Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, 2-Arm Parallel-Group, Multicenter, 24-Week Study Assessing the Safety and Efficacy of Lixisenatide in Older Patients with Type 2 Diabetes Inadequately Controlled on Their Current Diabetes Treatment Regimen

Summary

EudraCT number	2012-003292-19
Trial protocol	GB SE ES NO DE DK BG
Global end of trial date	19 February 2015

Results information

Result version number	v1 (current)
This version publication date	20 March 2016
First version publication date	20 March 2016

Trial information

Trial identification

Sponsor protocol code	EFC12703

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01798706
WHO universal trial number (UTN)	U1111-1132-9156
Other trial identifiers	Study Name: GetGoal-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	27 March 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of lixisenatide versus placebo over a period of 24 weeks on glycemic control, as evaluated by HbA1c reduction, in older type 2 diabetes mellitus (T2DM) subjects who were inadequately controlled with their current anti-diabetic treatment regimen.

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 received a stable regimen of anti-diabetic background therapy for at least 3 months prior to screening, during the placebo run-in period and the 24-week treatment period. Allowed background anti-diabetic therapy included metformin, sulfonylurea (except glibenclamide >10mg, gliclazide >160mg), meglitinides (except repaglinide >6mg), pioglitazone and basal insulin. Insulin glargine, neutral protamine hagedorn (NPH) insulin, detemir, lente and ultralente were considered as basal insulin.

Evidence for comparator: -

Actual start date of recruitment	10 June 2013
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	Norway: 16
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	Sweden: 33
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Bulgaria: 29
Country: Number of subjects enrolled	Denmark: 23
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	Australia: 19
Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	Peru: 86

Country: Number of subjects enrolled	South Africa: 11
Country: Number of subjects enrolled	United States: 36
Worldwide total number of subjects	350
EEA total number of subjects	175

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	344
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 73 centers in 13 countries between June 10, 2013 and February 19, 2015.

Pre-assignment

Screening details:

A total of 786 subjects were screened. 426 subjects underwent 4-week placebo run–in period. 436 subjects were screen failures and 76 subjects were run-in failures; the most frequent reason for screen and run-in failure was that glycosylated hemoglobin (HbA1c) criteria was not met at the end of run-in phase. A total of 350 subjects were randomized.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Lixisenatide

Arm description:

Lixisenatide 10 mcg once daily (QD) for 2 weeks post-randomization, then at a maintenance dose of 20 mcg QD up to Week 24.

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

Dosage and administration details:

Lixisenatide was self-administered QD 30 to 60 minutes before breakfast in the morning. If the maintenance dose of 20 mcg was not tolerated, dose could be reduced to 10 mcg.

Arm title	Placebo

Arm description:

Placebo matched to lixisenatide QD for 24 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo was self-administered QD 30 to 60 minutes before breakfast in the morning.

Number of subjects in period 1	Lixisenatide	Placebo
Started	176	174
Completed	155	153
Not completed	21	21
other than specified above	5	9
Adverse event	15	10
Poor compliance to protocol	1	-
Lack of efficacy	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Lixisenatide
Reporting group description:	
Lixisenatide 10 mcg once daily (QD) for 2 weeks post-randomization, then at a maintenance dose of 20 mcg QD up to Week 24.	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to lixisenatide QD for 24 weeks.	

Reporting group values	Lixisenatide	Placebo	Total
Number of subjects	176	174	350
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	74	74.4	
standard deviation	± 4	± 3.8	-
Gender categorical Units: Subjects			
Female	84	84	168
Male	92	90	182
Race Units: Subjects			
Caucasian/white	128	122	250
Black	3	0	3
Asian/Oriental	5	11	16
Other	40	41	81
Ethnicity Units: Subjects			
Hispanic	51	48	99
Not Hispanic	125	126	251
Number of Subjects with Categorical BMI Units: Subjects			
<30	102	96	198
≥30	74	78	152
Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean	29.91	30.09	
standard deviation	± 3.7	± 4.53	-
Body Weight Units: kg			
arithmetic mean	80.81	80.08	
standard deviation	± 14.54	± 16.76	-
Glycosylated Hemoglobin (HbA1c) Units: Percentage of HbA1c			

arithmetic mean	8.04	8.05	
standard deviation	± 0.72	± 0.69	-
Fasting Plasma Glucose (FPG)			
Units: mmol/L			
arithmetic mean	8.83	8.89	
standard deviation	± 2.38	± 2.26	-
2-Hour Postprandial Plasma Glucose (PPG)			
347 subjects (174 in lixisenatide arm and 173 in placebo arm) were included for PPG analysis.			
Units: mmol/L			
arithmetic mean	15.18	14.87	
standard deviation	± 3.78	± 3.69	-
Glucose Excursion			
345 subjects (173 in lixisenatide arm and 172 in placebo arm) were included for glucose excursion analysis.			
Units: mmol/L			
arithmetic mean	6.51	6.02	
standard deviation	± 3.15	± 3.17	-
7-Point self-monitored plasma glucose (SMPG)			
333 subjects (171 in lixisenatide arm and 162 in placebo arm) were included for 7-point SMPG analysis.			
Units: mmol/L			
arithmetic mean	9.79	9.97	
standard deviation	± 2.02	± 1.98	-
Duration of Diabetes			
Units: years			
arithmetic mean	13.63	14.63	
standard deviation	± 7.34	± 7.87	-

End points

End points reporting groups

Reporting group title	Lixisenatide
Reporting group description:	
Lixisenatide 10 mcg once daily (QD) for 2 weeks post-randomization, then at a maintenance dose of 20 mcg QD up to Week 24.	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to lixisenatide QD for 24 weeks.	

Primary: Absolute Change in HbA1c From Baseline to Week 24

End point title	Absolute Change in HbA1c From Baseline to Week 24
End point description:	
Change in HbA1c was calculated by subtracting baseline value from Week 24 value. Missing data was imputed using last on-treatment observation carried forward (LOCF). On-treatment period for this efficacy variable was defined as the time from the first dose of study drug up to 14 days after the last dose of study drug. Modified intent-to-treat (mITT) population: all randomized subjects who received at least one dose of study drug; and had both baseline and at least one post-baseline efficacy assessment, irrespective of compliance with study protocol/procedures. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline HbA1c assessment during on-treatment period.	
End point type	Primary
End point timeframe:	
Baseline, Week 24	

End point values	Lixisenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	172		
Units: percentage of hemoglobin				
least squares mean (standard error)	-0.57 (± 0.075)	0.06 (± 0.072)		

Statistical analyses

Statistical analysis title	Lixisenatide vs Placebo
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 basal insulin use at screening, randomization strata of Week -1 glomerular filtration rate (eGFR) [≥30 to <60, ≥60 ml/min/1.73 m^2],and country as fixed effects and baseline HbA1c value as a covariate.	
Comparison groups	Lixisenatide v Placebo

Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	ANCOVA
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	-0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	-0.464
Variability estimate	Standard error of the mean
Dispersion value	0.088

Notes:

[1] - Threshold for significance at 0.05 level.

Secondary: Change in 2-Hour PPG from Baseline to Week 24

End point title	Change in 2-Hour PPG from Baseline to Week 24

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 24 value. Missing data was imputed using LOCF. The on-treatment period for this efficacy variable was the time from the first dose of study drug up to the day of last dose of study drug. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline 2-hour PPG assessment during on-treatment period.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Lixisenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	144		
Units: mmol/L				
least squares mean (standard error)	-5.12 (± 0.392)	-0.07 (± 0.393)		

Statistical analyses

Statistical analysis title	Lixisenatide vs Placebo

Statistical analysis description:

Analysis was performed using ANCOVA model with treatment groups, randomization strata of Week -1 HbA1c [<8.0, ≥8.0%], randomization strata of basal insulin use at screening, randomization strata of Week -1 eGFR [≥30 to <60, ≥60 ml/min/1.73 m^2], and country as fixed effects and baseline 2-hour PPG value as a covariate.

Comparison groups	Lixisenatide v Placebo

Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001 [3]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-5.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.96
upper limit	-4.132
Variability estimate	Standard error of the mean
Dispersion value	0.464

Notes:

[2] - Hierarchical testing procedure was used to control type I error rate at 0.05. Testing was performed sequentially in order:
1. Change in PPG from Baseline to Week 24;
2. Change in Average 7-point SMPG from Baseline to Week 24;
3. Change in body weight from Baseline to Week 24;
4. Change in FPG from Baseline to Week 24;
5. Percentage of Subjects Requiring Rescue Therapy during 24-Week.
Hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.05.
[3] - Threshold for significance at 0.05 level.

Secondary: Change in Average 7-point SMPG Profiles from Baseline to Week 24

End point title	Change in Average 7-point SMPG Profiles from Baseline to Week 24

End point description:

Subjects recorded a 7-point plasma glucose profile measured before and 2 hours after each meal and at bedtime three times in a week before baseline, before visit Week 12 and before visit week 26 and the average value across the profiles performed in the week a visit for the 7-time points was calculated. Change in average 7-point SMPG was calculated by subtracting baseline value from Week 24 value. Missing data was imputed using LOCF. The on-treatment period for this efficacy variable was defined as the time from the first dose of study drug up to the day of last dose of study drug. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline 7-point SMPG assessment during on-treatment period.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Lixisenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	125		
Units: mmol/L				
least squares mean (standard error)	-1.15 (± 0.186)	-0.19 (± 0.189)		

Statistical analyses

Statistical analysis title	Lixisenatide vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Analysis was performed using ANCOVA model with treatment groups, randomization strata of Week -1 HbA1c [<8.0, ≥8.0%], randomization strata of basal insulin use at screening, randomization strata of Week -1 eGFR [≥30 to <60, ≥60 ml/min/1.73 m^2], and country as fixed effects and baseline 7-point SMPG value as a covariate.

Comparison groups	Lixisenatide v Placebo
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.39
upper limit	-0.527
Variability estimate	Standard error of the mean
Dispersion value	0.219

Notes:

[4] - Threshold for significance at 0.05 level.

Secondary: Change in Body Weight from Baseline to Week 24

End point title	Change in Body Weight from Baseline to Week 24

End point description:

Change in body weight was calculated by subtracting baseline value from Week 24 value. Missing data was imputed using LOCF. On-treatment period for this efficacy variable was defined as the time from the first dose of study drug up to 3 days after the last dose of study drug. Missing data was imputed using LOCF. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline body weight assessment during on-treatment period.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Lixisenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	173		
Units: kg				
least squares mean (standard error)	-1.47 (± 0.241)	-0.16 (± 0.228)		

Statistical analyses

Statistical analysis title	Lixisenatide vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Analysis was performed using ANCOVA model with treatment groups, randomization strata of Week -1 HbA1c [<8.0, ≥8.0%], randomization strata of basal insulin use at screening, randomization strata of Week -1 eGFR [≥30 to <60, ≥60 ml/min/1.73 m^2],and country as fixed effects and baseline body weight value as a covariate.

Comparison groups	Lixisenatide v Placebo
Number of subjects included in analysis	347
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.862
upper limit	-0.769
Variability estimate	Standard error of the mean
Dispersion value	0.278

Notes:

[5] - Threshold for significance at 0.05 level.

Secondary: Change in FPG from Baseline to Week 24

End point title	Change in FPG from Baseline to Week 24

End point description:

Change in FPG was calculated by subtracting baseline value from Week 24 value. Missing data was imputed using LOCF. The on-treatment period for this efficacy variable was the time from the first dose of study drug up to 1 day after the last dose of study drug. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline FPG assessment during on-treatment period.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Lixisenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	168		
Units: mmol/L				
least squares mean (standard error)	-0.3 (± 0.224)	0.01 (± 0.218)		

Statistical analyses

Statistical analysis title	Lixisenatide vs Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Analysis was performed using ANCOVA model with treatment groups, randomization strata of Week -1 HbA1c [<8.0, ≥8.0%], randomization strata of basal insulin use at screening, randomization strata of Week -1 eGFR [≥30 to <60, ≥60 ml/min/1.73 m^2], and country as fixed effects and baseline FPG value as a covariate.

Comparison groups	Lixisenatide v Placebo
Number of subjects included in analysis	339
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2347 [6]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.828
upper limit	0.204
Variability estimate	Standard error of the mean
Dispersion value	0.262

Notes:

[6] - Threshold for significance at 0.05 level.

Secondary: Percentage of Subjects Requiring Rescue Therapy during 24-Week Treatment Period

End point title	Percentage of Subjects Requiring Rescue Therapy during 24-Week Treatment Period

End point description:

Routine fasting SMPG and central laboratory FPG (and HbA1c after week 12) values were used to determine the requirement of rescue medication. If fasting SMPG value exceeded the specified limit for 3 consecutive days, the central laboratory FPG (and HbA1c after week 12) were performed. Threshold values - from baseline to Week 8: fasting SMPG/FPG >270 mg/dL (15.0 mmol/L), from Week 8 to Week 12: fasting SMPG/FPG >240 mg/dL (13.3 mmol/L), and from Week 12 to Week 24: fasting SMPG/FPG >200 mg/dL (11.1 mmol/L) or HbA1c >9%. mITT population.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Lixisenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	173		
Units: percentage of subjects				
number (not applicable)	2.9	10.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Plasma Glucose Excursions from Baseline to Week 24

End point title	Change in Plasma Glucose Excursions from Baseline to Week 24

End point description:

Plasma glucose excursion = 2-hour PPG minus plasma glucose 30 minutes prior to the liquid standardized breakfast meal test, before study drug administration. Change in plasma glucose excursions were calculated by subtracting baseline value from Week 24 value. Missing data was imputed using LOCF. The on-treatment period for this efficacy variable was the time from the first dose of study drug up to the day of last dose of study drug. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline plasma glucose excursion assessment during on-treatment period.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Lixisenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	143		
Units: mmol/L				
least squares mean (standard error)	-4.71 (± 0.331)	-0.25 (± 0.331)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Total Daily Basal Insulin Dose from Baseline to Week 24 (in Subjects who Took Basal Insulin as Background Therapy)

End point title	Change in Total Daily Basal Insulin Dose from Baseline to Week 24 (in Subjects who Took Basal Insulin as Background Therapy)

End point description:

Change in basal insulin dose was calculated by subtracting baseline value from Week 24 value. Missing data was imputed using LOCF. The on-treatment period for this efficacy variable was the time from the first dose of study drug up to the day of last dose of study drug. mITT population. Here, number of subjects analyzed=subjects with baseline and at least one post-baseline basal insulin dose assessment during on-treatment period.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Lixisenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	55		
Units: units				
least squares mean (standard error)	-2.97 (± 1.145)	-1.3 (± 1.076)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Symptomatic and Severe Symptomatic Hypoglycemia

End point title	Percentage of Subjects with Symptomatic and Severe Symptomatic Hypoglycemia

End point description:

Symptomatic hypoglycemia was an event with clinical symptoms that were considered to result from a hypoglycemic episode with an accompanying plasma glucose less than 60 mg/dL (3.3 mmol/L) or associated with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration if no plasma glucose measurement was available. Severe symptomatic hypoglycemia was symptomatic hypoglycemia event in which the subject required the assistance of another person and was associated with either a plasma glucose level below 36 mg/dL (2.0 mmol/L) or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration, if no plasma glucose measurement was available. Analysis was performed on safety population defined as all randomized subjects who received any amount of study drug.

End point type	Secondary

End point timeframe:

First dose of study drug up to 3 days after the last dose administration (maximum of 171 days)

End point values	Lixisenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176	174		
Units: percentage of subjects				
number (not applicable)				
Symptomatic hypoglycemia	7.4	5.7		
Severe symptomatic hypoglycemia	0.57	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with HbA1c Reduction >0.5% at Week 24 and did not Experienced Documented (Plasma Glucose <60 mg/dL) Symptomatic Hypoglycemia

End point title	Percentage of Subjects with HbA1c Reduction >0.5% at Week 24 and did not Experienced Documented (Plasma Glucose <60 mg/dL) Symptomatic Hypoglycemia

End point description:

The on-treatment period for HbA1c assessment was defined as the time from the first dose of study drug up to 14 days after the last dose of study drug. The on-treatment period for symptomatic hypoglycemia assessment was defined as the time from the first dose of study drug up to 1 day after the last dose of study drug. mITT population. Subjects without any post-baseline on-treatment value for HbA1c were counted as non-responders if they experienced at least one symptomatic hypoglycemia. Otherwise, they were counted as missing.

End point type	Secondary

End point timeframe:

Week 24

End point values	Lixisenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	172		
Units: percentage of subjects				
number (not applicable)	57.6	21.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Gastrointestinal Disorders

End point title	Percentage of Subjects with Gastrointestinal Disorders

End point description:

Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

Up to Day 171

End point values	Lixisenatide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176	174		
Units: percentage of subjects				
number (not applicable)	40.3	20.7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (AE) were collected from signature of the informed consent form up to the final visit (Day 171) regardless of seriousness or relationship to investigational Medicinal product (IMP).

Adverse event reporting additional description:

Reported adverse events and deaths are treatment-emergent adverse events that is AEs that developed/worsened and death that occurred during the 'on treatment period' (time from the first dose of study drug up to 3 days after the last dose of study drug).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Lixisenatide

Reporting group description:

Lixisenatide 10 mcg once daily (QD) for 2 weeks post-randomization, then at a maintenance dose of 20 mcg QD up to Week 24. (Median exposure: 169 days)

Reporting group title	Placebo

Reporting group description:

Placebo matched to lixisenatide QD for 24 weeks. (Median exposure: 169 days)

Serious adverse events	Lixisenatide	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 176 (4.55%)	10 / 174 (5.75%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lentigo Maligna			
subjects affected / exposed	1 / 176 (0.57%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 176 (0.57%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip Fracture			

subjects affected / exposed	1 / 176 (0.57%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull Fracture			
subjects affected / exposed	1 / 176 (0.57%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Compression Fracture			
subjects affected / exposed	0 / 176 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic Intracranial Haemorrhage			
subjects affected / exposed	1 / 176 (0.57%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic Aneurysm			
subjects affected / exposed	0 / 176 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypertensive Crisis			
subjects affected / exposed	1 / 176 (0.57%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	0 / 176 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Unstable			
subjects affected / exposed	1 / 176 (0.57%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			

subjects affected / exposed	0 / 176 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	0 / 176 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 176 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Unconsciousness			
subjects affected / exposed	1 / 176 (0.57%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss Of Consciousness			
subjects affected / exposed	0 / 176 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
subjects affected / exposed	0 / 176 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 176 (0.57%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain Lower			
subjects affected / exposed	0 / 176 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pancreatitis			
subjects affected / exposed	0 / 176 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 176 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal Failure Acute			
subjects affected / exposed	0 / 176 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Systemic Lupus Erythematosus			
subjects affected / exposed	1 / 176 (0.57%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 176 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Lixisenatide	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	89 / 176 (50.57%)	58 / 174 (33.33%)	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 176 (5.68%)	8 / 174 (4.60%)	
occurrences (all)	13	10	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	19 / 176 (10.80%)	13 / 174 (7.47%)	
occurrences (all)	28	18	
Nausea			
subjects affected / exposed	44 / 176 (25.00%)	13 / 174 (7.47%)	
occurrences (all)	61	15	
Vomiting			
subjects affected / exposed	10 / 176 (5.68%)	1 / 174 (0.57%)	
occurrences (all)	10	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	15 / 176 (8.52%)	22 / 174 (12.64%)	
occurrences (all)	20	29	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	30 / 176 (17.05%)	18 / 174 (10.34%)	
occurrences (all)	69	50	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2013	It included following changes: - The rescue medication was clarified as: only an increase by more than 20% in basal insulin for more than 7 days was considered a rescue therapy; - Pharmacokinetic (PK) sampling was clarified as: no pre-dose (before first study drug intake) PK assessment was needed for PK profile evaluation; - The cases of serious adverse events (SAEs) occurring after the end of the study period were clarified as: deaths post study (any deaths occurring after the end of the study judged by the Investigator as related to study drug).
12 March 2014	It included following changes: - A new safety committee, the Pancreatic Safety Assessment Committee (PSAC) was added to ensure the independent assessment of pancreatic event data; - Inclusion criteria was revised as: the current anti-diabetic regimen should be a pharmaceutical treatment. Subjects receiving only diet and lifestyle regimen were not eligible. - Stable dose of basal insulin was defined as a dose change during 3 months preceding screening visits, between -20% and +20% of the dose at Visit 1; - The discrepancy between exclusion criteria was corrected as: with a threshold of HbA1c > 7% required at visit 1 to enter the study; and basal insulin and sulfonyl urea adjustment in case of Hba1c ≥ 7%; - Correction in exclusion criteria: removal of the word single-blind since during run-in period only placebo was injected; - Regarding the final assessment before rescue therapy, removed the reference to Visit 22 to describe the final assessment visit before introducing the recue therapy; - Discrepancy between FPG values displayed in mg/dL and mmol/L were corrected; - Study drug dose adjustment was clarified: after Visit 13, the study drug dose should have been maintained at the 20 µg dose or to the 10 µg dose if the 20 µg dose could no longer be tolerated; - Correction of discrepancy regarding basal insulin and sulfonyl urea dose reduction that should occur the day before randomization and not the day of randomization; - Discrepancy regarding use of weight loss drugs was clarified: weight loss drugs were not allowed during the screening and double-blind treatment periods; - Re-screening was allowed only before entering the run-in period; - Alanine transaminase (ALT) increase was to be reported as an adverse events of special interest (AESI) with immediate notification to be in line with the updated requirements for safety information collection; Statistical analyses were corrected; - Creatinine clearance increase was clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported