Clinical trial results:
An open-label, randomized, three-parallel-group study on pharmacodynamic effects of 8-week QD treatment with lixisenatide compared to liraglutide in patients with type 2 diabetes not adequately controlled with insulin glargine with or without metformin

Summary

EudraCT number	2012-000027-40
Trial protocol	DE
Global end of trial date	25 July 2013

Results information

Result version number	v1 (current)
This version publication date	01 April 2016
First version publication date	26 March 2015

Trial information

Trial identification

Sponsor protocol code	PDY12625

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01596504
WHO universal trial number (UTN)	U1111-1124-1364

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 August 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effects of repeated subcutaneous (SC) doses of lixisenatide 20 microgram (mcg) once daily (QD) as compared to liraglutide 1.2 milligram (mg) QD or 1.8 mg QD in reducing post-prandial plasma glucose (PPG) assessed as area under the plasma glucose concentration- time curve (AUC) after a standardized breakfast at the end of an 8- week treatment period in subjects with type 2 diabetes mellitus (T2DM) not adequately controlled with insulin glargine (+/- metformin).

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: -

Evidence for comparator: -

Actual start date of recruitment	22 May 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 142
Worldwide total number of subjects	142
EEA total number of subjects	142

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)	86
From 65 to 84 years	56
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 8 centres in Germany between 22 May 2012 to 25 July 2013.

Pre-assignment

Screening details:

A total of 236 subjects were screened and 142 subjects were randomized and treated.

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	Lixisenatide 20 mcg

Arm description:

Lixisenatide for 8 weeks (up to Day 57) and a maintenance dose of 20 mcg QD.

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

Dosage and administration details:

Lixisenatide 10 mcg QD for 2 weeks followed by 20 mcg QD for 6 weeks (up to Day 57), to be self-administered with a pen-like injector (OptiClik®), under fasted conditions.

Arm title	Liraglutide 1.2 mg

Arm description:

Liraglutide for 8 weeks (up to Day 57) and a maintenance dose of 1.2 mg QD.

Arm type	Active comparator
Investigational medicinal product name	Liraglutide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Liraglutide 0.6 mg QD for 1 week followed by 1.2 mg QD for 7 weeks (up to Day 57), to be self-administered using a prefilled pen (Victoza®), under fasted conditions.

Arm title	Liraglutide 1.8 mg

Arm description:

Liraglutide for 8 weeks (up to Day 57) and a maintenance dose of 1.8 mg QD.

Arm type	Active comparator
Investigational medicinal product name	Liraglutide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Liraglutide 0.6 mg QD for 1 week followed by 1.2 mg QD for 1 week and then 1.8 QD mg for 6 weeks (up to Day 57), to be self-administered by using a prefilled pen (Victoza®) under fasted conditions.

Number of subjects in period 1	Lixisenatide 20 mcg	Liraglutide 1.2 mg	Liraglutide 1.8 mg
Started	48	47	47
Completed	46	44	46
Not completed	2	3	1
Consent withdrawn by subject	1	-	-
Adverse event	1	2	1
Subject's Private Reason	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Lixisenatide 20 mcg
Reporting group description:	
Lixisenatide for 8 weeks (up to Day 57) and a maintenance dose of 20 mcg QD.	
Reporting group title	Liraglutide 1.2 mg
Reporting group description:	
Liraglutide for 8 weeks (up to Day 57) and a maintenance dose of 1.2 mg QD.	
Reporting group title	Liraglutide 1.8 mg
Reporting group description:	
Liraglutide for 8 weeks (up to Day 57) and a maintenance dose of 1.8 mg QD.	

Reporting group values	Lixisenatide 20 mcg	Liraglutide 1.2 mg	Liraglutide 1.8 mg
Number of subjects	48	47	47
Age categorical Units: Subjects			
Adults (18-64 years)	33	29	24
From 65-84 years	15	18	23
Age continuous Units: years			
arithmetic mean	61.6	61.4	62.6
standard deviation	± 7.4	± 7.9	± 9.4
Gender categorical Units: Subjects			
Female	15	8	14
Male	33	39	33
Race Units: Subjects			
Caucasian/White	48	46	47
Other	0	1	0
Metformin Use at Screening Units: Subjects			
Yes	43	41	41
No	5	6	6
Weight Units: kilogram (kg)			
arithmetic mean	90.56	91.62	92.92
standard deviation	± 13.09	± 13.92	± 15.33
Body Mass Index (BMI) Units: kilogram per square metre (kg/m^2)			
arithmetic mean	30.68	30.52	31.17
standard deviation	± 4.34	± 4.01	± 4.34
Glycosylated Haemoglobin (HbA1c) at Screening (Day -7) Units: percentage of haemoglobin			
arithmetic mean	7.22	7.19	7.33
standard deviation	± 0.48	± 0.53	± 0.5

Duration of Diabetes			
Units: years			
median	11.41	10.51	12.53
full range (min-max)	2.1 to 32.4	3.9 to 21.1	4 to 31.6
Average Daily Insulin Glargine Dose at Baseline (Day -7)			
Units: units			
arithmetic mean	43.1	40.3	44.3
standard deviation	± 19.1	± 18.1	± 16.1
Plasma Glucose Corrected Area Under The Plasma Concentration-Time Curve From Time 0.5-4.5 Hours			
Number of subjects analysed for this parameter were 46, 43, and 45, respectively.			
Units: hour*millimole per litre (h*mmol/L)			
arithmetic mean	15.67	15.55	17.04
standard deviation	± 6.71	± 5.55	± 5.73

Reporting group values	Total		
Number of subjects	142		
Age categorical			
Units: Subjects			
Adults (18-64 years)	86		
From 65-84 years	56		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	37		
Male	105		
Race			
Units: Subjects			
Caucasian/White	141		
Other	1		
Metformin Use at Screening			
Units: Subjects			
Yes	125		
No	17		
Weight			
Units: kilogram (kg)			
arithmetic mean			
standard deviation	-		
Body Mass Index (BMI)			
Units: kilogram per square metre (kg/m^2)			
arithmetic mean			
standard deviation	-		
Glycosylated Haemoglobin (HbA1c) at Screening (Day -7)			
Units: percentage of haemoglobin			
arithmetic mean			

standard deviation	-		
Duration of Diabetes Units: years median full range (min-max)	-		
Average Daily Insulin Glargine Dose at Baseline (Day -7) Units: units arithmetic mean standard deviation	-		
Plasma Glucose Corrected Area Under The Plasma Concentration-Time Curve From Time 0.5-4.5 Hours			
Number of subjects analysed for this parameter were 46, 43, and 45, respectively.			
Units: hour*millimole per litre (h*mmol/L) arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Lixisenatide 20 mcg
Reporting group description: Lixisenatide for 8 weeks (up to Day 57) and a maintenance dose of 20 mcg QD.	
Reporting group title	Liraglutide 1.2 mg
Reporting group description: Liraglutide for 8 weeks (up to Day 57) and a maintenance dose of 1.2 mg QD.	
Reporting group title	Liraglutide 1.8 mg
Reporting group description: Liraglutide for 8 weeks (up to Day 57) and a maintenance dose of 1.8 mg QD.	

Primary: Change From Baseline to Day 56 in Plasma Glucose Corrected Area Under The Plasma Concentration-Time Curve (AUC) From Time 0.5 Hours to 4.5 Hours

End point title	Change From Baseline to Day 56 in Plasma Glucose Corrected Area Under The Plasma Concentration-Time Curve (AUC) From Time 0.5 Hours to 4.5 Hours

End point description:

Plasma glucose was assessed using the Gluco-quant Glucose/hexokinase assay. The range of the method was 3 to 1000 milligram per decilitre (mg/dL) with 1 mg/dL as limit of detection (LOD). Calculation of the AUC was made on Day -3 (baseline) and on Day 56 using the linear trapezoidal rule from time of breakfast start (30 minutes after study drug administration [time: 0.5 hours]) to 4 hours after breakfast start (time: 4.5 hours) and corrected by subtracting pre-breakfast plasma glucose concentration (time: 0.5 hours). Analysis was carried out on pharmacodynamic (PD) population defined as all randomized subjects, who received at least one dose of lixisenatide 20 microgram (mcg), liraglutide 1.2 milligram (mg) or liraglutide 1.8 mg, and had both a baseline assessment and at least one post-baseline assessment of any primary or secondary PD variables.

End point type	Primary

End point timeframe:

0.5 (8:00 clock time, prior to standardized breakfast), 0.67, 0.84, 1, 1.5, 2, 2.5, 3.5, 4.5 hours on Day -3 (baseline); 0.5 (prior to standardized breakfast), 0.67, 0.84, 1, 1.5, 2, 2.5, 3.5, 4.5 hours post study drug administration on Day 56

End point values	Lixisenatide 20 mcg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	43	45	
Units: h*mmol/L				
least squares mean (standard error)	-13.33 (± 1.11)	-7.32 (± 1.12)	-8.72 (± 1.16)	

Statistical analyses

Statistical analysis title	Lixisenatide vs Liraglutide 1.2 mg

Statistical analysis description:

Analysis was performed using linear fixed effects model with treatment and stratification factors (HbA1c levels on Day -7 [<8% and >=8%], use of metformin at screening [yes or no]) and the study site as

fixed effects and baseline plasma glucose AUC from 0.5 to 4.5 hours as covariate.

Comparison groups	Lixisenatide 20 mcg v Liraglutide 1.2 mg
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001
Method	Linear fixed effects model
Parameter estimate	Least squares mean difference
Point estimate	-6.01
Confidence interval	
level	95 %
sides	1-sided
lower limit	-7.77
Variability estimate	Standard error of the mean
Dispersion value	1.06

Notes:

[1] - To address multiplicity issue and ensure overall 1-sided level of 5%, Hochberg method was used for testing procedure of comparison between lixisenatide vs liraglutide 1.2 mg or 1.8 mg. p-values were ordered (p1<=p2) and following rules were applied:
1)if p2<=0.05: lixisenatide was superior to liraglutide (both dose)
2)if p2>0.05 and p1<=0.025: lixisenatide was superior to dose of liraglutide associated with p1
3)if p2>0.05 and p1>0.025: no comparison was declared as statistically significant.

Statistical analysis title	Lixisenatide vs Liraglutide 1. 8 mg

Statistical analysis description:

Analysis was performed using linear mixed effects model with treatment and stratification factors (HbA1c levels on Day -7 [<8% and >=8%], use of metformin at screening [yes or no]), and the study site as fixed effects and baseline plasma glucose AUC from 0.5 to 4.5 hours as covariate.

Comparison groups	Lixisenatide 20 mcg v Liraglutide 1.8 mg
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001
Method	Linear fixed effects model
Parameter estimate	Least squares mean difference
Point estimate	-4.61
Confidence interval	
level	95 %
sides	1-sided
lower limit	-6.34
Variability estimate	Standard error of the mean
Dispersion value	1.04

Notes:

[2] - To address multiplicity issue and ensure overall 1-sided level of 5%, Hochberg method was used for testing procedure of comparison between lixisenatide vs liraglutide 1.2 mg or 1.8 mg. p-values were ordered (p1<=p2) and following rules were applied:
1)if p2<=0.05: lixisenatide was superior to liraglutide (both dose)
2)if p2>0.05 and p1<=0.025: lixisenatide was superior to dose of liraglutide associated with p1
3)if p2>0.05 and p1>0.025: no comparison was declared as statistically significant.

Secondary: Change From Baseline to Day 56 in Plasma Glucose Corrected AUC From Time 0.5 Hours to 5.5 Hours

End point title	Change From Baseline to Day 56 in Plasma Glucose Corrected AUC From Time 0.5 Hours to 5.5 Hours

End point description:

Plasma glucose was assessed using the Gluco-quant Glucose/hexokinase assay. The range of the

method was 3 to 1000 mg/dL with 1 mg/dL as LOD. Calculation of the AUC was made on Day -3 (baseline) and on Day 56 using the linear trapezoidal rule from time of breakfast start (30 minutes after study drug administration [time: 0.5 hours]) to 5 hours after breakfast start (time: 5.5 hours) and corrected by subtracting pre-breakfast plasma glucose concentration (time: 0.5 hours). Analysis was carried out on PD population.

End point type	Secondary

End point timeframe:

0.5 (8:00 clock time, prior to standardized breakfast), 0.67, 0.84, 1, 1.5, 2, 2.5, 3.5, 4.5, 5.5 hours on Day -3 (baseline); 0.5 (prior to standardized breakfast), 0.67, 0.84, 1, 1.5, 2, 2.5, 3.5, 4.5, 5.5 hours post study drug administration on Day 56

End point values	Lixisenatide 20 mcg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	43	45	
Units: h*mmol/L				
least squares mean (standard error)	-13.82 (± 1.19)	-9.09 (± 1.21)	-10.33 (± 1.25)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With 2-Hour Postprandial Plasma Glucose <7.77 Millimole Per Litre (mmol/L) at Day 56

End point title	Number of Subjects With 2-Hour Postprandial Plasma Glucose <7.77 Millimole Per Litre (mmol/L) at Day 56

End point description:

Plasma glucose was assessed using the Gluco-quant Glucose/hexokinase assay. The range of the method was 3 to 1000 mg/dL with 1 mg/dL as LOD. The 2-hour PPG test measured blood glucose 2 hours after start of a standardized breakfast. Analysis was carried out on PD population.

End point type	Secondary

End point timeframe:

Day 56

End point values	Lixisenatide 20 mcg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	44	46	
Units: subjects				
number (not applicable)	35	13	11	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Day 56 in Postprandial Plasma Glucose (PPG) Excursion

End point title	Change From Baseline to Day 56 in Postprandial Plasma Glucose (PPG) Excursion

End point description:

Plasma glucose was assessed using the Gluco-quant Glucose/hexokinase assay. The range of the method was 3 to 1000 mg/dL with 1 mg/dL as LOD. PPG excursion was determined on Day -3 (Baseline) and Day 56 as the maximum change in PPG from time of breakfast start (time: 0.5 hours) until 5 hours later (time: 5.5 hours) subtracted from pre-meal plasma concentration. Analysis was carried out on PD population.

End point type	Secondary

End point timeframe:

0.67, 0.84, 1, 1.5, 2, 2.5, 3.5, 4.5, 5.5 hours on Day -3 (baseline); 0.67, 0.84, 1, 1.5, 2, 2.5, 3.5, 4.5, 5.5 hours post study drug administration on Day 56

End point values	Lixisenatide 20 mcg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	43	45	
Units: mmol/L				
least squares mean (standard error)	-3.26 (± 0.4)	-1.79 (± 0.4)	-2.5 (± 0.42)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Day 56 in Fasting Plasma Glucose (FPG)

End point title	Change From Baseline to Day 56 in Fasting Plasma Glucose (FPG)

End point description:

Plasma glucose was assessed using the Gluco-quant Glucose/hexokinase assay. The range of the method was 3-1000 mg/dL with 1 mg/dL as LOD. The value of FPG on Day -3 was the baseline. Analysis was carried out on PD population.

End point type	Secondary

End point timeframe:

0.5 hour (prior to standardized breakfast) on Day -3; 0.5 hour (prior to standardized breakfast) on Day 56

End point values	Lixisenatide 20 mcg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	44	45	
Units: mmol/L				
least squares mean (standard error)	0.1 (± 0.22)	0.12 (± 0.22)	0.13 (± 0.23)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Day 56 in Average 7-Point Self-Monitored Plasma Glucose (SMPG)

End point title	Change From Baseline to Day 56 in Average 7-Point Self-Monitored Plasma Glucose (SMPG)

End point description:

Seven-point SMPG (before breakfast, 2 hours post breakfast, before lunch, 2 hours post lunch, before dinner, 2 hours post dinner, and at bedtime) was measured using Freestyle Precision glucometer and average of the 7 measurements was calculated. Analysis was carried out on PD population.

End point type	Secondary

End point timeframe:

Before breakfast, 2 hours post breakfast, before lunch, 2 hours post lunch, before dinner, 2 hours post dinner, and at bedtime on Day -3 (Baseline) and on Day 56.

End point values	Lixisenatide 20 mcg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	44	46	
Units: mmol/L				
arithmetic mean (standard deviation)	-0.69 (± 1.19)	-0.76 (± 1.23)	-1.2 (± 1.09)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Day 56 in Corrected C-Peptide AUC From Time 0.5 Hours to 5.5 Hours

End point title	Change From Baseline to Day 56 in Corrected C-Peptide AUC From Time 0.5 Hours to 5.5 Hours

End point description:

C-peptide was assessed using the Electro Chemiluminescence Immuno Assay.The range of the method was 0.2 to 25 nanogram per millilitre (ng/mL) and the LOD was 0.07 ng/mL. Measurement was done on Day -3 (Baseline) and Day 56 as the maximum change in C-peptide from time of breakfast start (time: 0.5 hours) until 5 hours later (time: 5.5 hours) subtracted from pre-meal plasma concentration. Analysis was carried out on PD population.

End point type	Secondary

End point timeframe:

0.5 (8:00 clock time, prior to standardized breakfast), 0.67, 0.84, 1, 1.5, 2, 2.5, 3.5, 4.5, 5.5 hours on Day -3 (baseline); 0.5 (prior to standardized breakfast), 0.67, 0.84, 1, 1.5, 2, 2.5, 3.5, 4.5, 5.5 hours post study drug administration on Day 56

End point values	Lixisenatide 20 mcg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	43	45	
Units: Hour*nanomole per Litre (h*nmol/L)				
least squares mean (standard error)	-1.16 (± 0.37)	1.23 (± 0.37)	0.88 (± 0.39)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Day 56 in Corrected Glucagon AUC From Time 0.5 Hours to 5.5 Hours

End point title	Change From Baseline to Day 56 in Corrected Glucagon AUC From Time 0.5 Hours to 5.5 Hours

End point description:

Glucagon was assessed using the radioimmunoassay. The range of the method was 4.7 to 150 picomole per litre (pmol/L). Measurement was done on Day -3 (Baseline) and Day 56 as the maximum change in Glucagon from time of breakfast start (time: 0.5 hours) until 5 hours later (time: 5.5 hours) subtracted from pre-meal plasma concentration. Analysis was carried out on PD population.

End point type	Secondary

End point timeframe:

0.5 (8:00 clock time, prior to standardized breakfast), 0.67, 0.84, 1, 1.5, 2, 2.5, 3.5, 4.5, 5.5 hours on Day -3 (baseline); 0.5 (prior to standardized breakfast), 0.67, 0.84, 1, 1.5, 2, 2.5, 3.5, 4.5, 5.5 hours post study drug administration on Day 56

End point values	Lixisenatide 20 mcg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	43	45	
Units: Hour*nanogram per Litre (h*ng/L)				
least squares mean (standard error)	-16.56 (± 19.43)	11.58 (± 19.86)	5.6 (± 20.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Day 56 in HbA1C

End point title	Change From Baseline to Day 56 in HbA1C

End point description:

HbA1C was assessed using the high-performance liquid chromatography method. Analysis was carried

out on PD population

End point type	Secondary

End point timeframe:

Pre-dose (Hour 0) on Day 1 (Baseline) and Day 56

End point values	Lixisenatide 20 mcg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	44	46	
Units: percentage of haemoglobin				
least squares mean (standard error)	-0.58 (± 0.06)	-0.66 (± 0.06)	-0.74 (± 0.06)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Day 56 in Average Daily Insulin Glargine Dose

End point title	Change From Baseline to Day 56 in Average Daily Insulin Glargine Dose

End point description:

Analysis was carried out on PD population.

End point type	Secondary

End point timeframe:

Day -7 (Baseline), Day 56

End point values	Lixisenatide 20 mcg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	44	46	
Units: units				
arithmetic mean (standard deviation)	-4.7 (± 4.8)	-4.6 (± 6.8)	-4 (± 6.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Day 55 in Gastric Emptying Half Life (t1/2)

End point title	Change From Baseline to Day 55 in Gastric Emptying Half Life (t1/2)

End point description:

Gastric emptying was measured using 13C-octanoic acid breath test by isotope-selective non-dispersive infrared spectrometry. Analysis was carried out on PD population.

End point type	Secondary

End point timeframe:

0 (7:30 clock time, prior to standardized breakfast), 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 4.5, 5, 5.5 hours on Day -4 (baseline) and on Day 55

End point values	Lixisenatide 20 mcg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	44	46	
Units: minutes (min)				
least squares mean (standard error)	453.56 (± 58.24)	175.31 (± 58.49)	130.49 (± 60.27)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Day 55 in Gastric Emptying Coefficient

End point title	Change From Baseline to Day 55 in Gastric Emptying Coefficient

End point description:

Gastric emptying was measured using 13C-octanoic acid breath test by isotope-selective non-dispersive infrared spectrometry. Gastric emptying coefficient was derived from a mathematical formula that describes the gastric-emptying rate and gives an overall index of gastric emptying. Analysis was carried out on PD population.

End point type	Secondary

End point timeframe:

0 (7:30 clock time, prior to standardized breakfast), 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 4.5, 5, 5.5 hours on Day -4 (baseline) and on Day 55

End point values	Lixisenatide 20 mcg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	44	46	
Units: coefficient (unit-less)				
arithmetic mean (standard deviation)	-0.33 (± 1.09)	-0.34 (± 0.53)	-0.28 (± 0.52)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Day 57/58 in 24-Hour Mean Heart Rate

End point title	Change From Baseline to Day 57/58 in 24-Hour Mean Heart

	Rate

End point description:

The baseline value was the 24-hour mean on Day -2/-1 determined as overall, night- and day-time mean. Measurements were made every 15 minutes from 07:00 to 23:00 (daytime) and every 30 minutes from 23:00 to 07:00 (nighttime) at baseline and Day 57/58. Measurements were obtained after 10 minutes in the supine resting position. Analysis was carried out on PD population.

End point type	Secondary

End point timeframe:

Every 15 minutes from 07:00 clock time to 23:00 clock time (daytime) and every 30 minutes from 23:00 clock time to 07:00 clock time (nighttime) on Day -2/-1 (Baseline) and Day 57/58

End point values	Lixisenatide 20 mcg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42	43	44	
Units: beats per minute (bpm)				
least squares mean (standard error)	3.34 (± 1.33)	9.33 (± 1.24)	9.17 (± 1.31)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Day 57/58 in 24-Hour Mean Systolic Blood Pressure and Diastolic Blood Pressure

End point title	Change From Baseline to Day 57/58 in 24-Hour Mean Systolic Blood Pressure and Diastolic Blood Pressure

End point description:

The baseline value was the 24-hour means on Day -2/-1 determined as overall, night- and day-time mean. Measurements were made every 15 minutes from 07:00 to 23:00 (day time) and every 30 minutes from 23:00 to 07:00 (night time) at baseline and at Day 57/58. Measurements were obtained after 10 minutes in the supine resting position. Analysis was carried out on PD population.

End point type	Secondary

End point timeframe:

Every 15 minutes from 07:00 clock time to 23:00 clock time (daytime) and every 30 minutes from 23:00 clock time to 07:00 clock time (nighttime) on Day -2/-1 (Baseline) and Day 57/58

End point values	Lixisenatide 20 mcg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42	43	44	
Units: millimetre of mercury (mmHg)				
arithmetic mean (standard deviation)				
24-Hour Mean Systolic Blood Pressure	0.4 (± 6.4)	-0.5 (± 7.1)	-2.5 (± 7.7)	
24-Hour Mean Diastolic Blood Pressure	0.8 (± 4.1)	2.4 (± 4.7)	1.6 (± 4.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Day 57 in Body Weight

End point title	Change From Baseline to Day 57 in Body Weight

End point description:

Analysis was carried out on PD population.

End point type	Secondary

End point timeframe:

0.5 hours prior to standardized breakfast (7:30 clock time) on Day -1 (Baseline); 0.5 hours prior to study drug administration on Day 57

End point values	Lixisenatide 20 mcg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	44	46	
Units: kilogram				
least squares mean (standard error)	-1.61 (± 0.47)	-1.78 (± 0.48)	-2.42 (± 0.49)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Day 57 in Waist Circumference

End point title	Change From Baseline to Day 57 in Waist Circumference

End point description:

Analysis was carried out on PD population.

End point type	Secondary

End point timeframe:

0.5 hours prior to standardized breakfast (7:30 clock time) on Day -1 (Baseline); 0.5 hours prior to IMP administration on Day 57

End point values	Lixisenatide 20 mcg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	43	46	
Units: centimetre				
arithmetic mean (standard deviation)	-1.4 (± 4.66)	-1.93 (± 3.59)	-2.12 (± 4.95)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Day 56 in The Cumulative Score Mean on The Appetite Perception Using a Visual Analogue Scale After Standardized Solid Breakfast

End point title	Change From Baseline to Day 56 in The Cumulative Score Mean on The Appetite Perception Using a Visual Analogue Scale After Standardized Solid Breakfast

End point description:

Visual Analogue Scale, 100 millimetre (mm) in length with words anchored at each end, expressing the most positive and the most negative rating, was used to assess hunger, satiety, fullness and prospective food consumption. Analysis was carried out on PD population.

End point type	Secondary

End point timeframe:

0.5 (8:00 clock time, prior to standardized breakfast), 1.5, 2.5, 3.5, 4.5, 5.5 hours on Day -3; 0 (prior to standardized breakfast), 1.5, 2.5, 3.5, 4.5, 5.5 hours post study drug administration on Day 56

End point values	Lixisenatide 20 mcg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	44	46	
Units: millimeter(s)				
arithmetic mean (standard deviation)				
How hungry do you feel?	-3.7 (± 16.4)	-3.1 (± 16.8)	-1 (± 14.6)	
How satisfied do you feel?	4.5 (± 15.8)	8.9 (± 13.2)	3.6 (± 11)	
How full do you feel?	4.9 (± 17)	9.3 (± 15.6)	6.4 (± 13.8)	
How much do you think you can eat?	-6.4 (± 16.1)	-4.5 (± 15.7)	-7.2 (± 12)	

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 end of study regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported adverse events are treatment-emergent adverse events that developed/worsened during the 'on treatment period' (the time from the first drug injection [included] up to 3 days after the last injection of drug administration [included]).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Lixisenatide 20 mcg

Reporting group description:

Lixisenatide for 8 weeks (up to Day 57) and a maintenance dose of 20 mcg QD.

Reporting group title	Liraglutide 1.2 mg

Reporting group description:

Liraglutide for 8 weeks (up to Day 57) and a maintenance dose of 1.2 mg QD.

Reporting group title	Liraglutide 1.8 mg

Reporting group description:

Liraglutide for 8 weeks (up to Day 57) and a maintenance dose of 1.8 mg QD.

Serious adverse events	Lixisenatide 20 mcg	Liraglutide 1.2 mg	Liraglutide 1.8 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 48 (2.08%)	1 / 47 (2.13%)	0 / 47 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Coronary Artery Disease			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	0 / 47 (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
Myocardial Infarction			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	0 / 47 (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	Lixisenatide 20 mcg	Liraglutide 1.2 mg	Liraglutide 1.8 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 48 (54.17%)	27 / 47 (57.45%)	27 / 47 (57.45%)
Nervous system disorders			
Dizziness Postural			
subjects affected / exposed	3 / 48 (6.25%)	1 / 47 (2.13%)	0 / 47 (0.00%)
occurrences (all)	3	1	0
Headache			
subjects affected / exposed	4 / 48 (8.33%)	5 / 47 (10.64%)	8 / 47 (17.02%)
occurrences (all)	5	5	9
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 48 (6.25%)	1 / 47 (2.13%)	4 / 47 (8.51%)
occurrences (all)	4	1	4
Malaise			
subjects affected / exposed	3 / 48 (6.25%)	0 / 47 (0.00%)	1 / 47 (2.13%)
occurrences (all)	3	0	1
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	3 / 48 (6.25%)	7 / 47 (14.89%)	4 / 47 (8.51%)
occurrences (all)	4	9	4
Abdominal Pain			
subjects affected / exposed	2 / 48 (4.17%)	3 / 47 (6.38%)	1 / 47 (2.13%)
occurrences (all)	2	4	1
Abdominal Pain Upper			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	5 / 47 (10.64%)
occurrences (all)	1	0	5
Constipation			
subjects affected / exposed	0 / 48 (0.00%)	5 / 47 (10.64%)	3 / 47 (6.38%)
occurrences (all)	0	6	3
Diarrhoea			
subjects affected / exposed	3 / 48 (6.25%)	4 / 47 (8.51%)	5 / 47 (10.64%)
occurrences (all)	3	6	7
Dyspepsia			

subjects affected / exposed	3 / 48 (6.25%)	3 / 47 (6.38%)	4 / 47 (8.51%)
occurrences (all)	3	6	5
Flatulence			
subjects affected / exposed	2 / 48 (4.17%)	0 / 47 (0.00%)	4 / 47 (8.51%)
occurrences (all)	3	0	4
Nausea			
subjects affected / exposed	9 / 48 (18.75%)	8 / 47 (17.02%)	11 / 47 (23.40%)
occurrences (all)	11	9	14
Vomiting			
subjects affected / exposed	5 / 48 (10.42%)	2 / 47 (4.26%)	5 / 47 (10.64%)
occurrences (all)	9	2	5
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 47 (0.00%)	3 / 47 (6.38%)
occurrences (all)	0	0	3
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 48 (12.50%)	10 / 47 (21.28%)	5 / 47 (10.64%)
occurrences (all)	6	12	5
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	9 / 48 (18.75%)	9 / 47 (19.15%)	13 / 47 (27.66%)
occurrences (all)	9	9	15

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 September 2012	- Change in the Inclusion/Exclusion criteria: Subjects were eligible to enter in the screening phase with a stable dose of Neutral Protamine Hagedorn (NPH) or insulin glargine of at least 10 International units per day (IU/Day) (for at least 2 months prior to screening) instead of 20 units per day, alone or combined with a stable dose of metformin with or without Dipeptidyl peptidase (DPP)-IV inhibitor or sulfonylurea. Subjects receiving NPH or insulin glargine with metformin combined with DPP-IV inhibitors or sulfonylurea were eligible to enter in the screening phase provided that the run-in period will last 12 fixed weeks and subjects who received liraglutide 3 months prior to the time of screening were eligible. Inclusion of subjects who had received liraglutide provided that liraglutide treatment was stopped at least 3 months before the time of the screening for other reason than safety/tolerability issue or lack of efficacy. - Change in the run-in period: Either the run-in period was to be extended up to 12 weeks, if needed, in subjects treated with an initial therapy with NPH or insulin glargine of at least 10 IU/Day with or without metformin alone; or the run-in period was to be fixed to 12 weeks for subjects treated with an initial therapy with NPH or insulin glargine with metformin combined with DPP-4 inhibitor or sulfonylurea. This period was needed for reaching an appropriate baseline glycemic control after stopping DPP-4 inhibitor or sulfonylurea. - Change in the study/period flow charts and duration of participation: The changes in the run-in period with additional visits was to be included in the change in the study/period flow charts. The maximum duration of participation per subject was 23 weeks and one day +/- 2 days. Reporting timelines of SAE by the investigator have been changed from "within 1 working day" to "within 24 hours" following the European Commission (EC) guidance 2011/C 172/01 (dated 11 June 2011).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported