposed	0 / 255 (0.00%)	1 / 256 (0.39%)	0 / 206 (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
Rectal Haemorrhage			
subjects affected / exposed	1 / 255 (0.39%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermal Cyst			
subjects affected / exposed	0 / 255 (0.00%)	1 / 256 (0.39%)	0 / 206 (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
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	1 / 255 (0.39%)	1 / 256 (0.39%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Retention			
subjects affected / exposed	1 / 255 (0.39%)	0 / 256 (0.00%)	0 / 206 (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			
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 255 (0.00%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 255 (0.39%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 255 (0.39%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Column Stenosis			
subjects affected / exposed	0 / 255 (0.00%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 255 (0.00%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 255 (0.00%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected Skin Ulcer			
subjects affected / exposed	0 / 255 (0.00%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 255 (0.00%)	0 / 256 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia			
subjects affected / exposed	0 / 255 (0.00%)	1 / 256 (0.39%)	0 / 206 (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
Postoperative Abscess			
subjects affected / exposed	0 / 255 (0.00%)	0 / 256 (0.00%)	1 / 206 (0.49%)
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			
Electrolyte Imbalance			
subjects affected / exposed	0 / 255 (0.00%)	1 / 256 (0.39%)	0 / 206 (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

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

Non-serious adverse events	Fixed Ratio Combination	GLP-1 Receptor Agonist	Fixed Ratio Combination Whole Study period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 255 (27.06%)	48 / 256 (18.75%)	75 / 206 (36.41%)
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	14 / 255 (5.49%)	6 / 256 (2.34%)	15 / 206 (7.28%)
occurrences (all)	14	6	17
Nausea			
subjects affected / exposed	22 / 255 (8.63%)	6 / 256 (2.34%)	19 / 206 (9.22%)
occurrences (all)	30	6	30
Infections and infestations			
Influenza			
subjects affected / exposed	11 / 255 (4.31%)	6 / 256 (2.34%)	15 / 206 (7.28%)
occurrences (all)	12	6	19
Nasopharyngitis			
subjects affected / exposed	25 / 255 (9.80%)	23 / 256 (8.98%)	32 / 206 (15.53%)
occurrences (all)	27	26	37
Upper Respiratory Tract Infection			

subjects affected / exposed occurrences (all)	9 / 255 (3.53%) 11	12 / 256 (4.69%) 15	13 / 206 (6.31%) 17

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 September 2016	Main changes were the following: - A single-arm FRC 26-week extension period was introduced to provide additional assessment of all safety, efficacy and other endpoints over 52 weeks in total. - Pharmacokinetic and antibody assessments were added in the FRC treatment group to gain information about exposure to lixisenatide and to assess the immunogenicity of insulin glargine and lixisenatide. - Minor clarifications and corrections were also made.
12 May 2017	Main change was to allow inclusion of subjects receiving background treatment of SGLT2 inhibitors. - Minor clarifications and corrections were also made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported